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(REVIEW ARTICLE)

Antiplasmodial potential of *Lansium domesticum* Corrêa: A systematic review and critical appraisal of preclinical evidence

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Abstract

Background: Although *Lansium domesticum* Corrêa is widely used in Southeast Asian traditional medicine, its phytochemical diversity and antioxidant activity cannot be considered definitive evidence of antimalarial efficacy. A rigorous synthesis is required to distinguish specific anti-parasitic findings from data that only informs chemical characteristics or host-cell safety.

Objective: This review aims to critically synthesize 17 species-specific primary studies published between 2016 and 2026 to differentiate direct antiplasmodial evidence from translational-enabling data.

Methods: This systematic review was prospectively registered in PROSPERO (CRD420261458422). Systematic searches through July 2026 targeted studies reporting malaria-related endpoints. Evidence was classified as direct (whole-parasite assays, infected-animal models, or parasite-specific targets) or translational-enabling (phytochemical characterization, safety, or mechanistic evidence). Findings were synthesized narratively in accordance with the PRISMA 2020 statement and the Synthesis Without Meta-analysis (SWiM) reporting guideline.

Results: Seventeen studies were identified: four provided direct evidence and 13 were enabling. Root chloroform and methanol fractions exhibited potent *in vitro* inhibition (*IC50* 1.4–3.6 µg/mL), yet *in vivo* stem-bark data showed a non-monotonic response and a high risk of bias. A significant unit discrepancy (mg/mL vs. µg/mL) was identified in reports for dukunolides, and *in silico* docking results lack experimental confirmation. Currently, no lead candidate possesses matched parasite-host selectivity, standardized chemistry, or pharmacokinetic data.

Conclusion: *Lansium domesticum* is currently a source of preclinical leads rather than a validated antimalarial medicine. Future research must prioritize unit verification, standardized same-batch selectivity testing, mechanism validation, and rigorously controlled animal studies.

Keywords: Antiplasmodial; *Lansium domesticum*; Malaria; *Plasmodium falciparum*; Systematic review; Translational evidence

1. Introduction

Despite significant advancements in global health strategies, malaria continues to be a profound international burden, with the World Health Organization estimating 282 million cases and 610,000 deaths in 2024; notably, the African Region accounts for approximately 94% of these cases and 95% of the total mortality (1). The persistent geographical expansion of partial resistance to artemisinin highlights the critical necessity for the discovery of drug leads that are

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both chemically and mechanistically distinct from current therapies (2). Natural products represent a rational and historically successful source for drug discovery; however, their evaluation demands the same rigorous evidentiary discipline applied to synthetic agents, specifically regarding identity, reproducible potency, selectivity, mechanism, exposure, and safety.

Lansium domesticum Corrêa is a recognized member of the Meliaceae family, distributed across a range extending from Peninsular Thailand through Western and Central Malesia (3). Locally referred to as duku, langsat, longkong, or lanzones, the species is known to produce a diverse array of secondary metabolites, including limonoids, onoceranoid triterpenes, sesquiterpenoids, and phenolics (4,5). Between 2016 and 2026, the trajectory of research regarding this plant expanded from initial *in vivo* antiplasmodial assessments in mice to more specialized root-fraction assays, the isolation of specific limonoids, computational screenings, and various investigations into its activity within mammalian cell systems.

The interpretation of these developments is currently hindered by two interrelated methodological challenges. First, there is a frequent conflation of direct model-specific findings—such as whole-parasite inhibition or reduced parasitemia—with more limited propositions, including structural elucidation, cancer-cell cytotoxicity, or molecular docking. Second, the extreme heterogeneity of the test materials (determined by the plant part, cultivar, geography, solvent, and purity) results in *L. domesticum* preparations that are chemically non-equivalent. Conflating these distinct endpoints or materials creates an artificial sense of certainty, which in turn obscures the specific experimental data required to achieve clinical translation.

This systematic review evaluates 17 primary studies published between 2016 and 2026, classifying them *a priori* as either "direct" or "translational-enabling" evidence. By appraising methodological validity and following the PRISMA 2020 and SWiM reporting frameworks, this study characterizes how indirect evidence should inform the selection of drug candidates and defines a necessary stage-gated development pathway. The central argument of this review is that while the current body of literature provides strong support for lead discovery, it remains insufficient to validate therapeutic application.

2. Materials and methods

2.1. Review architecture and reporting standards

This systematic review utilized a dual-tier evidence framework to rigorously differentiate between direct antiplasmodial efficacy and broader translational-enabling data. The scope was delimited to species-specific primary studies published between January 1, 2016, and July 20, 2026. Following PRISMA 2020 and SWiM guidelines, studies were stratified into a "direct tier" (malaria-specific targets and models) and a "translational-enabling tier" (chemistry, safety, or mechanism). Narrative synthesis was employed as significant heterogeneity in materials and units precluded quantitative meta-analysis.

2.2. Eligibility and search strategy

Inclusion was restricted to primary data regarding attributable *L. domesticum* extracts or constituents. Reviews, non-species-specific reports, and studies outside the 10-year window were excluded. Computational docking was categorized as hypothesis-generating rather than definitive efficacy. An exhaustive search of global and Indonesian-language databases utilized taxonomic and malaria-specific strings through July 20, 2026, supplemented by backward and forward citation tracking.

2.3. Selection, extraction, and hierarchy

Following a multi-stage screening of 411 records, extraction captured critical variables: botanical authentication, cultivar, preparation method, parasite strain, and numerical variance. Studies were systematically classified based on their most malaria-proximal endpoint to establish an accurate evidence hierarchy.

2.4. Critical appraisal and synthesis conventions

Appraisal domains scrutinized botanical traceability, dose-response relationships, and bias control in animal models. Results were grouped into four layers: in vivo, in vitro, in silico, and enabling. To maintain data integrity, reported *IC50* and *LC50* units were retained exactly as published to identify discrepancies. Furthermore, selectivity indices were calculated strictly within individual studies to prevent misleading interpretations of parasite-host safety margins.

2.5. Methodological transparency and deviations

The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261458422) before completion of the review. Any deviations from the registered protocol, if applicable, are described in the manuscript.

3. Results and Discussion

3.1. Study selection and evidence architecture

The systematic search identified 17 primary studies published between 2016 and 2026 that met the eligibility criteria (Figure 1). The evidence architecture is stratified into four direct antiplasmodial studies—comprising one in vivo mouse model, two in vitro assays, and one in silico docking analysis—and 13 translational-enabling reports. The selection process followed a rigorous PRISMA-guided workflow, resulting in the inclusion of 17 eligible studies from an initial 411 records (Table 1).

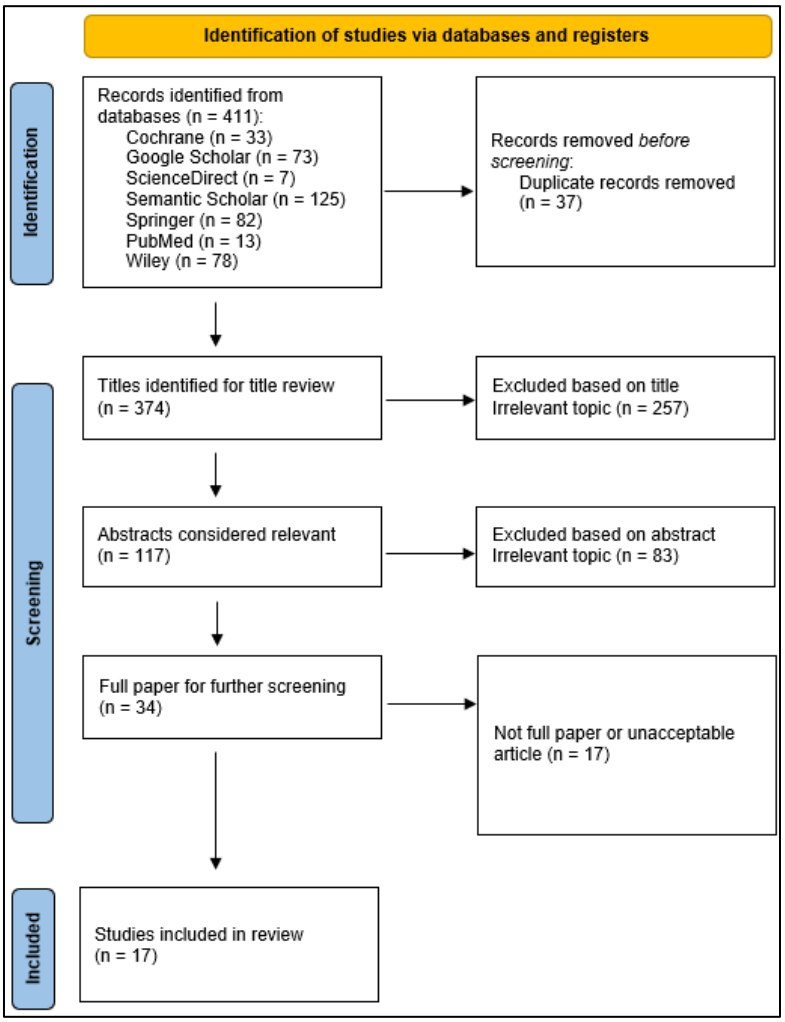

Figure 1 Study selection and evidence-tier classification

Table 1 Characteristics and direct findings of included *Plasmodium*-related studies

Study	Evidence tier; design and model	Material/intervention	Comparator and endpoint	Principal finding	Critical interpretation and efficacy status
Sudarjat, 2016 (8)	Direct; In vivo; *P. berghei*-infected Swiss mice; follow-up to day 13	Ethanolic stem-bark extract orally at 180, 360, or 720 mg/kg	3% powdered gum acacia; pyrimethamine–sulfadoxine; smear parasitaemia	Inhibition was 65.89%, 97.8%, and 88.5%, respectively; 360 mg/kg was reported as optimal.	Non-monotonic response, incomplete bias-control reporting, no exposure data, and no systematic organ-toxicity evaluation.
Khalili et al., 2017 (9)	Translational-enabling; in vitro mammalian-cell cytotoxicity	Duku fruit methanol, ethanol, and ethyl-acetate extracts; HT-29 cells	Solvent comparison; cytotoxic *IC50* and morphology across exposure times	Methanol extract *IC50* values of 6.79 and 50.0 µg/mL and ethyl-acetate values of 86 and 96 µg/mL were reported; ethanol did not reach *IC50*. Time-point mapping was not fully clear in the accessible abstract.	Host-cell liability signal only. No normal-cell, erythrocyte, or parasite assay; indirect and not antiplasmodial efficacy evidence.
Rudiyansyah et al., 2018 (10)	Translational-enabling; phytochemical isolation and structural elucidation	Seeds; seven tetranortriterpenoids	Spectroscopic structure elucidation; anti-TB, antibacterial, and cytotoxicity bioassays	Two new langsatides (A and B) plus five known dukunolides were structurally characterized.	Extends the seed-limonoid lead space related to the 2006 hit series and provides defined compounds for direct parasite retesting; indirect efficacy status.
Matsumoto et al., 2018 (11)	Translational-enabling; compound isolation with in vitro and in vivo antimutagenicity models	Leaf methanol extract; nine new lansium acids and nine known compounds	Ames antimutagenicity assay and oral in vivo micronucleus test	Several compounds were antimutagenic; oral lansionic acid was active in an in vivo micronucleus model.	Demonstrates structural breadth and oral biological exposure, but neither parasite killing nor an antimalarial mechanism; indirect efficacy status.
Yunus et al., 2018 (12)	Translational-enabling; organismal toxicity screen	Leaf ethanol extract; *Artemia salina* BSLT	Qualitative phytochemical screening and BSLT *LC50*	Phenolics, saponins, triterpenoids, and steroids were detected; *LC50* was 32.713 µg/mL.	Nonspecific toxicity flag supporting formal mammalian and erythrocyte testing; BSLT cannot define human safety or antiplasmodial efficacy.

Fadhilah et al., 2020 (13)	Translational-enabling; bioassay-guided cancer/normal-cell comparison	Fruit-peel extract, fractions, and lamesticumin A; T47D and Vero cells	Matched T47D and Vero *IC50* values; calculated within-study cell-selectivity ratios	*IC50* (T47D/Vero, µg/mL): extract A 29.41/66.10; fraction B 43.51/77.53; fraction C 25.56/81.12; lamesticumin A 15.68/47.46. Ratios were 2.25, 1.78, 3.17, and 3.03.	Rare within-study normal-cell comparison, but these are cancer selectivity ratios—not parasite selectivity indices—and do not establish antiplasmodial efficacy.
Sinaga et al., 2022 (5)	Translational-enabling; compound isolation and mammalian-cell cytotoxicity	Stem bark cv. Kokossan; three sesquiterpenoids; MCF-7 cells	Compound-level MCF-7 *IC50*	*IC50* values were 17.97, 121.65, and 201.57 µg/mL.	Introduces a non-limonoid chemotype and documents mammalian-cell activity; no normal-cell, erythrocyte, or parasite data.
Rudiyansyah et al., 2022 (7)	Direct; In vitro; *P. falciparum* 3D7; 48-h Giemsa microscopy	Root crude extract and n-hexane, chloroform, and methanol fractions	Growth inhibition; *IC50*	*IC50* (µg/mL): chloroform 1.4; methanol 3.6; crude 5.8; n-hexane 29.4.	Strong fraction-level signal; active molecules, independent replication, variance, and host-cell selectivity remain unresolved.
Lubis et al., 2022 (14)	Translational-enabling; extract cytotoxicity and cancer-pathway assays	Leaf ethanol, ethyl-acetate, and n-hexane extracts; HepG2 cells	*IC50*; cell-cycle, apoptosis, and PI3K/Akt expression assays	*IC50* values were 19.93 ± 0.93, 267.06 ± 3.24, and 216.47 ± 2.87 µg/mL; the ethanol extract was associated with S-phase arrest, apoptosis, and altered PI3K/Akt expression.	Shows mammalian-cell bioactivity, but cancer-pathway observations do not establish a parasite target and cannot be imported into an antimalarial mechanism.
Yansyah et al., 2023 (15)	Direct; In vitro; *P. falciparum* 3D7; Giemsa microscopy	Root limonoids dukunolide G and dukunolide C	Chloroquine reference; *IC50*	*IC50* values were reported as 0.48 and 2.74 mg/mL; chloroquine was 0.001 mg/mL.	Major unit concern: 0.48 mg/mL equals 480 µg/mL if literal. Raw calculations or author verification are required before potency ranking.
Alvarez et al., 2023 (16)	Translational-enabling; bioassay-guided mammalian-cell activity and proteomics	Leaf hexane fractions; A549, CCD19-Lu, and PNT2 cells; migration and proteomics	Cancer-versus-normal-cell comparison; A549 *IC50*; migration; network/proteomic analyses	Fractions LH6-6 and LH7-6 had A549 *IC50* values of 2.694 and 2.883 µg/mL; LH6-6 reduced migration and altered mitochondrial-process proteins.	Potency overlaps some parasite-assay ranges, making matched host-cell testing urgent; different material/model and absent parasite testing preclude

					causal cross-study comparison.
Sinaga et al., 2023 (17)	Translational-enabling; cultivar/solvent extract comparison and cytotoxicity	Stem bark cv. Kokosan; four solvent extracts; MCF-7 cells	MCF-7 *IC50* across solvent extracts; antimicrobial screening and terpenoid elucidation	*IC50* values (µg/mL): n-hexane 42.95; ethyl acetate 72.84; ethanol 74.50; n-butanol 12,088.33.	Demonstrates pronounced solvent dependence and the need for chemical fingerprinting rather than treating "bark extract" as one intervention; indirect efficacy status.
Mayanti et al., 2023 (18)	Translational-enabling; compound chemistry and cytotoxicity	Fruit peels and seeds cv. Kokossan; kokosanolides E, F, and G; MCF-7 cells	Compound-level MCF-7 *IC50*	*IC50* values were 45.90, 168.20, and 18.41 µg/mL.	Adds defined triterpenoids for future parasite testing while documenting mammalian-cell activity that requires matched selectivity assessment.
Mayanti et al., 2024 (19)	Translational-enabling; compound chemistry and cytotoxicity	Fruit-peel onoceranoids cv. Kokossan; MCF-7 cells	Compound-level MCF-7 *IC50*	*IC50* values were >150, 17.11, and 19.66 µg/mL.	Shows compound-level heterogeneity within one structural family; no inference about malaria is valid without parasite and host-cell assays.
Mayanti et al., 2025 (20)	Translational-enabling; compound chemistry and cytotoxicity	Fruit-peel lansioside E plus two known onoceranoids; MCF-7 cells	Compound-level MCF-7 *IC50*	*IC50* values were 39.83, 271.90, and 17.11 µg/mL.	Expands the glycosylated onoceranoid series and reinforces the distinction between structural novelty and antiplasmodial validation.
Hanum et al., 2025 (21)	Direct; In silico; PfLDH docking plus predicted physicochemical, ADME, and toxicity filters	Forty-seven reported metabolites; four candidates advanced	Oxamate and chloroquine comparators; docking score	Scores (kcal/mol): aromadendrene −7.2; isoledene −6.3; hexadecanoic acid −6.0; cis-3-hexen-1-ol −4.1.	Hypothesis-generating only: no PfLDH enzyme assay, whole-parasite confirmation, exposure measurement, or experimental safety evidence.

Septiyanti et al., 2026 (22)	Translational-enabling; matched cancer/normal-cell activity plus in silico mechanism	Stem bark cv. Piedjietan; methyl lansic; MCF-7 and CV-1 cells	MCF-7/CV-1 *IC50*; ERα docking, molecular dynamics, and predicted ADMET	*IC50* was 7.78 µg/mL in MCF-7 and 620.30 µg/mL in CV-1 (calculated ratio 79.73); ERα interaction was predicted.	Demonstrates compound- and context-specific cell selectivity, but neither the ratio nor ERα mechanism is transferable to malaria; indirect efficacy status.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; BSLT, brine shrimp lethality test; IC50, concentration producing 50% inhibition; PfLDH, Plasmodium falciparum lactate dehydrogenase. "Direct" denotes a measured Plasmodium-related endpoint. "Translational-enabling" denotes evidence relevant to identity, reproducibility, host-cell liability, or mechanism that does not demonstrate antiplasmodial efficacy.

Table 2 Critical appraisal of evidence validity and translational relevance across all included studies (n = 17)

Evidence class	Key strengths	Principal limitations	Safety/selectivity status	Concern
Direct in vivo (8)	Three doses, controls, serial parasitaemia.	Non-monotonic; route ambiguity; incomplete allocation/blinding, variance, chemistry, and exposure.	No organ toxicity, histopathology, PK, or therapeutic margin.	High
Direct in vitro (7,15)	Whole-parasite 3D7 data, fractionation, isolated limonoids, reference drug.	No independent replication; active fraction chemistry unresolved; mg/mL–µg/mL conflict.	No matched mammalian/erythrocyte testing or parasite SI.	High
Direct in silico (21)	Defined target, comparators, multi-step filtering.	No enzyme assay, human-LDH counterscreen, parasite confirmation, or target engagement.	Predicted ADME/toxicity only.	High
Enabling extracts/organismal (9,12,14,16,17)	Quantitative assays, solvent comparisons, selected normal-cell/mechanistic readouts.	Materials do not match parasite samples; multicomponent preparations; oncology mechanisms are not malaria mechanisms.	Liability signals only; no matched parasite–host/erythrocyte package.	High for malaria
Enabling compounds (10,11,13,18–20,22,23)	Modern structural characterization; compound-level assays; some normal-cell comparisons.	Mostly single cancer-cell models; no parasite confirmation; novelty/oncology selectivity not transferable.	No complete same-batch parasite SI or systemic exposure/safety data.	High for malaria

Concern reflects risk to antimalarial inference, not author integrity or journal quality.

Table 3 Proposed translational decision framework for *L. domesticum* antiplasmodial leads

Gate	Required evidence	Decision criterion	Current status	Priority action
1. Identity and reproducibility	Voucher, accepted taxonomy, cultivar/geography, extraction SOP, chromatographic fingerprint, marker quantification, batch limits.	Independent batches show comparable chemistry and parasite activity.	Not met.	Standardize one seed-limonoid series and one active root-fraction workflow.
2. Parasite confirmation	Full curves in sensitive and resistant *P. falciparum* strains; reference drugs; biological replicates; orthogonal readout.	Reproducible potency with assay-quality criteria and no optical/readout interference.	Partially met in single laboratories.	Independent replication of domesticulides and root fractions.
3. Selectivity and erythrocyte compatibility	Normal human cells, hepatocytes, uninfected erythrocytes/haemolysis, same-batch comparison.	Clear parasite-to-host window with prespecified advancement threshold.	Not met for leading antiplasmodial samples.	Run parasite and host panels in parallel; report complete curves.
4. Chemical attribution and mechanism	Bioassay-guided isolation, re-purification, mixture reconstruction, target assay, counterscreens, target engagement.	Activity follows a defined molecule or reproducible mixture and mechanism survives orthogonal testing.	Partially met for seed limonoids; target unvalidated.	Verify units; test PfLDH and alternative pathways experimentally.
5. Developability and exposure	Solubility, stability, permeability, protein binding, microsomal/hepatocyte stability, formulation, PK.	Free exposure reaches active concentrations for an adequate duration.	Not met.	Generate early ADME and oral PK before large efficacy studies.
6. Rigorous in vivo efficacy and safety	Randomized/blinded design, sample-size justification, oral dose-ranging, exposure-response, recrudescence, organ safety.	Reproducible parasite clearance with exposure-linked safety margin.	Preliminary signal only; high concern.	Repeat with standardized candidate and ARRIVE-compliant reporting.
7. Product and clinical readiness	Manufacturing controls, regulatory toxicology, interaction testing, phase-appropriate human studies.	Quality-controlled product with acceptable preclinical package and ethical clinical rationale.	No evidence.	Do not initiate clinical use of crude or unstandardized preparations.

3.2. Selectivity and material reproducibility

Selectivity remains the main limitation because parasite inhibition may result from parasite-specific activity, erythrocyte injury, cytotoxicity, redox effects, or assay interference. Therefore, candidates require matched evaluation of parasite activity, erythrocyte viability, human cell cytotoxicity, and hepatocyte liability, with time-kill and stage-specific assays where feasible. Overlapping concentrations across studies do not confirm nonspecific toxicity but warrant standardized selectivity testing.

Material heterogeneity also limits reproducibility. Variations in *Lansium domesticum* varieties, plant parts, and extraction methods require authenticated vouchers, standardized taxonomy and extraction protocols, chromatographic fingerprinting, and defined quality-control criteria to ensure reproducible biological effects (6).

3.3. In vitro evidence

The earliest eligible study demonstrated that fruit-skin and aqueous leaf extracts inhibited both drug-sensitive (3D7) and chloroquine-resistant (T9) *P. falciparum*, with fruit-skin extracts also disrupting intraerythrocytic development. Activity against the resistant T9 strain suggests that the antiplasmodial effect is not limited to chloroquine-sensitive parasites (4). However, the absence of complete concentration–response data, extract standardization, and selectivity assessment precludes reliable comparison of potency.

The strongest in vitro evidence was reported in a 2022 root study, where chloroform and methanol fractions showed greater potency against 3D7 (IC_{50} = 1.4 and 3.6 µg/mL, respectively) than the crude extract (5.8 µg/mL) and the *n*-hexane fraction (29.4 µg/mL), indicating enrichment of active constituents through fractionation (7). Nevertheless, incomplete chemical characterization and the lack of matched host-cell toxicity data prevent confirmation of a favorable therapeutic window. Consequently, these findings support the fractions as promising screening hits rather than validated lead candidates.

3.4. In vivo evidence

An in vivo study by Sudarjat demonstrated that oral administration of ethanolic stem-bark extract at doses of 180, 360, and 720 mg/kg reduced parasitaemia by 65.89%, 97.8%, and 88.5%, respectively, through day 13, with the 360 mg/kg dose producing an effect comparable to the positive control (8). However, the lower inhibition observed at 720 mg/kg suggests a non-monotonic dose–response relationship, which weakens confidence in dose-dependent efficacy. This pattern may reflect pharmacokinetic limitations, antagonistic constituents within the extract, toxicity-related host responses, or experimental variability. Because the study did not include exposure measurements, detailed toxicity evaluation, or comprehensive methodological controls, the biological basis of this response remains uncertain and warrants further investigation.

3.5. In silico evidence

A 2025 computational study evaluated 47 reported *L. domesticum* metabolites against *Plasmodium falciparum* lactate dehydrogenase (PfLDH) and prioritized four compounds based on predicted physicochemical, pharmacokinetic, and toxicity properties (21). Among these, aromadendrene exhibited the most favorable docking score (−7.2 kcal/mol), whereas hexadecanoic acid was predicted to form interactions near the enzyme's active site. These findings support the use of molecular docking as an effective hypothesis-generating tool for identifying potential antimalarial candidates. However, docking predictions alone cannot establish target engagement, enzyme inhibition, antiplasmodial efficacy, or safety. Therefore, these computational hits should be regarded as preliminary candidates that require validation through recombinant PfLDH inhibition assays, selectivity testing against human LDH isoforms, and whole-parasite experiments before they can be considered promising antimalarial leads.

3.6. Cross-layer synthesis: selectivity as the key translational gap

Integrating the available in vitro, in vivo, and in silico evidence reveals that the principal barrier to translation is the absence of robust selectivity data. Although several *L. domesticum* preparations demonstrated antiplasmodial activity, no study has simultaneously established botanical authentication, chemical standardization, reproducible efficacy against both drug-sensitive and drug-resistant *P. falciparum* strains, complete concentration–response relationships, mammalian-cell cytotoxicity, erythrocyte safety, and a quantified parasite selectivity index. Consequently, the current evidence cannot determine whether the observed parasite inhibition reflects genuine parasite-selective activity or nonspecific host toxicity. Notably, root fractions exhibited the lowest reported IC_{50} values, yet their active constituents and therapeutic window remain undefined, while available cytotoxicity studies evaluated different plant materials and therefore cannot be directly integrated with the antiplasmodial findings (7).

Accordingly, neither selective safety nor nonspecific toxicity can be concluded from the existing evidence. The most defensible interpretation is that standardized validation is required, using chemically characterized materials tested in parallel for antiplasmodial activity, mammalian-cell cytotoxicity, erythrocyte viability, and selectivity under identical experimental conditions.

3.7. Critical appraisal across evidence layers

Quality appraisal further explains the limited certainty of the available evidence. Although the included studies collectively suggest biological potential, methodological heterogeneity substantially weakens comparability and reproducibility. None of the four direct antimalarial studies fulfilled all predefined low-risk quality criteria, whereas the 13 translational-enabling studies mainly contributed supportive mechanistic or chemical evidence rather than direct efficacy. Common strengths included compound characterization, quantitative concentration–response analysis, and the use of normal-cell comparators. However, these were offset by recurrent limitations, including the absence of parasite assays, use of unmatched plant materials, reliance on single-cell-line toxicity models, incomplete extract standardization, and extrapolation of anticancer or molecular docking findings to antimalarial activity. Therefore, the overall evidence remains exploratory rather than confirmatory despite the consistency of several promising observations.

3.8. Implications for translational development

Given these limitations, further development should follow a stepwise translational framework rather than relying solely on reported biological activity. Botanical authentication and chemical standardization should precede comparative pharmacological studies to ensure reproducibility. Subsequent investigations should independently confirm antiplasmodial efficacy while simultaneously establishing host-cell selectivity before progressing to animal studies. Only after demonstrating a reproducible mechanism of action, adequate pharmacokinetic exposure, and an acceptable safety profile should dose optimization and clinical translation be considered (Table 3). Such a staged approach minimizes the risk of advancing candidates whose apparent activity is attributable to experimental variability or inadequate selectivity.

3.9. Strengths, limitations, and clinical boundary

This review provides a comprehensive synthesis of all 17 eligible studies by distinguishing direct antimalarial evidence from translational-enabling studies, preserving original quantitative outcomes, identifying substantial discrepancies in reported potency, and integrating phytochemical and toxicity evidence without overstating efficacy. Nevertheless, several limitations reduce confidence in the overall conclusions, including the incomplete availability of original screening records, unverified duplicate study selection and data extraction, the small and heterogeneous evidence base, inconsistent reporting quality, reliance on a tailored appraisal framework, and potential publication or outcome-reporting bias. These limitations primarily affect the certainty of the evidence rather than its overall direction.

From a clinical perspective, no *L. domesticum* preparation has yet demonstrated the manufacturing quality, pharmacokinetic profile, safety, dosage, or therapeutic efficacy required for clinical use. Therefore, the available evidence supports *L. domesticum* only as a promising source of antimalarial candidates for further investigation and does not justify the use of crude or insufficiently standardized preparations as substitutes for evidence-based malaria diagnosis and treatment.

4. Conclusion

The synthesized evidence from the 2016–2026 period establishes that *Lansium domesticum* Corrêa functions as a promising source of preclinical antiplasmodial leads rather than a validated antimalarial medicine. The most persuasive direct findings are the quantitative inhibition demonstrated by seed-derived limonoids against multidrug-resistant *P. falciparum* K1 and the activity of root chloroform and methanol fractions against the 3D7 strain. While *in vivo* mouse studies provide some biological support, the certainty of these results is undermined by a high risk of bias, a lack of comprehensive safety data, and observed non-monotonic dose-responses. Furthermore, computational docking results for PfLDH are strictly hypothesis-generating and require experimental confirmation. Although 13 recently identified enabling studies have expanded the chemical series and illustrated that mammalian-cell activity is highly dependent on the specific compound, cultivar, and solvent system, they have not provided evidence of additional antiplasmodial efficacy.

To advance this research toward clinical relevance, priority must be given to unit verification, same-batch parasite and host selectivity testing, and uninfected-erythrocyte compatibility assessments. Future investigations also require strict

botanical and chemical standardization, independent replication, mechanism validation, and detailed pharmacokinetic profiling alongside rigorously randomized and blinded animal studies. Given these current evidence constraints, crude or unstandardized preparations of *L. domesticum* must not be recommended as a substitute for established, guideline-based malaria diagnosis and treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no competing interests.

Statement of ethical approval

This review was based exclusively on published literature and involved no new human or animal research. Accordingly, ethical approval and informed consent were not required.

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Author contributions

Fanny—conceptualization, methodology, investigation, data curation, and writing–original draft; Salwa Adilah Ningtiyas—supervision, validation, and writing–review and editing; Sadakata Sinulingga—investigation, data curation, and writing–review and editing. All authors should confirm that the final contribution statement complies with the CRediT taxonomy and approve the submitted manuscript.

Data availability

All data included in this review are available in the cited publications and summarized in the manuscript tables. The final screening and data extraction file should be deposited in an open repository before or upon submission, subject to the target journal's policy.

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