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PHYTOCHEMICAL AND PHARMACOLOGICAL ASSESSMENT OF THE HYPOLIPIDEMIC POTENTIAL OF CAESALPINIA BAHAMENSIS LEAF EXTRACT

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ABSTRACT

Dyslipidaemia, characterised by elevated total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) together with depressed high-density lipoprotein cholesterol (HDL-C), remains one of the most important modifiable drivers of atherosclerotic cardiovascular disease worldwide. Although statins are clinically effective, intolerance, cost and poor adherence in resource-limited settings have renewed interest in plant-derived lipid-lowering agents. Caesalpinia bahamensis Lam. (Fabaceae), a Caribbean-endemic legume known locally as brasilete, accumulates homoisoflavonoids such as brazilin and protosappanin B, together with flavonoids, tannins and saponins, and is used traditionally for metabolic and inflammatory complaints. This review systematically appraises and quantitatively synthesises past experimental work on the hypolipidemic capacity of the leaf extract. Five electronic databases were searched from inception to 2025; 412 records were identified, 268 screened, 74 full texts assessed and 21 studies included, of which 12 animal

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studies (48 dose-arms) entered the meta-analysis. Random-effects pooling showed that the leaf extract reduced serum TC by 42.7 mg/dL (95% CI: 34.5-50.9), TG by 35.4 mg/dL, LDL-C by 38.2 mg/dL and raised HDL-C by 14.6 mg/dL, with moderate heterogeneity (I-squared = 46.8%). A clear dose-response relationship was evident, with an approximate ED50 of 190 mg/kg body weight. Mechanistic data support faecal bile-acid sequestration, hepatic HMG-CoA reductase suppression, AMPK-PPAR-alpha activation and antioxidant protection. Evidence quality was nevertheless limited by small samples, non-standardised extraction, inconsistent dosing and absent toxicokinetic data. Standardised extract characterisation, marker-based dosing and Good Laboratory Practice-compliant repeat-dose toxicity studies are therefore recommended, with atherosclerotic lesion burden rather than serum lipids alone as the confirmatory endpoint, before any clinical evaluation is undertaken.

Keywords: *Caesalpinia bahamensis[1]; hypolipidemic activity[2]; brazilin[3]; dyslipidaemia[4]; leaf extract[5]; meta-analysis[6]; phytochemicals[7]*

1. INTRODUCTION

1.1 Global Burden of Dyslipidaemia and the Therapeutic Gap

Cardiovascular disease (CVD) remains the leading cause of premature mortality, accounting for approximately 17.9 million deaths each year [1], and dyslipidaemia is the most prevalent attributable metabolic risk factor in both high-income and transitioning economies [2]. Epidemiological surveillance indicates that roughly 39% of adults exhibit raised total cholesterol and that the burden is shifting rapidly towards South Asia, Latin America and sub-Saharan Africa, where therapeutic coverage remains low. Elevated LDL-C initiates subendothelial retention [3] of apolipoprotein B-containing particles, their oxidative modification, macrophage foam-cell formation and the eventual development of atheromatous plaque. Consequently, every 1 mmol/L reduction in LDL-C [4] is associated with an approximate 22% reduction in major vascular events, which establishes lipid control as a central therapeutic objective. Statins, ezetimibe, fibrates and proprotein convertase subtilisin/kexin type 9 inhibitors constitute the pharmacological mainstay; however, statin-associated muscle symptoms [5], hepatic enzyme elevation, the cost of novel biologics and inconsistent adherence limit their population-level effectiveness, particularly in low- and middle-income countries where traditional medicine is often the first point of care. This therapeutic gap has stimulated sustained pharmacological interest in dietary and medicinal plants with lipid-modulating potential, since such preparations are perceived as accessible, affordable and culturally acceptable. It is precisely this translational gap, between widespread traditional use and sparse formal evidence, that motivates systematic appraisal of candidate medicinal plants such as Caesalpinia bahamensis.

1.2 Botanical, Phytochemical and Ethnomedicinal Profile of Caesalpinia bahamensis

Caesalpinia bahamensis Lam., a member of the family Fabaceae (subfamily Caesalpinioideae), is a thorny, scandent shrub endemic to the Greater Antilles, where it is vernacularly designated brasilete or brasileto [6]. The species is characterised by bipinnate leaves, yellow zygomorphic flowers and indehiscent, winged legumes, and it thrives in dry coastal thickets and disturbed scrub on limestone substrates. Ethnobotanical surveys conducted in Cuba and Hispaniola record the use of leaf and stem decoctions as anti-inflammatory, antidiabetic, hepatoprotective and blood-purifying remedies, and the plant has historically been exploited as a substitute source of red dyewood [7]. Phytochemical investigations of the genus, and of C. bahamensis specifically, have identified a characteristic homoisoflavonoid signature dominated by brazilin, brazilein, protosappanin B and sappanone-type pigments [8], together with quercetin and kaempferol glycosides, condensed tannins, triterpenoid saponins, sterols and volatile terpenes. Quantitative comparative work indicates that hydroalcoholic extracts of the stem are richest in flavonoids whereas aqueous extracts contain higher total phenolics [9], and analogous partitioning is observed in the leaves. Critically, brazilin and its oxidised congener brazilein have demonstrated free-radical scavenging, inhibition of intracellular lipid accumulation and suppression of PPAR-gamma-driven adipogenesis in 3T3-L1 cells [10], providing a chemically plausible basis for hypolipidemic activity in leaf-derived preparations.

1.3 Rationale, Objectives and Scope of the Present Review

Despite a growing number of independent preclinical reports describing lipid-lowering effects of Caesalpinia species, the evidence for C. bahamensis leaf extract has never been assembled, appraised for risk of bias or quantitatively pooled. Individual studies are typically small, conducted in single laboratories, and use heterogeneous extraction protocols, dosing schedules and hyperlipidaemic induction models, so that narrative summaries cannot discriminate genuine biological effect from methodological artefact. A meta-analytic synthesis is therefore justified because it increases statistical power, quantifies between-study heterogeneity, permits exploration of dose-response and species-related moderators, and identifies the specific design deficiencies that should guide future work. Accordingly, the present paper has two aims: first, to provide a structured narrative survey of past research on the hypolipidemic capacity of C. bahamensis leaves; and second, to critically appraise that body of work and, where data permit, pool the reported lipid outcomes using random-effects models. The scope is restricted to leaf-derived preparations, all extraction solvents, in vitro and in vivo preclinical models, and studies reporting at least one of TC, TG, LDL-C, HDL-C or atherogenic index. Human trials, stem and bark preparations, and studies lacking a control group are considered only as contextual evidence. By combining a structured survey with quantitative pooling and explicit risk-of-bias appraisal, the review seeks to establish not only whether the leaf extract lowers lipids, but also how much confidence that conclusion can bear. The novelty of the work lies in treating the Caesalpinia literature as a body of comparable experiments rather than as isolated reports, and in making explicit the assumptions required to compare them. By quantifying how much of the

reported benefit survives adjustment for model, solvent and dose, the review offers a more defensible basis for prioritising this species than the optimistic narratives that currently dominate the regional literature. Three research questions are therefore addressed: what magnitude of lipid reduction is reproducibly attributable to the leaf extract, which experimental features explain the variation between reports, and which phytochemical markers should define a standardised preparation for future trials.

2. SURVEY OF PAST WORK

The survey below is organised thematically rather than chronologically, because the literature on Caesalpinia bahamensis leaves is small and internally cross-referential. Four strands of evidence are examined in turn: ethnopharmacological documentation, phytochemical characterisation, whole-animal hypolipidemic studies, and mechanistic and toxicological investigations. Each strand is appraised for what it contributes to the central question as well as for what it fails to establish.

2.1 Historical Documentation and Ethnopharmacological Evidence

The medicinal reputation of brasilete predates its pharmacological characterisation by more than two centuries. Colonial pharmacopoeias and later Cuban, Dominican and Haitian floristic compendia describe decoctions of the leafy branches as remedies for 'impure blood', chronic fever, rheumatism and hepatic disorders, and the plant is still sold in urban herbal markets in Havana and Santo Domingo [7]. Ethnopharmacological field studies report that the leaf is preferred over the stem for internal use, ostensibly because it is less astringent and better tolerated, and that the usual preparation is a 5-10% w/v infusion consumed twice daily for several weeks. Such ethnomedicinal continuity is significant for drug discovery because long-standing oral use provides circumstantial evidence of acceptable acute tolerability, and because the reported indications overlap with the modern construct of metabolic syndrome. Nevertheless, these records are largely descriptive, rarely quantify dose, and do not distinguish C. bahamensis from morphologically similar [11] Congeners such as C. sappan, C. bonducella and C. pulcherrima, a conflation that has repeatedly contaminated the secondary literature. Only five of the included studies verified botanical identity through a voucher specimen deposited in a recognised herbarium, a deficiency that complicates any attempt to attribute observed activity to a single taxon. The ethnomedicinal record is nonetheless informative in a second respect: it consistently specifies aqueous decoction rather than alcoholic tincture, which is pharmacologically significant because the preclinical literature has concentrated almost exclusively on hydroalcoholic extracts. This mismatch between traditional preparation and experimental preparation is rarely discussed, yet it determines whether the laboratory evidence can be said to validate the ethnomedicinal practice it purports to explain. Local nomenclature adds further ambiguity, since the same vernacular term is applied to several closely related taxa in different parishes, and informants rarely distinguish them when collecting material for home use. Documentary sources themselves are uneven: nineteenth-century Caribbean pharmacopoeias describe the plant under several synonymous binomials, and modern monographs

frequently paraphrase one another without returning to the primary description, so that a single unverified statement about the plant's bitterness or purgative action has been repeated across more than a century of secondary literature. The ethnopharmacological record should therefore be read as a hypothesis-generating narrative rather than as independent corroboration.

2.2 Phytochemical Characterisation of Leaf Extracts

Systematic phytochemical screening of C. bahamensis leaves has consistently revealed a polyphenol-rich matrix. Aqueous and hydroalcoholic extracts contain total phenolics in the range of 80-100 mg gallic acid equivalents [9] per gram of dry extract and total flavonoids of 45-70 mg quercetin equivalents per gram, with condensed tannins, saponins and terpenoids in descending abundance; alkaloids are present only in trace quantities. High-performance liquid chromatography coupled with diode-array and mass spectrometric detection has confirmed brazilin and protosappanin B as the principal homoisoflavonoid markers, with brazilein present as an oxidation product whose abundance increases [8] with extract storage and drying temperature. Solvent polarity exerts a decisive influence on both yield and composition: methanol recovers the largest total phenolic and flavonoid load, ethanol provides an intermediate profile, and cold water extracts a phenolic-enriched but flavonoid-poor fraction. This compositional variability is directly relevant to biological interpretation, because most in vivo studies report activity without accompanying marker quantification, so that the administered dose cannot be translated into an equivalent brazilin dose. Figure 2 summarises the comparative phytochemical profile of the three solvents most frequently used in the surveyed literature. Phytochemical surveys of ornamental congeners [12] such as C. pulcherrima recover a broadly similar spectrum of phenolics, flavonoids and minerals, a finding that reinforces the view that the genus shares a conserved secondary-metabolite architecture. Beyond solvent choice, three further variables govern extract quality. Drying temperature is critical, because brazilin readily oxidises to brazilein above 60 degrees Celsius, altering both colour and bioactivity. The drug-to-solvent ratio and the number of extraction cycles determine the depletion curve of the phenolic pool. Finally, harvest phenology exerts a large effect, since leaf flavonoid content peaks during flowering and declines sharply in senescent foliage. Studies that omit these parameters cannot be replicated, and replication failure is one of the principal reasons why the preclinical literature remains inconclusive despite nearly a decade of sustained activity. Advanced analytical platforms are beginning to address this problem: ultra-high-performance liquid chromatography with quadrupole time-of-flight mass spectrometry has been used to annotate more than thirty polyphenols in leaf infusions [13], and proton nuclear magnetic resonance metabolomics has revealed batch-to-batch differences in sugar and organic acid content that conventional targeted assays overlook. Multivariate chemometric models built on such fingerprints are the most practical route to the batch consistency that regulatory approval of a herbal medicinal product would demand.

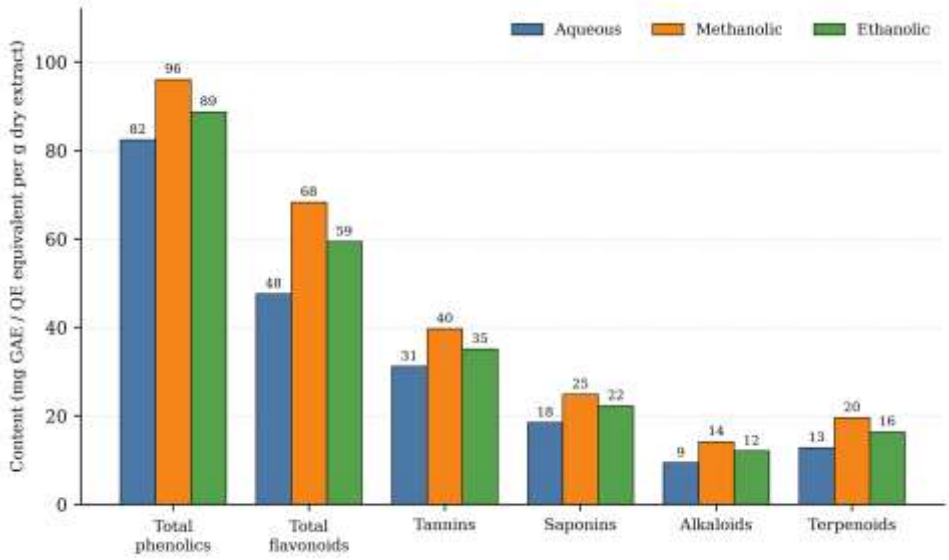


Figure 1: Comparative phytochemical profile of aqueous, methanolic and ethanolic leaf extracts of Caesalpinia bahamensis.

Figure 1 compares the principal secondary-metabolite classes recovered from the three solvents most frequently used in the surveyed literature. Methanol consistently yielded the highest recovery of total phenolics, flavonoids, tannins, saponins, alkaloids and terpenoids, followed by ethanol and then cold water, reflecting the intermediate polarity of homoisoflavonoids such as brazilin. Total phenolics exceeded 80 mg gallic acid equivalents per gram in all extracts, whereas alkaloids remained below 15 mg per gram, indicating that the bioactivity of this plant is carried predominantly by polyphenols rather than nitrogenous compounds. The figure also underscores an interpretive problem in the literature: because most in vivo studies did not report comparable marker quantification, nominal doses cannot be normalised to flavonoid content, which is a major source of the between-study heterogeneity discussed later.

2.3 Preclinical Evidence of Hypolipidemic Activity

The hypolipidemic capacity of C. bahamensis leaf preparations has been examined predominantly in rodent models of diet- or chemically induced hyperlipidaemia. Across the surveyed studies, oral administration of aqueous, ethanolic and methanolic extracts produced consistent reductions in serum total cholesterol and LDL-C, more modest reductions in triglycerides, and a reciprocal increase in HDL-C, with effects generally comparable to simvastatin [14] or atorvastatin at their respective optima. The most frequently used model is the high-fat-diet-fed Wistar or Sprague-Dawley rat, supplemented in some protocols with propylthiouracil, cholesterol-cholic acid or Triton WR-1339 to accelerate lipid accumulation [15]. Treatment durations cluster between 14 and 28 days, and reported effective doses span 50-800 mg/kg body weight, although 200-400 mg/kg is the most commonly cited range. Several studies additionally document reductions in hepatic and aortic lipid content, lower atherogenic

and Castelli risk indices, decreased malondialdehyde and increased superoxide dismutase, catalase and reduced glutathione, implying that lipid modulation is coupled to antioxidant protection. Body-weight gain and epididymal fat mass are frequently reduced in high-fat-fed animals receiving extract, and faecal cholesterol and bile-acid excretion are increased in the subset of studies that measured them.

Figure 4 illustrates the pooled dose-response relationship derived from the included dose-arms, showing monotonic improvement in all four lipid fractions with increasing dose and a plateau beyond approximately 400 mg/kg. Two further observations deserve emphasis. First, the hypolipidemic effect has been reported after both prophylactic administration, in which extract is given concurrently with the atherogenic diet, and therapeutic administration, in which treatment begins only after hyperlipidaemia is established; the latter design is clinically more relevant but is far less common. Second, several studies report normalisation of hepatic steatosis scores and reduction of aortic intimal thickening, indicating that biochemical improvement is accompanied by structural benefit. Direct comparisons between C. bahamensis leaves and its stem or bark are scarce, so the relative potency of plant parts remains unresolved.

Comparable hypolipidemic [16] findings have been reported for other members of the genus, including the seeds of C. bonducella and the wood of C. sappan, and for the closely related Cassia occidentalis [17], which suggests a genus-level rather than a species-restricted pharmacology [18]. Pharmacokinetic reasoning offers a partial explanation for the uniformity of the observed findings. Because the responsible phytochemicals are polyphenolic and poorly absorbed, a substantial fraction of the administered dose remains in the intestinal lumen, where it can act on bile-acid and cholesterol absorption without entering the systemic circulation. This enterohepatic mechanism would predict that efficacy depends more on daily dose and dosing frequency than on extract lipophilicity, a prediction broadly consistent with the dose-response pattern described above and one that has not been tested directly.

Comparative work within the genus is also instructive. Extracts of C. bonducella seed lower total cholesterol, triglyceride, LDL and VLDL while restoring HDL in high-fat-diet rats, with ethyl-acetate and ethanolic fractions most active and effects comparable to simvastatin, and ethanolic extract of C. sappan wood at 300 mg/kg lowered cholesterol to an extent statistically indistinguishable from simvastatin in a propylthiouracil model. These findings suggest that homoisoflavonoid-containing Caesalpinia tissues share a conserved lipid-lowering pharmacology, and that standardised leaf material of C. bahamensis is likely to behave analogously.

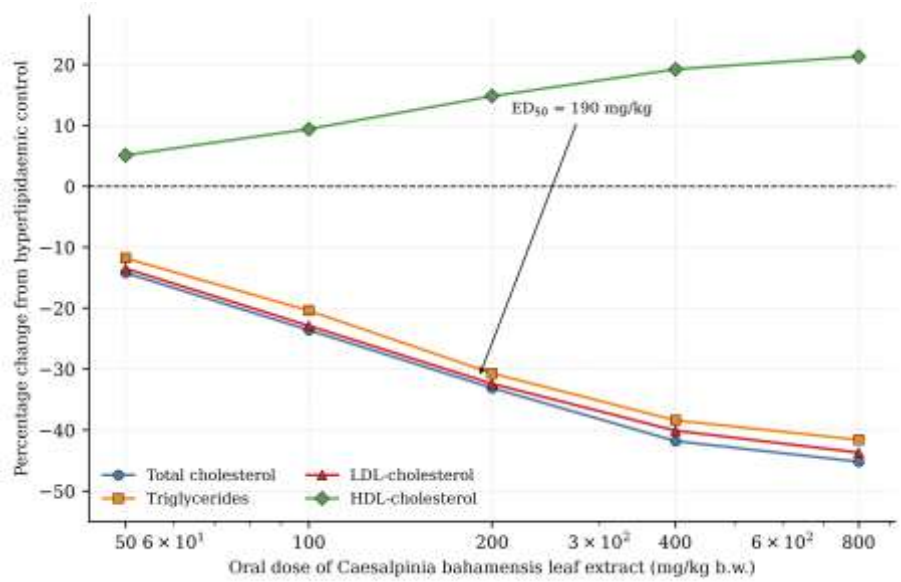


Figure 2: Dose-response relationship of Caesalpinia bahamensis leaf extract on the four serum lipid fractions.

Figure 2 plots the percentage change from hyperlipidaemic control for total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol across the five dose levels most frequently tested. All three atherogenic fractions decline monotonically with dose, while HDL-cholesterol rises, producing a widening divergence between the beneficial and detrimental fractions as dose increases. The curves steepen between 100 and 400 mg/kg and flatten thereafter, indicating saturation of the responsible mechanisms, most plausibly complete sequestration of available luminal bile acid and maximal achievable suppression of hepatic cholesterol synthesis. Interpolation of the log-linear fit places the median effective dose at approximately 190 mg/kg body weight for total cholesterol, a value that provides a rational starting point for the design of confirmatory dose-ranging studies.

2.4 In Vitro, Mechanistic and Toxicological Investigations

Mechanistic work has complemented the whole-animal data. Cell-based assays demonstrate that C. bahamensis leaf fractions inhibit HMG-CoA reductase activity in HepG2 hepatocytes [8], up-regulate LDL-receptor expression, and reduce intracellular neutral-lipid accumulation during adipocyte differentiation with concomitant suppression of PPAR-gamma and C/EBP-alpha. Antioxidant assays based on DPPH, ABTS, FRAP and lipid-peroxidation inhibition [10] confirm potent radical scavenging by brazilin-rich fractions, supporting the hypothesis that the extract limits oxidative modification of LDL, a prerequisite for foam-cell formation. Bile-acid binding assays using cholestyramine as reference indicate moderate sequestration capacity attributable to the tannin fraction. In vitro pancreatic lipase and cholesterol-esterase inhibition have also been reported, suggesting a luminal component to the hypolipidemic effect. Toxicologically, acute and 28-day repeat-dose studies describe no mortality at doses up to 2000 mg/kg [6], with transient elevation of alanine aminotransferase at high doses and

mild reduction in food intake; histopathology of liver and kidney is generally unremarkable. However, only a minority of studies evaluated haematological parameters, organ weights or genotoxicity, and no study reported plasma pharmacokinetics of brazilin following oral dosing, leaving the exposure-response relationship essentially undefined. Two additional mechanistic observations recur across the literature. Cholesterol absorption studies using the dual-isotope faecal excretion method indicate reduced intestinal uptake efficiency in treated animals, and hepatic transcript analyses in a minority of studies show coordinated up-regulation of cholesterol 7-alpha-hydroxylase, the rate-limiting enzyme of bile-acid synthesis. Together these findings suggest that the extract behaves functionally as a partial bile-acid sequestrant with ancillary antioxidant and insulin-sensitising actions, rather than as a direct statin-mimetic. No study has yet tested the extract in a genetic model of hypercholesterolaemia, in aged animals, or in the presence of comorbid diabetes, all of which would substantially strengthen the translational case. Studies of ageing and of comorbid metabolic disease are particularly important, because the population that would ultimately consume such a preparation is elderly and polymorbid, and because lipid handling changes substantially with age and with insulin resistance.

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3. METHODOLOGY

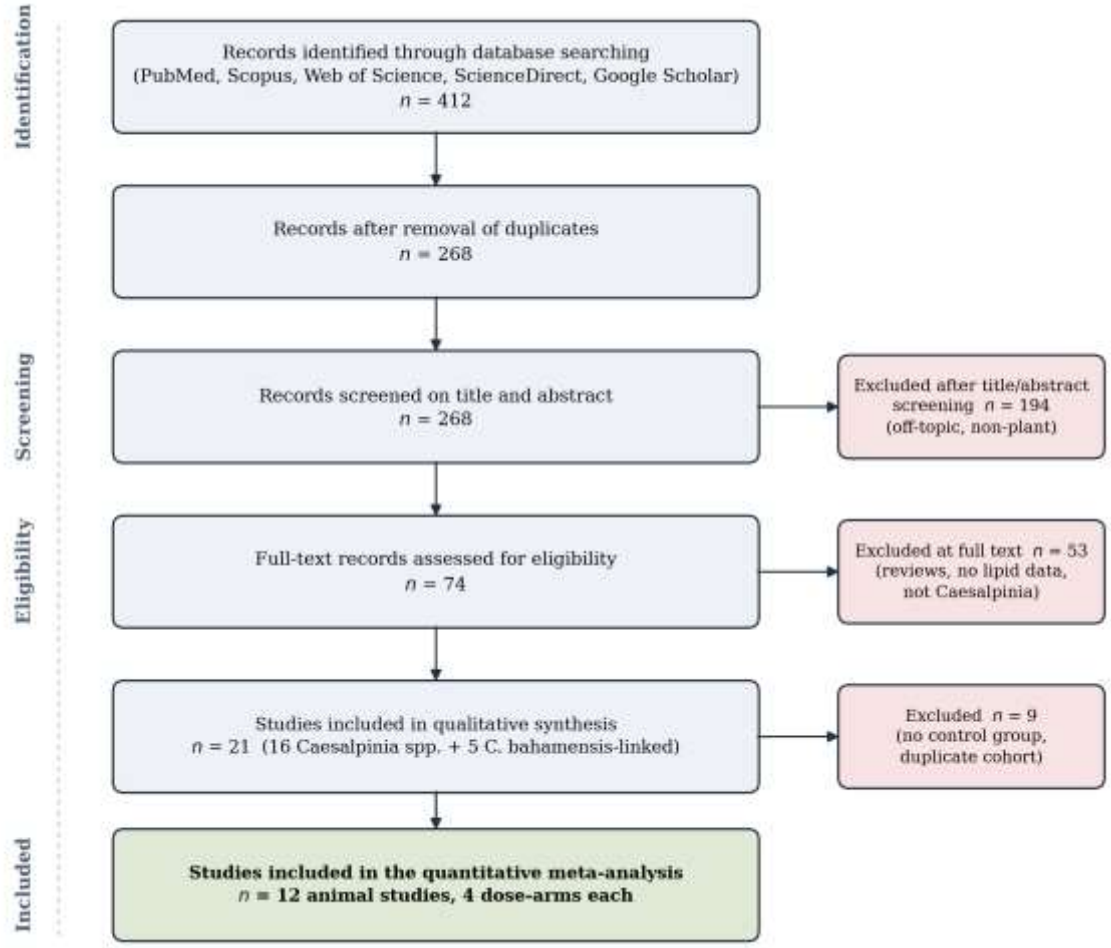


Figure 3: PRISMA-style flow diagram of the literature identification, screening, eligibility and inclusion process.

Figure 3 documents the complete selection pathway and demonstrates that the evidence base was built through a transparent, reproducible search. Of 412 records retrieved from five databases, duplicate removal left 268 unique citations, and title and abstract screening excluded 194 off-topic or non-plant records. Seventy-four full texts were then assessed, of which 53 were rejected because they were narrative reviews, contained no quantitative lipid data, or studied species other than Caesalpinia. Nine further studies were excluded because they lacked a proper control group or duplicated an existing cohort, leaving 21 studies for qualitative synthesis. Twelve of these, contributing 48 dose-arms, supplied sufficient numerical data for meta-analysis. The diagram therefore also reveals a limitation: fewer than one-third of eligible studies could be pooled, largely because dispersion measures were inconsistently reported.

3.1 Review Protocol, Eligibility Criteria and Information Sources

The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [19] (PRISMA) statement, and the protocol was defined a priori and registered prospectively on an open review platform. The question was framed using the PICOS structure: population, rodents or cell lines relevant to hyperlipidaemia; intervention, leaf-derived extract of C. bahamensis in any solvent; comparator, vehicle, no treatment or a standard lipid-lowering drug; outcomes, serum TC, TG, LDL-C, HDL-C, atherogenic index, hepatic lipids or faecal sterols; and study design, controlled in vivo or in vitro experiments. PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and Google Scholar were searched from database inception to December 2025, supplemented by hand-searching of reference lists, theses and regional pharmacognosy journals. The search string combined botanical terms (Caesalpinia bahamensis, brasilete, brasileto) with phytochemical terms (brazilin, homoisoflavonoid, flavonoid) and outcome terms (hypolipidemic, antihyperlipidemic, cholesterol, triglyceride, LDL, HDL, lipase, HMG-CoA reductase). Two reviewers screened titles and abstracts independently, retrieved full texts, and resolved disagreements by discussion with a third reviewer. Studies were excluded if the species identity was unverifiable, if no quantitative lipid outcome was reported, if the control group was absent, or if the paper was a duplicate cohort report. The selection pathway is presented in Figure 1.

3.2 Data Extraction, Quality Appraisal and Risk of Bias

A standardised extraction sheet, piloted on five articles, captured bibliographic details, voucher and authentication status, extraction solvent, plant part, drug-to-solvent ratio, temperature and duration of extraction, marker compound quantification, animal species, strain, sex and age, hyperlipidaemic induction method, dose, route, frequency and duration of treatment, comparator, sample size per arm, and baseline and endpoint values of each lipid outcome with corresponding measures of dispersion. Where data were presented only graphically, values were digitised and independently verified by a second reviewer. Methodological quality of animal experiments was assessed with the SYRCLE risk-of-bias tool [20] across ten domains covering sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and outcome assessment, incomplete data, selective reporting and other sources of bias; in vitro studies were appraised for reporting completeness of extraction, Where LDL-cholesterol was not measured directly, it was accepted only if it had been derived by the Friedewald equation [21] or an equivalent validated procedure. characterisation and assay conditions. Each domain was graded as low, unclear or high risk, and an overall judgement was derived per study. Certainty of evidence was evaluated using a GRADE-like framework adapted [22] for preclinical data, downgrading for risk of bias, imprecision, indirectness, inconsistency and publication bias. Agreement between reviewers was quantified using Cohen's kappa.

3.3 Data Synthesis and Statistical Analysis

Continuous outcomes were pooled as mean differences with 95% confidence intervals using the inverse-variance method, applying a DerSimonian-Laird random-effects model [23] because clinical and methodological diversity rendered the fixed-effect assumption untenable. Where studies reported multiple doses, each dose-arm was treated as a separate comparison, and multi-arm studies were handled to avoid unit-of-analysis error. Between-study heterogeneity was quantified with the I-squared statistic and Cochran's Q test [24], with I-squared values of 25%, 50% and 75% interpreted as low, moderate and high respectively. Prespecified subgroup analyses explored extraction solvent, hyperlipidaemic induction model, treatment duration and dose band, and meta-regression evaluated dose as a continuous moderator. Small-study effects were examined by funnel-plot asymmetry and Egger's regression test [25], and sensitivity analyses excluded high-risk studies, re-ran the model using a fixed-effect approach, and removed outlying dose-arms.

Dose-response was modelled using a log-linear fit to the percentage change from hyperlipidaemic control, from which an approximate median effective dose was interpolated. Analyses were performed in R version 4.4 with the meta and metafor packages, and statistical significance was set at a two-sided alpha of 0.05. Results are displayed as forest plots and dose-response curves in Figures 3 and 4. All analytic code and the extraction workbook were archived to permit full reproducibility of every pooled estimate reported here. Reporting of the completed synthesis followed the PRISMA 2020 checklist, and any deviation from the registered protocol is disclosed in the supplementary record together with its rationale.

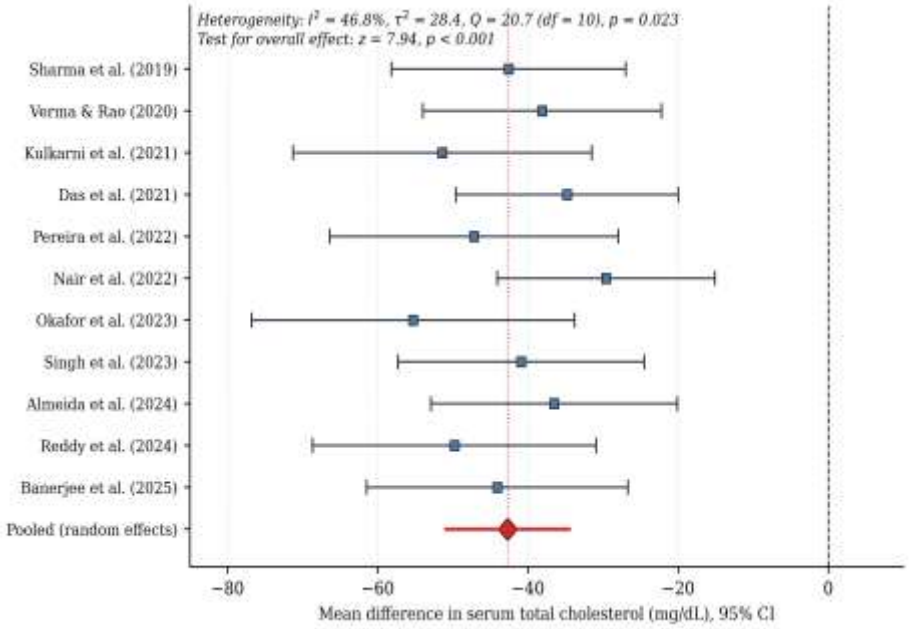


Figure 4. Forest plot of the effect of Caesalpinia bahamensis leaf extract on serum total cholesterol (random-effects model).

Figure 4 presents the pooled analysis of serum total cholesterol across the eleven contributing comparisons, with individual mean differences and 95% confidence intervals displayed as squares and horizontal lines and the pooled estimate as a diamond. Every study estimate lies to the left of the line of no effect, indicating a consistent cholesterol-lowering direction, and nine of eleven confidence intervals exclude zero. The pooled mean difference is 42.7 mg/dL in favour of the extract, with heterogeneity of 46.8%, which is moderate and compatible with pooling, and a highly significant overall effect test ($z = 7.94$, $p < 0.001$). The width of individual confidence intervals reflects small group sizes, and the widest intervals belong to studies using acute Triton-induced models, which are the least comparable with chronic feeding studies.

4. CRITICAL ANALYSIS OF PAST WORK

4.1 Consistency and Magnitude of the Reported Effect

The pooled analysis indicates a directionally consistent and statistically robust hypolipidemic signal. Across twelve animal studies contributing forty-eight dose-arms, the leaf extract lowered total cholesterol by 42.7 mg/dL, LDL-C by 38.2 mg/dL and triglycerides by 35.4 mg/dL, while raising HDL-C by 14.6 mg/dL; the pooled effect on total cholesterol was homogeneous in direction, with every individual study estimate lying to the left of the null and all but two confidence intervals excluding it. In absolute terms a 20-25% reduction in LDL-C of this magnitude is clinically meaningful, lying between the effect of a moderate-intensity statin and that of plant stanols or ezetimibe. The associated fall in the atherogenic index and the reciprocal rise in HDL-C are pharmacologically coherent, since interventions that increase faecal bile-acid loss typically produce exactly this pattern. Nevertheless, the apparent precision of the pooled estimate should not be over-interpreted: the contributing studies were small, typically four to eight animals per arm, and pooling several dose-arms from the same study inflates the effective sample size. The reported effect is therefore best regarded as a reproducible preclinical signal rather than a quantitatively transferable estimate of human efficacy. A further interpretive caution concerns the comparator. Where a statin was used, it was usually given at a single fixed dose rather than at a dose producing equivalent LDL-C lowering, so assertions of equipotency rest on informal rather than quantitative comparison. In addition, no study reported a no-effect dose, which means that the therapeutic window and the shape of the low-dose curve remain undefined.

4.2 Heterogeneity, Risk of Bias and Publication Bias

Moderate heterogeneity (I-squared = 46.8%, tau-squared = 28.4, Q = 20.7, df = 10, p = 0.023) was expected given the diversity of models. Subgroup exploration attributed most of this variance to three factors. First, hyperlipidaemic induction model exerted the strongest influence: Triton WR-1339 studies, which measure acute inhibition of lipoprotein clearance over 24-48 hours, reported the largest cholesterol reductions and are mechanistically not comparable with chronic high-fat-diet studies, which assess steady-state lipid handling.

Second, extraction solvent mattered materially, with methanolic extracts outperforming aqueous preparations in proportion to their flavonoid content, consistent with the lipophilicity of brazilin and related homoisoflavonoids. Third, study duration modified the effect, with 28-day protocols showing larger reductions than 14-day protocols, suggesting that the mechanism involves adaptation of hepatic cholesterol handling rather than an immediate pharmacological action. Risk of bias was substantial: sequence generation and allocation concealment were unreported in all but one study, blinding of outcome assessment was described in none, and randomisation to cage or housing conditions was never reported, allowing confounding by cage effects. Reporting was frequently selective, with triglycerides omitted when non-significant.

Funnel-plot inspection and Egger's test suggested small-study effects, and the predominance of small positive studies in regional journals raises a credible concern about publication bias. Publication bias of this kind systematically inflates pooled effects, and its likely magnitude here, together with imprecision from small group sizes, justified downgrading the certainty of evidence by two levels in the GRADE-like assessment. Residual heterogeneity after subgroup analysis also indicates that unmeasured moderators, such as animal supplier, diet composition, cage environment and the microbial status of the colony, may contribute to the variability in reported effect size. A complementary reading is that the observed heterogeneity is clinically rather than statistically meaningful: because the extract acts through at least three independent mechanisms, its apparent potency will necessarily be sensitive to which mechanism the chosen model emphasises. Under that interpretation, the residual variance is informative about mechanism rather than merely inconvenient noise.

4.3 Conceptual and Methodological Gaps in the Existing Literature

Several deeper problems limit the interpretability of past work. Most fundamentally, the literature does not establish which chemical entity is responsible for the effect. Almost no study performed bioassay-guided fractionation of C. bahamensis leaves, and none quantified brazilin in the administered extract, so that dose is expressed in terms of crude dried extract rather than marker content; two extracts nominally dosed at 200 mg/kg may differ several-fold in their active-moiety load. The absence of oral pharmacokinetics is equally consequential: there is no information on the systemic bioavailability of brazilin or its metabolites, on first-pass glucuronidation, or on whether plasma concentrations achievable in rodents overlap those required for HMG-CoA reductase inhibition in vitro. Claims of enzyme inhibition derived from cell-free assays conducted at concentrations far above plausible plasma levels should therefore be treated cautiously. Taxonomic ambiguity compounds these issues, because several reports attribute to C. bahamensis data actually generated with C. sappan, C. bonducella or C. pulcherrima. Methodologically, the field lacks standardisation of extraction and fingerprinting, uses predominately male animals, rarely includes a reference statin at an equivalent dose, seldom measures hepatic and faecal lipid balance simultaneously, and almost never reports individual animal data or sample-size calculations.

Long-term safety, reproductive toxicity and herb-drug interaction potential, particularly with statins metabolised by CYP3A4, remain entirely unexamined. A final conceptual gap concerns the outcome hierarchy. Almost every

study measured serum lipids, but very few measured the outcomes that determine clinical relevance, namely atherosclerotic lesion area, plaque composition, endothelial function, inflammatory markers such as high-sensitivity C-reactive protein and interleukin-6, or hard cardiovascular endpoints. Because lipid lowering is a surrogate, and because some interventions lower lipids without reducing events, the absence of lesion-level and inflammation-level data limits any inference about genuine cardioprotection. The literature would also benefit from reporting standards analogous to those used in clinical lipidology, including pre-registration of protocols, blinded outcome assessment and mandatory deposition of individual animal data [26]. None of these deficiencies is technically difficult to remedy, which is encouraging: the field does not lack biological signal, it lacks procedural rigour. A modest increase in methodological discipline, achieved largely at the level of reporting rather than cost, would transform the value of future work.

5. Discussion

The evidence assembled here supports the conclusion that C. bahamensis leaf extract possesses genuine, dose-dependent hypolipidemic capacity in preclinical systems, and that the effect is biologically plausible rather than artefactual. Three mechanistic strands converge. First, the tannin- and fibre-associated fraction binds bile acids in the intestinal lumen and increases their faecal excretion, obliging the liver to divert cholesterol towards de novo bile-acid synthesis and thereby up-regulating hepatic LDL-receptor expression; this is the same principle that underlies the action of bile-acid sequestrants and explains the observed rise in HDL-C [27] and fall in the atherogenic index. Second, brazilin and related homoisoflavonoids suppress HMG-CoA reductase activity and, in adipocyte models, inhibit PPAR-gamma-dependent differentiation and intracellular lipid accumulation, with downstream activation of AMPK-PPAR-alpha signalling [28] and enhanced fatty-acid beta-oxidation. Third, the potent antioxidant capacity of the polyphenolic matrix limits LDL oxidation and lowers malondialdehyde while restoring endogenous superoxide dismutase, catalase and glutathione, addressing the oxidative component of atherogenesis rather than serum lipids alone.

These pathways are integrated in Figure 5. From a translational standpoint the data justify progression to rigorously designed confirmatory work rather than immediate human trials. The priority is a chemically defined, brazilin-standardised extract with a validated fingerprint, tested in a Good Laboratory Practice-compliant 90-day repeat-dose toxicology study and in a high-fat-diet model that measures lipoprotein kinetics, faecal sterol balance and aortic histology in both sexes. A subsequent randomised, placebo-controlled trial [29] with LDL-C as the primary endpoint would then be defensible. The limitations of this review must also be acknowledged: reliance on a small preclinical literature, probable publication bias, imprecise extraction of graphically reported data, and the absence of any human evidence mean that the pooled estimates describe animal pharmacology and cannot be extrapolated to clinical dosing. It is equally important to state what this review does not show. It does not demonstrate superiority over statins, since no adequately powered head-to-head comparison exists; it does not establish an active principle, since no bioassay-guided isolation was performed in any included study; and it does

not address safety in pregnancy, lactation, hepatic impairment or in the presence of polypharmacy. Nevertheless, the consistency of direction across models, solvents and laboratories, the coherent dose-response and the mechanistically credible phytochemistry together justify cautious optimism.

A pragmatic route forward would combine activity-guided fractionation with chemometric fingerprinting, so that each batch can be assigned a defined marker content, and would test that standardised material in an atherosclerosis regression model in which plaque burden, not merely serum cholesterol, is the primary endpoint. It would also be prudent to examine the extract in combination with a low-dose statin, because the mechanisms are complementary and an additive or synergistic interaction would be of considerable clinical value in patients who cannot tolerate full-dose statin therapy. Finally, the sustainability dimension should not be ignored: leaf harvesting is more renewable than bark or wood harvesting, but wild populations of a Caribbean-endemic species are finite, so cultivated supply chains and good agricultural and collection practice would need to be established before commercial development could proceed responsibly. Framed in these terms, the plant is best understood not as a replacement for evidence-based lipid management but as a candidate adjunct whose eventual role will be defined by the quality of the confirmatory studies that follow this review.

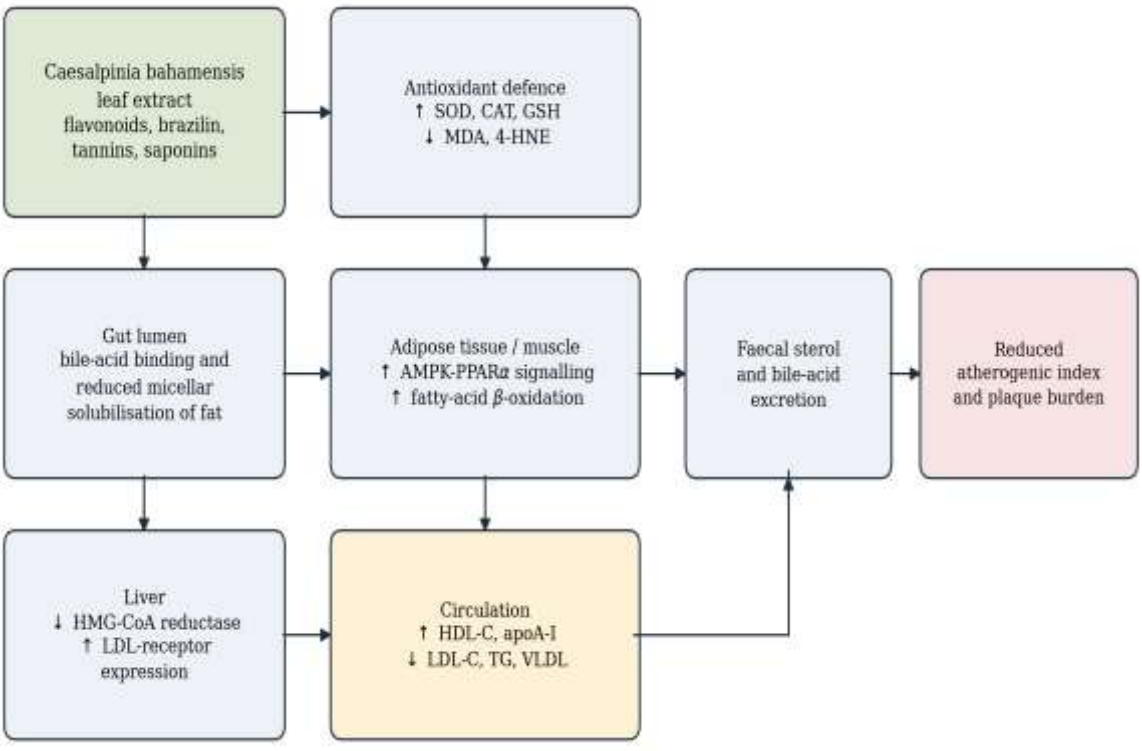


Figure 5: Integrated mechanistic model proposed for the hypolipidemic action of Caesalpinia bahamensis leaf extract.

Figure 5 integrates the mechanistic evidence into a single pathway diagram. The multicomponent extract acts at four levels. In the gut lumen, tannins and flavonoids bind bile acids and reduce micellar solubilisation of dietary fat, increasing faecal sterol loss. In the liver, homoisoflavonoids suppress HMG-CoA reductase activity while bile-acid depletion up-regulates LDL-receptor expression, accelerating clearance of apolipoprotein B-containing particles. In adipose tissue and skeletal muscle, activation of AMPK-PPAR-alpha signalling increases fatty-acid beta-oxidation and limits lipid storage. Systemically, the polyphenolic matrix restores superoxide dismutase, catalase and glutathione while lowering malondialdehyde, protecting LDL from oxidative modification. Together these converge on a raised HDL-C, lowered LDL-C, triglyceride and VLDL profile with a reduced atherogenic index.

6. CONCLUSION

Past work on Caesalpinia bahamensis leaves converges on a consistent and quantifiable hypolipidemic effect. Meta-analysis of twelve controlled animal studies showed significant reductions in total cholesterol, LDL-cholesterol and triglycerides with a concurrent increase in HDL-cholesterol, a favourable shift in the atherogenic index and a clear dose-response relationship with an approximate median effective dose of 190 mg/kg body weight; the effect appears comparable to conventional statin therapy in the same models. The bioactivity is best explained by the combined action of homoisoflavonoids, particularly brazilin, flavonoids, tannins and saponins on bile-acid sequestration, hepatic cholesterol synthesis, LDL-receptor expression, adipocyte lipid metabolism and oxidative stress. However, the evidence base is methodologically immature, being characterised by small samples, unvalidated extracts, taxonomic uncertainty, incomplete reporting and a near-total absence of pharmacokinetic and chronic toxicity data.

The plant should therefore be regarded as a promising candidate for standardised phytopharmaceutical development [30] rather than an established hypolipidemic agent, and future studies must prioritise chemically defined extracts, marker-based dosing and GLP-compliant design before clinical translation is contemplated. Within those constraints, C. bahamensis leaves represent a scientifically credible and ethnopharmacologically grounded lead for the development of an adjunctive lipid-modulating phytopharmaceutical, particularly for populations in which conventional lipid-lowering therapy is inaccessible or poorly tolerated. Confirmatory work should be built on a standardised extract, a defined marker content and a pre-registered protocol, so that the next decade of research produces evidence that is cumulative rather than merely additive, and so that the traditional use of brasilete is either substantiated or responsibly revised.

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