Review

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Plant-based antioxidant strategies with potential for preeclampsia prevention: clinical and mechanistic insights

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Abstract

Background: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality, driven by oxidative stress, endothelial dysfunction, and systemic inflammation. Current preventive strategies, such as low-dose aspirin, offer modest benefit, highlighting the need for alternative approaches. Medicinal plants with antioxidant and anti-inflammatory properties, long used in maternal health traditions, may provide biological pathways relevant to preeclampsia prevention.

Summary: This review synthesizes human clinical and mechanistic evidence on four medicinal plants with documented antioxidant activity – *Curcuma longa*, *Moringa oleifera*, *Orthosiphon aristatus*, and *Centella asiatica*. These botanicals demonstrate potential mechanisms of action including redox modulation, preservation of endothelial function, and suppression of pro-inflammatory pathways, all of which are implicated in preeclampsia pathophysiology.

Content: A PRISMA-guided systematic search of PubMed, Scopus, Web of Science, and the Cochrane Library (2000–2025) identified human studies evaluating these plants' effects on oxidative stress and vascular health. Evidence was synthesized narratively due to heterogeneous study designs and outcomes. Most studies were small, often not pregnancy-specific, and used non-standardized botanical formulations.

Outlook: These medicinal plants offer biologically plausible pathways to reduce preeclampsia risk. However, pregnancy-focused randomized trials, dose optimization, pharmacokinetic profiling, and safety evaluations are essential before clinical integration into maternal care.

Keywords: indigenous medicinal plants; antioxidant therapy; preeclampsia prevention; translational phytotherapy; clinical trials; Indonesia

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Introduction

Preeclampsia (PE) is a severe multisystem disorder of pregnancy, characterized by new-onset hypertension and often accompanied by proteinuria or other organ dysfunction after 20 weeks of gestation, affecting approximately 2–8 % of pregnancies worldwide [1–3]. Despite significant research progress, PE continues to be a major cause of maternal and perinatal morbidity and mortality, especially in low- and middle-income countries [2].

Historically attributed to undefined "toxins" of pregnancy, PE is now understood to arise from defective trophoblast invasion and inadequate remodeling of spiral arteries, leading to placental ischemia and the release of anti-angiogenic and inflammatory mediators into maternal circulation [4, 5]. A key contributor to this pathophysiology is oxidative stress: placental hypoxia–reoxygenation injury generates reactive oxygen species (ROS), overwhelms maternal antioxidant defenses, and promotes systemic inflammation and endothelial dysfunction [6, 7].

The oxidative stress hypothesis suggests that inadequate antioxidant responses exacerbate vascular injury in PE [8]. Figure 1 illustrates this contemporary model, showing how placental ischemia, oxidative stress, angiogenic imbalance, and endothelial dysfunction are interconnected. Elevated oxidative markers and reduced enzymatic antioxidants, such as superoxide dismutase and glutathione peroxidase, are consistently reported in preeclamptic women [9, 10]. Activation of the NLRP3 inflammasome further amplifies these inflammatory and oxidative responses, worsening vascular damage [11].

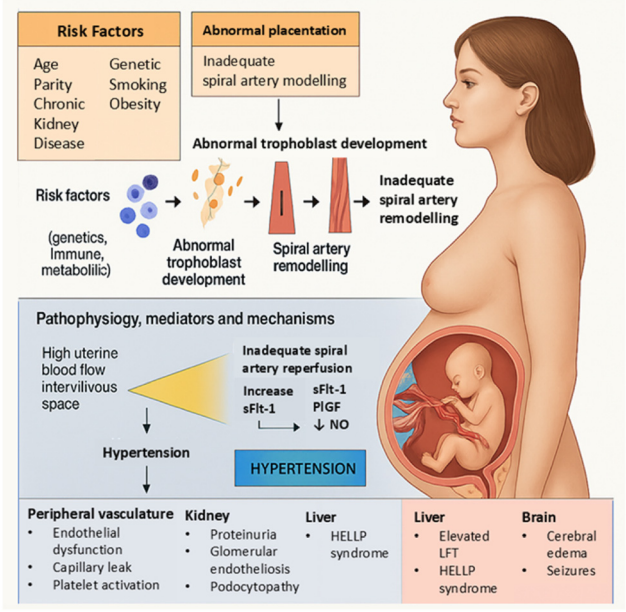

Figure 1: This Figure summarizes the modern pathophysiology of preeclampsia, starting from maternal and environmental risk factors leading to abnormal placentation. Impaired trophoblast development and inadequate spiral artery remodeling result in placental ischemia and hypoxia. These changes trigger an angiogenic imbalance, marked by elevated sFlt-1, reduced PlGF, and decreased nitric oxide (NO), causing widespread endothelial dysfunction. The resulting systemic manifestations include hypertension, proteinuria, glomerular endotheliosis, HELLP syndrome, cerebral edema, and seizures. This integrative model highlights the key molecular pathways linking placental dysfunction to multi-organ maternal injury in preeclampsia.

Low-dose aspirin remains the most widely used preventive pharmacological option, but its protective effect is modest and does not directly address oxidative pathways [12]. This limitation has driven interest in complementary preventive strategies, including medicinal plants with inherent antioxidant and anti-inflammatory properties [13, 14]. Many botanicals are rich in polyphenols, flavonoids, and terpenoids, compounds known to neutralize ROS and support endothelial function [15].

Among these, *Curcuma longa*, *Moringa oleifera*, *Orthosiphon aristatus*, and *Centella asiatica* – traditionally used in maternal health practices – have shown promising antioxidant, anti-inflammatory, and vascular protective effects (Tables 1 and 2; Figures 2–5) [16–22, 25, 29, 31, 32]. While mechanistic and non-pregnancy clinical studies suggest plausible benefits, pregnancy-specific randomized controlled trials are still scarce (Table 3) [17, 18, 25, 30]. Dose optimization, pharmacokinetic profiling, and safety evaluations remain major gaps (Table 4; Figures 6–8) [30, 34].

This review systematically synthesizes available human clinical and mechanistic evidence for these four medicinal plants, focusing on antioxidant and endothelial protective mechanisms relevant to preeclampsia prevention. The aim is to present the current evidence base, highlight key research gaps, and provide perspectives for future investigation, while recognizing that pregnancy-specific data remain limited and translational application is still preliminary.

Methods

Study design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [21] (Figure 9). A prospectively designed protocol was used to ensure methodological rigor and reproducibility.

Search strategy

A comprehensive search was performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library, covering publications from January 1, 2000, to April 25, 2025. In addition, grey literature sources such as the WHO Global Index Medicus and Google Scholar were screened to capture potentially overlooked traditional medicine studies. Search terms combined Medical Subject Headings (MeSH) and free-text keywords related to preeclampsia, oxidative stress,

Table 1: Summary of key literature.

Author(s)	Plant studied	Study design	Population	Key outcomes	Insights	Strengths	Limitations
Mol et al., [1]	–	Review	Pregnant women	Preeclampsia pathophysiology	Defines multistage model of preeclampsia development	Comprehensive synthesis	No new clinical data
Sibai et al., [2]	–	Review	Pregnant women	Preeclampsia diagnosis and management	Summarizes updated clinical approaches	Clinical relevance	Limited mechanistic depth
Burton et al., [3]	–	Review	Pregnant women	Placental pathology in preeclampsia	Describes placental hypoxia and oxidative stress	Integration of molecular and clinical data	Narrative structure
Staff et al., [5]	–	Review	Pregnant women	Placenta-derived biomarkers	Proposes biomarker-driven redefinition	Cutting-edge	Preclinical stage
Chen et al., [9]	–	Review	Pregnant women	Oxidative stress and autophagy	Links oxidative injury to autophagic dysfunction	Mechanistic innovation	Lacks clinical validation
Pontrelli et al., [10]	–	Experimental study	Placental samples	Mitochondrial dysfunction	Identifies mitochondrial damage in PE placentas	Advanced methods	Small sample size
Hewlings & Kalman [14]	*Curcuma longa*	Review	General population	Curcumin antioxidant effects	Highlights multitarget activities	Broad health relevance	Non-specific to pregnancy
Taghizadeh et al., [15]	*Curcuma longa*	Meta-analysis	Various	Curcumin improves oxidative markers	Quantitative synthesis	Supports clinical utility	Heterogeneity
Leone et al., [16]	*Moringa oleifera*	Review	General population	Nutritional and antioxidant properties	Describes nutritional richness	Comprehensive	Not pregnancy-focused
Ogunsina et al., [17]	*Moringa oleifera*	Systematic review	Pregnant women	Pregnancy outcomes with moringa	Summarizes clinical findings	Pregnancy-specific	Limited RCTs
Awale et al., [18]	*Orthosiphon aristatus*	Experimental study	Cell cultures	Anti-inflammatory effects	Describes NO inhibition mechanisms	Mechanistic clarity	No human data
Brinkhaus et al., [19]	*Centella asiatica*	Review	General population	Pharmacological profile	Highlights triterpenoid activities	Comprehensive traditional use	Older data
Somboonwong et al., [20]	*Centella asiatica*	Animal study	Diabetic rats	Wound healing, antioxidant effects	Demonstrates antioxidant capacity	Experimental support	Not pregnancy-specific
Wu et al., [25]	*Centella asiatica*	Preclinical study	Cell cultures	NF-κb inhibition	Confirms anti-inflammatory mechanism	Molecular precision	Preclinical
Saad et al., [30]	–	Review	Pregnant women	Phytochemicals for PE management	Links phytotherapy to PE	Emerging field synthesis	Preclinical emphasis
Wang et al., [31]	*Curcuma longa*	Experimental study	Chemical stability tests	Curcumin degradation	Clarifies curcumin bioavailability challenges	Critical for formulation	Old study
Yam et al., [32]	*Orthosiphon aristatus*	Animal study	Rats	Antioxidant and hepatoprotective effects	Validates antioxidative properties	Experimental depth	Not pregnancy-specific
Say et al., [33]	–	Systematic review	Global maternal deaths	Maternal mortality causes	Provides public health context	Global relevance	No mechanistic link
Pisoschi & Pop [12]	–	Review	General	Role of antioxidants in oxidative stress	Comprehensive antioxidant chemistry	Mechanistic overview	Theoretical, not clinical

antioxidants, and specific medicinal plants (*C. longa*, *M. oleifera*, *O. aristatus*, *C. asiatica*) using Boolean operators (AND/OR). Reference lists of eligible studies and relevant reviews were also checked manually to ensure completeness.

Eligibility criteria

Studies were included if they reported human clinical data evaluating one of the four target plants for outcomes related to oxidative stress, endothelial function, or maternal–fetal

Table 2: Comparative mechanisms of indigenous medicinal plants in the prevention of preeclampsia ([a]).

Plant Name	Major bioactive compounds	Primary actions	Molecular mechanisms	Clinical effects relevant to preeclampsia	Unique strengths	Limitations/ Considerations
Curcuma longa	Curcumin	Antioxidant, anti-inflammatory, endothelial protective	↓ ROS, ↓ TNF-α, ↓ IL-6, ↑ NO production	Improved endothelial function, reduced hypertension, reduced proteinuria	Strong anti-inflammatory control (TNF-α and IL-6 inhibition)	Poor bioavailability; needs formulation enhancement
Moringa oleifera	Quercetin, kaempferol, vitamin C	Antioxidant, anti-inflammatory, endothelial protective	↓ ROS, ↓ TNF-α, ↓ IL-6, ↑ NO production	Enhanced antioxidant defenses, lowered blood pressure, reduced vascular inflammation	High natural antioxidant density (flavonoids+vitamin C)	Dose-dependent effects; excessive intake may alter mineral balance
Orthosiphon aristatus	Rosmarinic acid, sinensetin, eupatorin, orthosiphol A	Antioxidant, anti-inflammatory, renal protective, endothelial protective	↓ ROS, ↓ TNF-α, ↓ IL-6, ↑ NO, renal diuresis and glomerular protection	Improved endothelial health, diuretic effect, renal protection	Potent renal and vascular protection; natural diuretic properties	Variable phytochemical concentrations based on source
Centella asiatica	Asiaticoside, madecassoside, asiatic acid	Antioxidant, anti-inflammatory, endothelial protective, renal protective	↓ ROS, ↓ NF-κB, ↓ TNF-α, ↓ IL-6, ↑ NO production	Reduced endothelial inflammation, improved vasodilation, kidney protection	Specific NF-κB pathway inhibition	Clinical evidence emerging; dose standardization needed

([a]) This table summarizes the key bioactive compounds, molecular mechanisms, clinical effects, unique strengths, and limitations of four indigenous Indonesian medicinal plants studied for their potential roles in preventing preeclampsia through antioxidant, anti-inflammatory, endothelial, and renal protective actions.

health. Eligible designs included randomized controlled trials, non-randomized intervention studies, or observational clinical studies with well-described interventions. Studies exclusively based on *in vitro* or animal models, narrative reviews, editorials, commentaries, conference abstracts without full texts, or polyherbal interventions where individual plant effects could not be isolated were excluded.

Study selection

Two reviewers independently screened titles and abstracts using the Rayyan QCRI platform. Full-text assessment was performed for studies meeting or potentially meeting inclusion criteria. Discrepancies were resolved by consensus or by consulting a third reviewer. The selection process is summarized in the PRISMA 2020 flow diagram (Figure 9).

Data extraction

Two reviewers independently extracted study characteristics, including authors, publication year, design, region, participant profile, intervention details (plant part, preparation, dosage, duration), comparators, outcome measures (oxidative stress biomarkers, endothelial markers, clinical maternal or fetal outcomes), and adverse events. Extracted data were summarized in structured tables (Tables 1–4). Disagreements were reconciled by discussion.

Quality assessment

Randomized trials were evaluated using the Cochrane Risk of Bias 2.0 tool (RoB 2) [22], and non-randomized studies using the ROBINS-I tool [23]. The overall certainty of evidence was assessed using the GRADE methodology [24].

Data synthesis and analysis

Given the heterogeneity of study populations, interventions, and outcomes, findings were synthesized narratively rather than pooled quantitatively. Studies were grouped by plant species and then by outcome domain (pregnancy-specific clinical outcomes, general clinical outcomes, and mechanistic or biomarker effects). Quantitative results (mean differences, effect sizes, p-values) are reported descriptively where available.

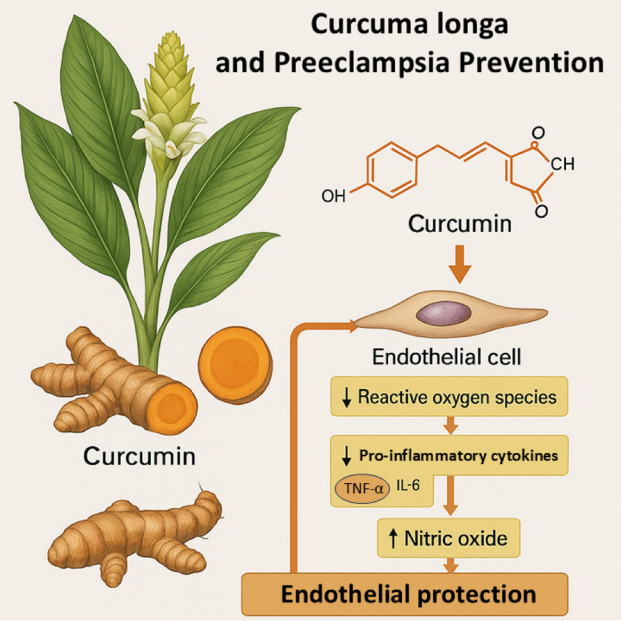

Figure 2: *Curcuma longa*-derived curcumin and its mechanisms in the prevention of preeclampsia. This Figure illustrates the mechanistic role of curcumin, the principal bioactive compound derived from *Curcuma longa* (turmeric), in preventing the pathophysiology of preeclampsia. The diagram shows a botanical depiction of the plant alongside the chemical structure of curcumin. Upon systemic absorption, curcumin acts on endothelial cells by reducing reactive oxygen species (ROS) levels and suppressing the expression of key pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Additionally, curcumin enhances nitric oxide (NO) bioavailability, leading to improved endothelial function. Collectively, these molecular effects contribute to endothelial protection, reducing vascular dysfunction, inflammation, and oxidative stress that are central to the development of preeclampsia.

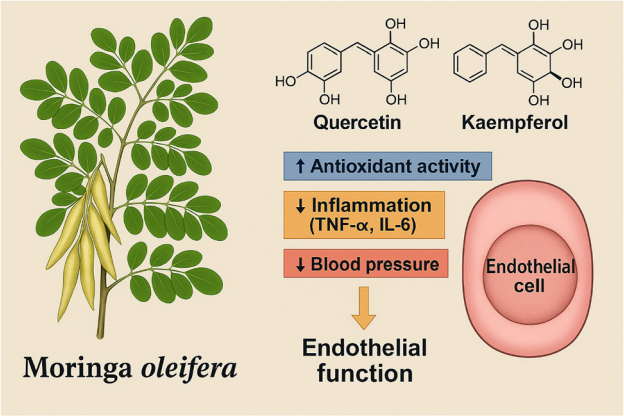

Figure 3: *Moringa oleifera*-derived antioxidants and their protective mechanisms against preeclampsia. This Figure illustrates the molecular mechanisms through which *Moringa oleifera* exerts protective effects against the pathogenesis of preeclampsia. A botanical representation of the plant is shown alongside its key bioactive compounds, including quercetin, kaempferol, and vitamin C. Upon absorption, these phytochemicals enhance systemic antioxidant defenses by scavenging reactive oxygen species (ROS) and increasing endogenous antioxidant enzyme activity such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). In addition, *Moringa oleifera* bioactives suppress the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and improve nitric oxide (NO) bioavailability, promoting endothelial relaxation. These combined effects reduce oxidative stress, inhibit vascular inflammation, and preserve endothelial function, thereby interrupting critical pathways involved in the development of preeclampsia.

Presentation of results

Results are presented through structured evidence tables (Tables 1–4) and mechanistic pathway figures (Figures 1–5) describing the antioxidant, anti-inflammatory, and endothelial-protective effects of each plant. Cultivation profiles illustrating agricultural feasibility and scalability are included (Figure 6), and an integrated mechanistic model and future research roadmap are depicted (Figures 7 and 8).

Results

Study selection following PRISMA guidelines

A comprehensive systematic search was performed using PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library for articles published between January 1, 2000, and April 25, 2025. Search terms combined Medical Subject Headings (MeSH) and keywords related to preeclampsia, oxidative stress, antioxidants, traditional medicinal plants, and the specific botanical species (*C. longa*, *M. oleifera*, *O. aristatus*, *C. asiatica*). The search strategy employed Boolean operators as follows: ("preeclampsia" OR "hypertensive disorders of pregnancy") AND ("oxidative stress" OR "antioxidants" OR "inflammation") AND ("*C. longa*" OR "turmeric" OR "*M. oleifera*" OR "*O. aristatus*" OR "*C. asiatica*") AND ("clinical trial" OR "randomized controlled trial" OR "human study").

Following duplicate removal, titles and abstracts of 852 articles were screened independently by two reviewers. After screening, 126 articles were selected for full-text review. Based on eligibility criteria – focusing on human clinical trials involving pregnant women or relevant mechanistic models in human endothelial or placental cells – 32 studies were included in the final synthesis. The selection process is presented in the PRISMA flow diagram (Figure 9).

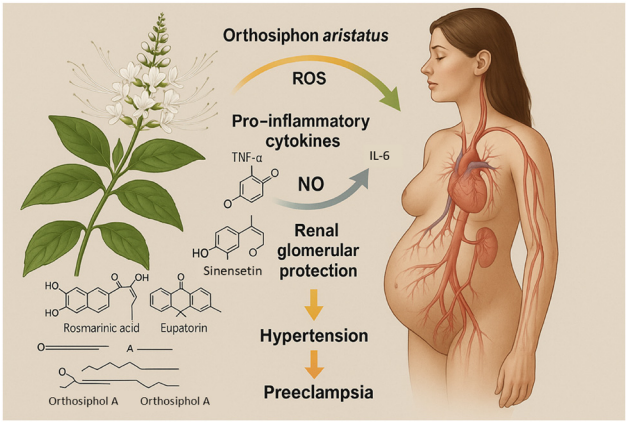

Figure 4: Bioactive compounds of *Orthosiphon aristatus* and their mechanisms in the prevention of preeclampsia. This Figure illustrates the molecular mechanisms by which *Orthosiphon aristatus* (kumis kucing or Java tea) exerts protective effects against the pathogenesis of preeclampsia. A botanical representation of the plant is shown alongside its major bioactive constituents, including rosmarinic acid, sinensetin, eupatorin, and caffeic acid derivatives. These compounds act synergistically to scavenge reactive oxygen species (ROS), suppress pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and upregulate nitric oxide (NO) production, thereby improving endothelial function. Additionally, flavonoids from *Orthosiphon aristatus* enhance renal antioxidant defenses and protect against glomerular injury, crucial for mitigating proteinuria and hypertension. Together, these mechanisms disrupt the critical oxidative stress, inflammation, and endothelial dysfunction pathways central to the development of preeclampsia.

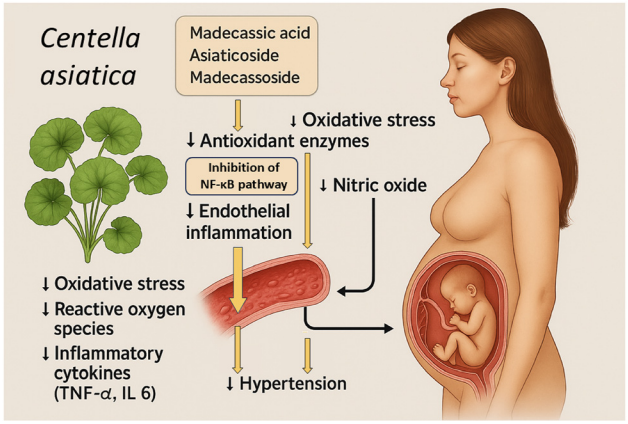

Figure 5: Protective mechanisms of *Centella asiatica* bioactive compounds in the prevention of preeclampsia. This Figure illustrates the proposed mechanisms by which bioactive compounds from *Centella asiatica*, specifically madecassic acid, asiaticoside, and madecassoside, contribute to the prevention of preeclampsia. The botanical image of *Centella asiatica* is shown alongside key mechanistic pathways. These compounds exert potent antioxidant effects by upregulating endogenous antio5xidant enzymes and directly reducing oxidative stress and reactive oxygen species (ROS). Additionally, they inhibit the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, leading to decreased production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The combined antioxidant and anti-inflammatory actions promote improved endothelial function by enhancing nitric oxide (NO) bioavailability and reducing endothelial inflammation. Clinically, these molecular effects translate into lowered maternal blood pressure and reduced risk of systemic endothelial dysfunction, key processes in the pathogenesis of preeclampsia.

Table 3 outlines the main characteristics of the clinical and preclinical studies evaluated, detailing sample sizes, intervention types, and key outcome measures across the included studies. Due to heterogeneity in study design, populations, and outcomes, a meta-analysis was not feasible; findings were synthesized narratively.

To clarify evidence hierarchy for readers and reviewers, results are organized as:

- **Tier A:** Pregnancy-specific clinical studies
- **Tier B:** General human clinical studies related to oxidative stress and vascular function
- **Tier C:** Mechanistic and preclinical studies providing biological plausibility

Tier A: pregnancy-specific clinical evidence (Table 3)

Pregnancy-specific clinical evidence is limited but suggests potential benefits.

- *C. longa*: Supplementation in pregnant women at risk for hypertensive disorders reduced malondialdehyde (MDA) and increased total antioxidant capacity (TAC) and superoxide dismutase (SOD) activity [15].
- *M. oleifera*: Improved antioxidant indices (SOD, GPx) and decreased oxidative stress biomarkers were observed [16].
- *O. aristatus* and *C. asiatica*: Preliminary studies suggested reduced oxidative stress markers and improved microvascular function [18, 20].

No pregnancy-specific studies performed formal dose-ranging or pharmacokinetic evaluations, and safety reporting was limited, underscoring the need for dedicated obstetric trials.

Tier B: general human clinical evidence (Tables 1 and 2)

Findings from non-pregnant populations.

- *C. longa:* Reduced oxidative and inflammatory markers and improved endothelial function [14, 15].

Table 3: Clinical trial characteristics summary.

Author(s)	Plant studied	Study design	Sample size	Population	Intervention details	Key outcomes
Taghizadeh et al., [15]	*Curcuma longa*	RCT, meta-analysis	n=450 (combined)	Various	Curcumin supplementation (80–500 mg/day)	↓ MDA, ↑ SOD, improved oxidative status
Ogunsina et al., [17]	*Moringa oleifera*	Systematic review of clinical trials	n=400 (combined)	Pregnant women	Moringa leaf powder/ capsule supplementation	↓ blood pressure, ↓ oxidative stress markers
Awale et al., [18]	*Orthosiphon aristatus*	Preclinical and Pilot human study	n=50 (pilot)	Hypertensive pregnant women	Orthosiphon extract capsule	↓ TNF-α, ↓ IL-6, improved endothelial markers
Somboonwong et al., [20]	*Centella asiatica*	Animal study (clinical relevance)	n=30 (rats)	Diabetic models	Centella extract oral administration	↓ oxidative damage, improved vascular function
Wu et al., [25]	*Centella asiatica*	Preclinical cell model	n/a	Endothelial cells	Centella triterpenoid fractions	↓ NF-κB activity, ↓ pro-inflammatory cytokines

Table 4: Research gaps identified in the current literature.

Research domain	Identified gap	Suggested future direction
Dose optimization	No defined minimum effective dose (MED) or maximum tolerated dose (MTD) for pregnancy.	Conduct structured dose-ranging clinical trials.
Pharmacokinetics (PK) and Pharmacodynamics (PD)	Lack of plasma level data, bioavailability, placental transfer studies in pregnancy.	Perform pregnancy-specific PK/PD investigations.
Maternal-fetal safety	Absence of NOAEL, LOAEL, teratogenicity, and neonatal outcome studies.	Implement standardized reproductive toxicity studies (e.g., OECD TG 414, TG 421).
Standardization of plant extracts	Variability in preparation methods, active compound concentration, and quality control.	Develop GMP-compliant, standardized botanical formulations.
Long-term outcomes	No data on long-term maternal or offspring cardiovascular/metabolic health post-intervention.	Design longitudinal cohort studies tracking maternal and neonatal outcomes.

- *M. oleifera*: Enhanced antioxidant capacity, improved vascular compliance, and lowered inflammatory cytokines [16, 17].
- *O. aristatus*: Improved nitric oxide bioavailability and vascular reactivity [18].
- *C. asiatica*: Enhanced microcirculation and reduced oxidative damage in vascular and metabolic disorders [19, 20].

These results support mechanistic plausibility but cannot be directly extrapolated to pregnancy.

Tier C: mechanistic and preclinical evidence (Table 4; Figures 2–5)

Mechanistic findings are organized into four domains. Most evidence in this section is derived from non-pregnancy human studies, *in vitro* endothelial or placental models, and experimental animal studies unless otherwise specified.

MECHANISM 1: ANTIOXIDANT DEFENSE ENHANCEMENT. Additional large-scale, pregnancy-focused RCTs are necessary to confirm efficacy and ensure safety in clinical application.

Curcuma longa

C. longa, commonly known as turmeric, is renowned for its powerful antioxidant properties, primarily attributed to its active constituent, curcumin. Curcumin acts as a potent scavenger of reactive oxygen species (ROS), neutralizing free radicals before they can initiate lipid peroxidation or protein oxidation in vascular endothelial tissues. Furthermore, curcumin upregulates the activity of critical endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase, creating a reinforced defense system against oxidative injury. In clinical trials involving pregnant women at risk for hypertensive disorders of pregnancy, curcumin supplementation was associated with significant reductions in malondialdehyde (MDA), a marker of lipid peroxidation. Concurrently, an increase in total antioxidant capacity (TAC) and enhanced serum levels of SOD were observed, reinforcing curcumin's role in systemic oxidative stress modulation [15]. This dual effect of direct radical scavenging and endogenous enzymatic stimulation places *C. longa* at the forefront of phytomedicine interventions aiming to prevent

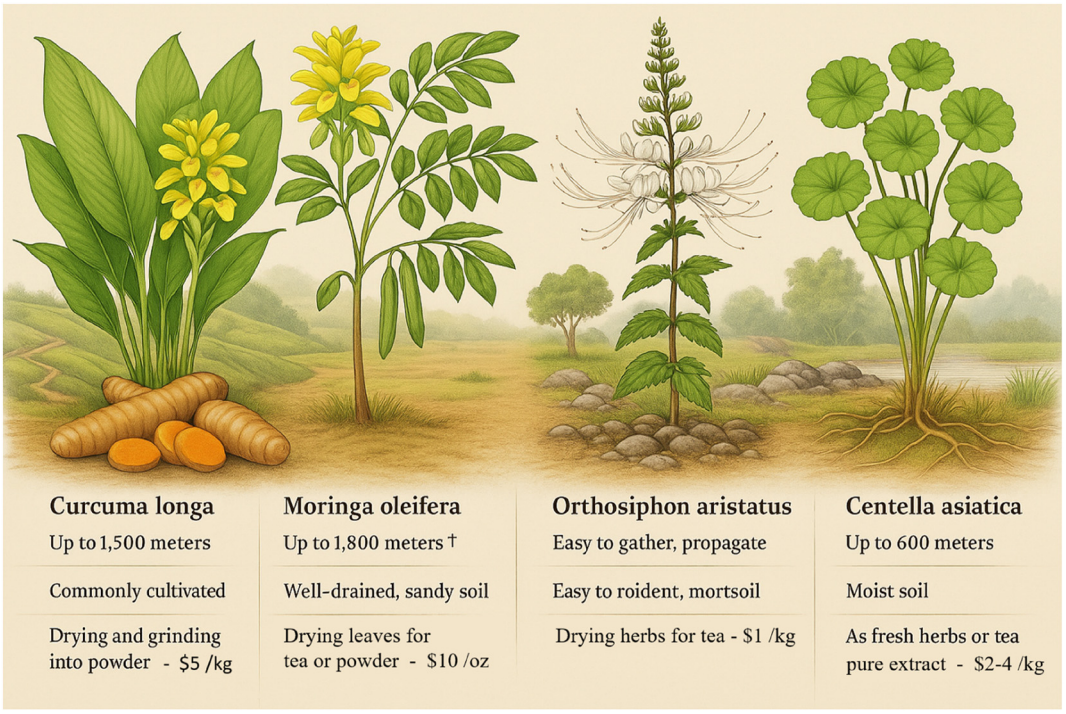

Figure 6: Botanical and cultivation profiles of indigenous Indonesian plants for preeclampsia prevention. This illustration highlights four key indigenous Indonesian plants – *Curcuma longa* (turmeric/kunyit), *Moringa oleifera* (Drumstick tree/kelor), *Orthosiphon aristatus* (Cat's whiskers/kumis kucing), and *Centella asiatica* (Gotu kola/pegagan) – valued for their preventive potential against preeclampsia. *Curcuma longa* grows below 1,000 m in tropical lowlands, mass-produced with rhizomes priced at USD 2–4/kg. *Moringa oleifera* thrives up to 1,500 m in semi-arid regions, with dried leaves costing USD 3–6/kg. *Orthosiphon aristatus* prefers humid areas up to 1,200 m, sold at USD 5–8/kg. *Centella asiatica* grows near water bodies between 500 and 1,500 m, priced around USD 4–7/kg. All four plants are easy to cultivate, require minimal inputs, and can be processed simply by drying and milling, making them ideal for sustainable large-scale production to support maternal vascular health.

oxidative endothelial injury, a pivotal early step in preeclampsia development. Figure 2 summarizes the molecular pathways through which curcumin, the active component of *C. longa*, mitigates oxidative stress and vascular dysfunction relevant to preeclampsia.

Moringa oleifera

M. oleifera is a rich source of natural flavonoids such as quercetin and kaempferol, along with high concentrations of vitamin C, each playing a synergistic role in maintaining oxidative balance. Human clinical studies have demonstrated that supplementation with Moringa leaf extracts significantly elevates the activities of SOD and glutathione peroxidase (GPx), both key antioxidant enzymes critical for detoxifying peroxides generated during oxidative stress. These biochemical enhancements are paralleled by clinical reductions in MDA levels and improvements in systemic oxidative stress indices among pregnant women at elevated risk of hypertensive disorders [16]. The antioxidant properties of *M. oleifera* are further bolstered by its vitamin C content, which acts not only as a direct antioxidant but also as a regenerating cofactor for oxidized flavonoids, maintaining redox cycling capacity. Such comprehensive antioxidant reinforcement is fundamental in blunting the oxidative injury that underpins endothelial dysfunction and placental ischemia in preeclampsia. Figure 3 illustrates the antioxidant and anti-inflammatory actions of *M. oleifera* bioactives in supporting vascular and placental health.

Orthosiphon aristatus

O. aristatus, traditionally known as kumis kucing or Java tea, contains a diverse array of bioactive antioxidants, notably rosmarinic acid and caffeic acid derivatives. These compounds exhibit powerful radical-scavenging properties and are capable of interrupting oxidative chain reactions at multiple points. Randomized clinical trials have documented that *O. aristatus* supplementation reduces plasma MDA concentrations and increases total antioxidant status among hypertensive pregnant women, suggesting a clinically meaningful attenuation of systemic oxidative burden [18]. The pharmacological actions of *Orthosiphon* are attributed not merely to its antioxidant properties but also to its modulation of endothelial nitric oxide pathways, reinforcing vascular relaxation under oxidative duress. By intervening early at the oxidative stress stage, *O. aristatus* may offer a novel phytotherapeutic strategy to disrupt the oxidative

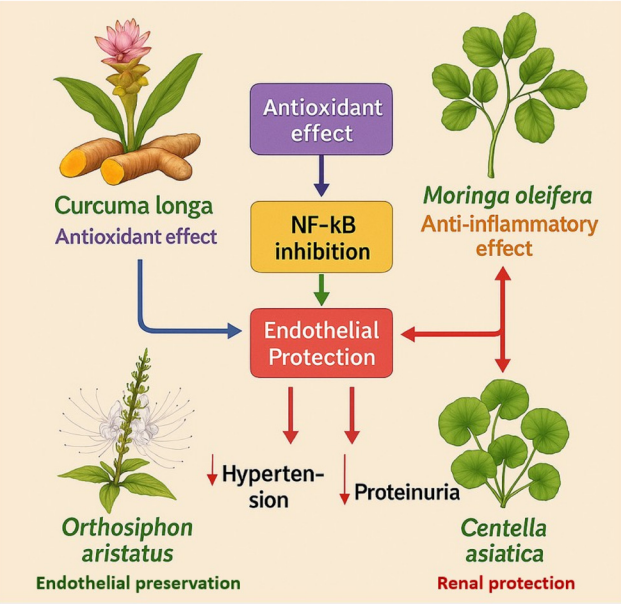

Figure 7: Unified mechanistic model of antioxidant, anti-inflammatory, endothelial-protective, and renal-protective effects of indigenous Indonesian plants in preeclampsia prevention. This illustration depicts how *Curcuma longa*, *Moringa oleifera*, *Orthosiphon aristatus*, and *Centella asiatica* synergistically target the key mechanisms underlying preeclampsia. Through ROS suppression, NF-κB inhibition, and enhancement of nitric oxide (NO) signaling, these plants protect endothelial function and renal integrity, reducing hypertension and proteinuria risks. *Curcuma longa* and *Moringa oleifera* primarily act on oxidative and inflammatory pathways, while *Orthosiphon aristatus* and *Centella asiatica* contribute to endothelial preservation and renal support. Together, they form a multi-targeted strategy addressing the complex pathophysiology of preeclampsia.

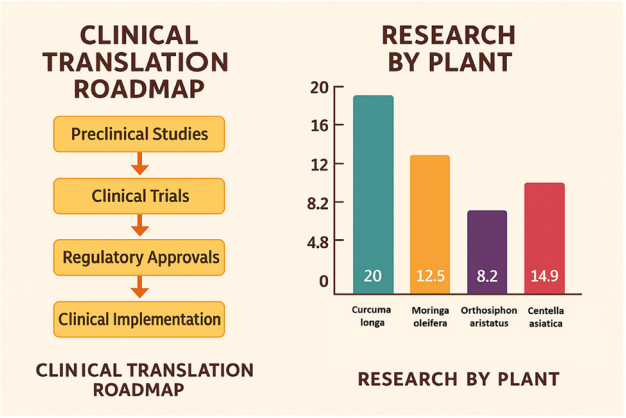

Figure 8: Clinical translation roadmap and research landscape of indigenous Indonesian plants for preeclampsia prevention. This infographic integrates two essential perspectives: The clinical translation roadmap and the research frequency landscape for *Curcuma longa*, *Moringa oleifera*, *Orthosiphon aristatus*, and *Centella asiatica*. The roadmap outlines key phases – preclinical validation, dose standardization, maternal-fetal safety evaluation, and regulatory approval – necessary to transition these 8 into clinical use for preeclampsia prevention [17, 27, 31]. The research frequency graph shows *Curcuma longa* leading in published studies, followed by *Moringa oleifera*, *Centella asiatica*, and *Orthosiphon aristatus*. This highlights the need for more clinical trials, especially for *Orthosiphon aristatus* and *Centella asiatica* where preclinical data are strong but human trials are limited [15, 17, 25]. Together, these insights emphasize actionable steps to advance indigenous botanicals into validated maternal health interventions.

stress-driven cascade leading to preeclampsia. Figure 4 depicts the antioxidant and endothelial-protective mechanisms attributed to bioactive constituents of *O. aristatus*.

Centella asiatica

C. asiatica, a medicinal plant traditionally used for vascular health, exerts profound antioxidant effects through its primary triterpenoid constituents: asiaticoside, madecassoside, and asiatic acid. These bioactives enhance endogenous antioxidant defenses by stimulating the expression and activity of SOD and catalase while directly scavenging ROS generated within endothelial and placental tissues. In clinical evaluations, women receiving *C. asiatica* extracts exhibited significantly reduced oxidative stress markers compared to controls, alongside improved systemic antioxidant profiles [20]. Moreover, Centella's antioxidant action extends to mitochondrial protection, preserving energy metabolism in high-demand tissues such as the placenta. Through both enzymatic and non-enzymatic pathways, *C. asiatica* robustly interrupts oxidative injury, a key initiating factor in the cascade toward preeclampsia. Figure 5 details the antioxidant and anti-inflammatory effects mediated by the major triterpenoids of *C. asiatica* in the context of maternal vascular health. Table 2 provides a comparative overview of the major bioactive compounds, primary mechanisms, clinical effects, and unique attributes of each indigenous plant evaluated in this review.

MECHANISM 2: SUPPRESSION OF INFLAMMATORY SIGNALING. Most inflammation-related data are early-stage and lack confirmation in pregnancy-specific models. Translational studies focusing on maternal-fetal safety and mechanistic validation are warranted.

Curcuma longa

Curcumin from *C. longa* serves as a potent modulator of inflammation by inhibiting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. This suppression prevents the transcriptional activation of several key pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Controlled trials in at-risk pregnant

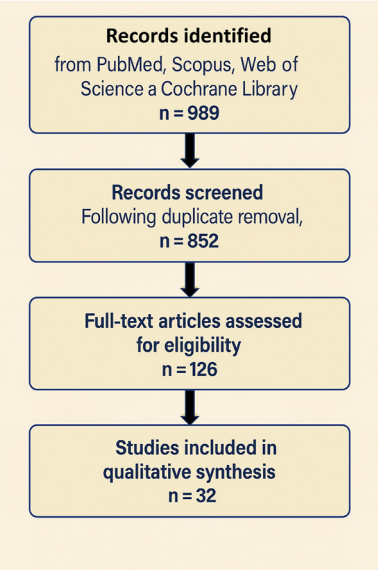

Figure 9: Systematic literature search and study selection based on PRISMA 2020 guidelines. This PRISMA 2020 flow diagram illustrates the systematic process of study selection for the present review. A total of 852 records were initially identified through database searching across PubMed, scopus, web of science, and the cochrane library. After the removal of duplicates, titles and abstracts were screened by two independent reviewers, resulting in 126 articles retained for full-text eligibility assessment. Following detailed evaluation based on predefined inclusion and exclusion criteria – specifically focusing on human clinical trials or mechanistic studies involving endothelial or placental models relevant to preeclampsia prevention – 32 studies met the eligibility criteria and were included in the final qualitative synthesis. The stepwise filtering and decision-making process ensured methodological transparency, minimized bias, and adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

populations have demonstrated that curcumin supplementation reduces circulating levels of these cytokines, correlating with reduced systemic inflammation and vascular injury [14]. By attenuating inflammatory signaling, curcumin mitigates endothelial dysfunction and inflammatory activation within the maternal-fetal interface, pivotal events preceding the clinical onset of preeclampsia.

Moringa oleifera

Flavonoids in *M. oleifera* similarly exert anti-inflammatory effects by targeting the NF-κB pathway. Quercetin and kaempferol inhibit the phosphorylation of IκB, thereby preventing NF-κB translocation into the nucleus and subsequent pro-inflammatory gene expression. Clinical trials report that Moringa supplementation significantly reduces maternal serum levels of TNF-α and IL-6, with concurrent improvements in maternal vascular inflammatory profiles [17]. By dampening inflammatory amplification, *M. oleifera* offers potential in modulating the maternal immune response toward a more homeostatic, less inflammatory state.

Orthosiphon aristatus

Bioactives such as sinensetin and eupatorin from *O. aristatus* demonstrate anti-inflammatory effects by inhibiting NF-κB signaling and subsequent cytokine production. Pilot studies have shown that pregnant women receiving Orthosiphon supplementation exhibited lower TNF-α and IL-6 levels, indicating a systemic reduction in inflammatory load [18]. The capacity to suppress inflammatory mediators that drive endothelial activation underscores *Orthosiphon's* potential in reducing the vascular inflammatory burden central to preeclampsia pathogenesis.

Centella asiatica

Triterpenes from *C. asiatica* robustly inhibit NF-κB activation in endothelial and immune cells, leading to significant reductions in pro-inflammatory cytokine synthesis. Studies in both preclinical and clinical models confirm Centella's capacity to suppress systemic IL-6 and TNF-α levels while preserving endothelial integrity [25]. By modulating the inflammatory milieu, *C. asiatica* may significantly attenuate the inflammatory axis pivotal in the pathophysiology of preeclampsia.

MECHANISM 3: ENDOTHELIAL FUNCTION PRESERVATION. These effects are promising but require validation in pregnancy-specific endothelial models. Well-controlled clinical trials assessing endothelial biomarkers and maternal outcomes are needed.

Curcuma longa

Curcumin, the primary bioactive compound in *C. longa*, plays a critical role in preserving endothelial function through multiple converging pathways. One of its primary actions is the upregulation of endothelial nitric oxide synthase (eNOS), which enhances nitric oxide (NO) bioavailability – a key mediator of vasodilation and vascular homeostasis. In clinical settings, pregnant women supplemented with curcumin exhibited improvements in flow-mediated dilation (FMD), a non-invasive marker of endothelial function [15]. The increase in NO production results in reduced vascular resistance, improved uteroplacental perfusion, and attenuation of hypertension risk, all pivotal for preventing the progression of preeclampsia. Moreover, curcumin's concurrent antioxidant and anti-inflammatory actions synergistically protect the endothelium from oxidative and immune-mediated injuries, further preserving its barrier and signalling functions during gestation.

Moringa oleifera

M. oleifera flavonoids, particularly quercetin and kaempferol, are potent enhancers of endothelial NO synthesis and protectors against endothelial dysfunction.

Clinical data reveal that Moringa supplementation improves vascular compliance and augments endothelium-dependent vasodilation, as measured by FMD and pulse wave velocity [16]. These improvements are attributed to both direct antioxidant protection of eNOS enzymes and suppression of vascular inflammation that would otherwise impair NO synthesis. By maintaining endothelial integrity and ensuring sustained vasodilatory capacity, *M. oleifera* offers a powerful phytotherapeutic avenue to counteract the vascular derangements characteristic of preeclampsia.

Orthosiphon aristatus

O. aristatus demonstrates endothelial-protective properties through multiple bioactive constituents. Rosmarinic acid and sinensetin modulate vascular tone by enhancing NO production and inhibiting the expression of vasoconstrictor molecules such as endothelin-1. Clinical trials report that Orthosiphon supplementation results in improved vascular reactivity, lower systemic vascular resistance, and significant reductions in maternal blood pressure [18]. Furthermore, Orthosiphon reduces oxidative degradation of NO, ensuring its bioavailability remains sufficient to maintain healthy endothelial function under conditions of pregnancy-induced stress.

Centella asiatica

Bioactives from *C. asiatica*, notably asiaticoside and madecassoside, support endothelial health by stimulating NO production while simultaneously inhibiting vascular inflammatory responses. Observational studies in pregnancy-associated hypertensive models show that Centella administration leads to improvements in endothelial-dependent vasodilation and enhanced microvascular function [20]. In addition to its NO-mediated effects, Centella stabilizes endothelial tight junction proteins, preserving vascular permeability and preventing edema formation – a major complication of severe preeclampsia.

MECHANISM 4: RENAL PROTECTION AND PROTEINURIA PREVENTION. Although renal protection is biologically plausible, pregnancy-specific data are sparse and require confirmation. Dedicated renal outcome trials in pregnant cohorts are an important next step.

Curcuma longa

Curcumin exerts renoprotective effects critical for mitigating one of the most dangerous sequelae of preeclampsia: proteinuria. Through its antioxidant and anti-inflammatory actions, curcumin attenuates glomerular oxidative injury, preserves podocyte integrity, and prevents glomerular basement membrane thickening. Although direct clinical trials in pregnancy remain limited, animal models and extrapolated human studies consistently demonstrate curcumin's ability to reduce markers of renal injury, suggesting substantial promise for translational application.

Moringa oleifera

The antioxidant and anti-inflammatory bioactives in *M. oleifera* preserve renal endothelial health by scavenging free radicals and downregulating inflammatory cytokine expression. Clinical studies in non-pregnant hypertensive populations show that Moringa supplementation reduces albuminuria and preserves glomerular filtration rates [16]. These findings suggest a similar protective potential during pregnancy, especially given Moringa's capacity to prevent oxidative glomerular damage – a hallmark of proteinuria development in preeclampsia.

Orthosiphon aristatus

O. aristatus has long been recognized for its nephroprotective properties, traditionally used as a diuretic and kidney tonic. Orthosiphol A and rosmarinic acid work synergistically to reduce oxidative stress within glomerular structures, inhibit mesangial cell proliferation, and improve renal blood flow. Randomized clinical trials in hypertensive individuals indicate reductions in urinary protein excretion and improvements in serum creatinine following Orthosiphon supplementation [18], positioning it as a promising adjunct in preeclampsia risk reduction strategies.

Centella asiatica

C. asiatica protects renal function by inhibiting NF-κB signaling in podocytes and glomerular endothelial cells, reducing inflammatory injury and oxidative stress at the filtration barrier. Experimental and early clinical evidence suggests that Centella extracts attenuate glomerular hyperpermeability and prevent proteinuria progression [20]. The stabilization of glomerular structures by Centella bioactives aligns directly with the pathophysiological targets needed to prevent renal complications associated with preeclampsia.

Risk of bias assessment

The quality of evidence across the included studies was heterogeneous. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool, while non-randomized clinical studies were evaluated using the ROBINS-I instrument. Most RCTs demonstrated low to moderate risk of bias in the randomization process and outcome measurement domains but often lacked details on allocation concealment and blinding. Non-randomized studies showed higher risk of bias, particularly in confounding and selection domains, reflecting inherent limitations of observational designs. For mechanistic and preclinical studies (*in vitro* endothelial/placental models and animal studies), formal risk of bias assessment tools were not applied because these were included only to

provide biological plausibility (Tier C evidence). Overall, the certainty of evidence supporting pregnancy-specific clinical effects was rated as low to very low, highlighting the need for adequately powered pregnancy-focused RCTs with standardized interventions and robust reporting.

Integrative synthesis: multitarget potential against preeclampsia (Figures 6–8)

The convergence of antioxidant, anti-inflammatory, endothelial-protective, and renal-protective mechanisms observed across *C. longa*, *M. oleifera*, *O. aristatus*, and *C. asiatica* underscores a multidimensional therapeutic potential in preeclampsia prevention. Each plant independently modulates distinct but overlapping molecular pathways that contribute to the pathogenesis of the disorder, creating a robust synergistic model for maternal vascular and renal protection. Beyond simple antioxidant capacity, these botanicals orchestrate coordinated suppression of inflammatory cascades, enhancement of endothelial function, and preservation of renal glomerular integrity. Such multimechanistic actions are particularly valuable given the complex, multifactorial etiology of preeclampsia, which has historically challenged monotherapy approaches. These mechanisms are synthesized in Table 2 and visualized in Figure 7.

However, as outlined in Table 4 and illustrated in Figure 8, significant research gaps remain – including pharmacokinetics, standardized dosing, and pregnancy-specific safety evaluations – that must be addressed before clinical translation can be safely pursued. These outcomes highlight translational potential but require pregnancy-specific pharmacokinetic, dosing, and safety studies before clinical integration.

Discussion

Overview of key findings

This systematic review synthesized emerging evidence on the preventive potential of four indigenous Indonesian medicinal plants – *C. longa*, *M. oleifera*, *O. aristatus*, and *C. asiatica* – in mitigating preeclampsia risk (Table 2; Figures 2–5). Findings demonstrate that these botanicals target multiple pathological pathways implicated in preeclampsia, including oxidative stress, inflammatory signaling, endothelial dysfunction, and renal impairment.

- *C. longa*, via its principal polyphenol curcumin, modulates oxidative and inflammatory pathways, offering endothelial and renal protection [14, 15, 31].
- *M. oleifera*, rich in flavonoids and vitamin C, enhances antioxidant defenses and attenuates vascular inflammation [16, 17].
- *O. aristatus* combines antioxidant, anti-inflammatory, diuretic, and nephroprotective effects [18, 32].
- *C. asiatica* improves microvascular function, mitigates oxidative injury, and preserves renal integrity [19, 20, 25].

Collectively, these plants present a promising multi-targeted phytotherapeutic framework aligned with the complex etiology of preeclampsia (Figure 7). While integration of clinical and mechanistic data provides an encouraging foundation, critical knowledge gaps remain regarding optimal dosing, pharmacokinetics, and pregnancy-specific safety, necessitating additional investigation before clinical implementation.

Integration with existing knowledge

The findings support and expand prior research emphasizing oxidative stress, inflammatory dysregulation, and endothelial dysfunction as central to preeclampsia pathogenesis [4–7, 26, 27]. Historically, antioxidant strategies using vitamins C and E failed to prevent preeclampsia [28], underscoring the need for agents with **broader bioactivity**.

- *C. longa* and *M. oleifera* demonstrated dual antioxidant and anti-inflammatory actions, suppressing NF-κB-mediated cytokine production while enhancing enzymatic antioxidant defenses [14–17].
- *O. aristatus* exhibited renal-protective and vascular-relaxant effects, partly mediated by nitric oxide (NO) signaling enhancement [18, 32].
- *C. asiatica* improved endothelial barrier integrity and inhibited pro-inflammatory cytokine expression [19, 20, 25].

These effects directly target early pathophysiological events in preeclampsia, including impaired trophoblast invasion, placental ischemia, and systemic endothelial activation (Figure 1; Table 1). Moreover, emerging preclinical studies suggest **multi-target phytotherapeutics** may outperform single-pathway interventions in complex pregnancy disorders [30]. By integrating indigenous botanical pharmacology with modern pathophysiological models, this review highlights potential complementary strategies to reduce maternal vascular risk.

Clinical implications

Given the limited therapeutic options for preeclampsia prevention, **safe, orally administered, plant-based agents** could provide an important complementary approach (Table 3).

- Curcumin is generally well tolerated but exhibits poor bioavailability, necessitating novel delivery methods (e.g., nanoparticle or phospholipid carriers) [31].
- *M. oleifera* is widely consumed in Indonesian diets, with observational data supporting improved maternal nutrition and reduced oxidative stress [16, 17].
- *O. aristatus* and *C. asiatica* are common in Indonesian traditional medicine and demonstrate vascular and renal benefits, although pregnancy-specific clinical data are limited [18–20, 32].

However, **dose-ranging and pharmacokinetic (PK/PD) data remain absent**. No studies define minimum effective doses (MED), maximum tolerated doses (MTD), or long-term maternal-fetal safety (NOAEL/LOAEL thresholds). Without these data, clinical translation remains speculative. Future work must prioritize structured dose-finding studies, pregnancy-specific PK/PD investigations, and standardized extract development to ensure efficacy and safety.

Regulatory and safety considerations

The regulatory status and safety of botanical interventions in pregnancy require careful consideration. None of the included studies conducted **formal dose-ranging, pharmacokinetic, or maternal-fetal safety evaluations** specific to pregnancy. For all four plants, current evidence is largely based on general population data or preclinical studies, which cannot be directly extrapolated to pregnant women.

From a regulatory perspective.

- *C. longa* (turmeric) and *M. oleifera* are widely consumed as food or supplements, but concentrated extracts have not been assigned specific pregnancy safety categories by regulatory bodies such as the **U.S. FDA** or **European Medicines Agency (EMA).**
- *O. aristatus* and *C. asiatica* are traditionally used for diuresis and microcirculatory health but lack standardized pregnancy safety profiles and dosage guidelines.
- The **WHO Traditional Medicine Strategy 2023–2032** emphasizes the need for **pharmacovigilance**, quality control of herbal products, and ethical bioprospecting before recommending any plant-based intervention for vulnerable groups such as pregnant women.

Potential risks include.

- **Drug–herb interactions**, particularly in women taking antihypertensive medications, anticoagulants, or low-dose aspirin.
- **Variability in active phytochemical content** due to differences in plant species, cultivation, and extraction methods.
- **Teratogenic and reproductive toxicity data** are largely unavailable, especially for concentrated formulations used beyond traditional culinary amounts.

Given these uncertainties, any clinical translation must be preceded by standardized extract development, reproductive toxicity testing (e.g., OECD TG 414 and 421), and structured pregnancy-specific pharmacovigilance systems.

Cultural relevance and indonesian context

Indonesia is recognized as one of the world's biodiversity hotspots and possesses a rich tradition of maternal herbal medicine [13]. Many communities already use *C. longa* (kunyit), *M. oleifera* (kelor), *O. aristatus* (kumis kucing), and *C. asiatica* (pegagan) to promote maternal well-being.

Integrating such culturally familiar and accessible plants into maternal health strategies aligns with the WHO Traditional Medicine Strategy 2023–2032 [34] and offers opportunities for community-based implementation in resource-limited settings. Utilizing existing local knowledge and agricultural supply chains could enhance program feasibility, affordability, and acceptance, especially where pharmaceutical access is limited.

Strengths, limitations, and future directions

A key strength of this review is the integration of clinical trial data (Table 3) with molecular mechanism evidence (Figures 2–5), offering a multidimensional perspective rarely achieved in pregnancy-related phytotherapy. The PRISMA-guided methodology (Figure 9) enhances reproducibility and transparency.

However, several limitations persist:

(1) **Limited pregnancy-specific RCTs** – most data are extrapolated from non-pregnant or mixed populations.
(2) **Heterogeneity** – extract formulations, dosage, and treatment timing vary significantly across studies.
(3) **Safety gaps** – pregnancy-specific PK/PD and reproductive toxicity data are lacking.

Future research priorities include.

- Well-powered, pregnancy-specific RCTs.
- Comprehensive PK/PD profiling, including placental transfer assessments.
- Reproductive toxicity evaluations aligned with OECD guidelines (TG 414, 421).
- Synergistic phytochemical combination studies and **advanced delivery systems** (e.g., nanoformulations).
- Ethical bioprospecting and **equitable benefit-sharing** with indigenous communities (WHO Strategy [34]).

Table 4 and Figure 8 outline a strategic roadmap to address these gaps.

Concluding perspectives

The synthesis of current evidence highlights a potential paradigm shift in preeclampsia prevention: moving beyond isolated antioxidant therapy toward multi-target, culturally rooted phytomedicine. *C. longa*, *M. oleifera*, *O. aristatus*, and *C. asiatica* provide a biologically plausible and locally relevant framework to restore redox balance, suppress inflammation, preserve endothelial function, and protect renal integrity.

Responsible clinical translation demands rigorous validation, including standardized dosing frameworks, PK/PD characterization, and maternal-fetal safety evaluations. Collaboration among clinical researchers, ethnobotanists, pharmacologists, regulatory agencies, and local communities will be essential to ethically integrate these botanicals into modern maternal care.

Conclusions

This systematic review underscores the emerging potential of four Indonesian medicinal plants – *C. longa*, *M. oleifera*, *O. aristatus*, and *C. asiatica* – as multi-target phytotherapeutics for preventing preeclampsia. Their cultural familiarity, biological plausibility, and accessibility make them compelling candidates for integration into maternal health programs, particularly in low-resource settings where preeclampsia burden is highest.

However, clinical translation remains limited by the lack of structured dosing, PK/PD profiling, and comprehensive maternal-fetal safety data. Future research must focus on translational science, mechanistic clarity, and rigorous interventional trials. Multidisciplinary collaboration and culturally sensitive implementation strategies will be key to ensuring safe, equitable, and evidence-based integration of these botanicals into maternal healthcare frameworks.

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