Review / Derleme

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Modulation of oxidative stress and angiogenic pathways by natural compounds in experimental preeclampsia: A narrative review focusing on MDA, sFlt-1, and PlGF

Deneysel preeklampsi modellerinde doğal bileşiklerin oksidatif stres ve anjiyojenik yolları modüle etmesi: MDA, sFlt-1 ve PlGF'ye odaklanan bir anlatımsal derleme

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Abstract

Objective: To synthesize current evidence on the effects of natural compounds on oxidative stress and angiogenic biomarkers, particularly malondialdehyde (MDA), soluble fms-like tyrosine kinase-1 (sFlt-1), and placental growth factor (PlGF), in experimental models of preeclampsia.

Materials and Methods: A narrative review was conducted of studies retrieved from PubMed, Scopus, ScienceDirect, and Web of Science (2016-2026). Experimental animal studies that evaluated natural compounds and reported outcomes related to MDA, sFlt-1, PlGF, or angiogenic pathways were included. Study quality was assessed descriptively using the Joanna Briggs Institute framework.

Results: Nine relevant experimental studies were included in the narrative synthesis. Interventions included *Astragalus* spp., pomegranate juice, young kopyor coconut water, soybean tempeh extract, *Cosmos caudatus* extract, *Nigella sativa*, *Puerariae lobatae* Radix, and olive leaf extract. Most interventions significantly reduced MDA and sFlt-1 levels, indicating reductions in oxidative stress and anti-angiogenic activity. Several compounds increased expression of PlGF and/or vascular endothelial growth factor, suggesting improved placental angiogenesis. Beneficial effects on placental morphology, blood pressure, proteinuria, and fetal outcomes were also reported.

Conclusion: Natural compounds may ameliorate oxidative stress and angiogenic imbalance in experimental models of preeclampsia by reducing MDA and sFlt-1 levels and enhancing PlGF-mediated angiogenesis. These findings support their potential as adjunctive therapies for preeclampsia, although further mechanistic studies and clinical trials are needed to confirm their efficacy and safety. As this narrative review is based exclusively on findings from experimental animal models, these results should be interpreted with caution and not be directly extrapolated to clinical practice until they are confirmed by human studies.

Keywords: Angiogenesis, malondialdehyde, natural compounds, PlGF, preeclampsia, sFlt-1

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Öz

Amaç: Deneysel preeklampsi modellerinde doğal bileşiklerin oksidatif stres ve anjiyojenik biyobelirteçler, özellikle malondialdehit (MDA), çözünür fms benzeri tirozin kinaz-1 (sFlt-1) ve plasental büyüme faktörü (PlGF) üzerindeki etkilerine ilişkin mevcut kanıtları sentezlemektir.

Gereç ve Yöntemler: PubMed, Scopus, ScienceDirect ve Web of Science'tan (2016-2026) elde edilen çalışmaların anlatımsal bir derlemesi yapıldı. Doğal bileşikleri değerlendiren ve MDA, sFlt-1, PlGF veya anjiyojenik yollarla ilgili sonuçları bildiren deneysel hayvan çalışmaları dahil edildi. Çalışma kalitesi, Joanna Briggs Enstitüsü çerçevesi kullanılarak tanımlayıcı olarak değerlendirilmiştir.

Bulgular: Anlatımsal senteze dokuz ilgili deneysel çalışma dahil edilmiştir. Müdahaleler arasında *Astragalus* spp., nar suyu, genç kopyor hindistan cevizi suyu, soya tempeh özü, *Cosmos caudatus* özü, *Nigella sativa*, *Puerariae lobatae* Radix ve zeytin yaprağı özü yer almıştır. Çoğu müdahalenin, MDA ve sFlt-1 seviyelerini önemli ölçüde azaltarak oksidatif stresi ve anti-anjiyojenik aktiviteyi azalttığı gösterilmiştir. Birkaç bileşiğin, PlGF ve/veya vasküler endotelyal büyüme faktörünün ekspresyonunu artırarak plasental anjiyogenezi iyileştirdiği düşünülmüştür. Plasental morfoloji, kan basıncı, proteinüri ve fetal sonuçlar üzerinde de faydalı etkiler bildirilmiştir.

Sonuç: Doğal bileşikler, MDA ve sFlt-1 seviyelerini azaltarak ve PlGF aracılı anjiyogenezi artırarak preeklampsi deneysel modellerinde oksidatif stresi ve anjiyojenik dengesizliği iyileştirebilir. Bu bulgular, preeklampsi için yardımcı tedaviler olarak potansiyellerini desteklemektedir, ancak etkinliklerini ve güvenliklerini doğrulamak için daha fazla mekanistik çalışma ve klinik denemeye ihtiyaç vardır. Bu anlatımsal derleme yalnızca deneysel hayvan modellerinden elde edilen bulgulara dayandığından, bu sonuçlar dikkatli bir şekilde yorumlanmalı ve insan çalışmalarıyla doğrulanana kadar doğrudan klinik uygulamaya aktarılmamalıdır.

Anahtar Kelimeler: Anjiyogenez, malondialdehit, doğal bileşikler, PlGF, preeklampsi, sFlt-1

Introduction

Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality, affecting approximately 2-8% of pregnancies worldwide and contributing to preterm birth, fetal growth restriction, and long-term cardiovascular complications in both mothers and offspring[1,2]. Because the only definitive treatment remains delivery of the placenta, there is an urgent need for adjunctive strategies that target the underlying pathophysiology while preserving maternal and fetal safety[3]. The pathogenesis of preeclampsia involves abnormal placentation, placental hypoperfusion, oxidative stress, and endothelial dysfunction[4]. Placental ischemia triggers excessive reactive oxygen species (ROS) production and the release of antiangiogenic factors, particularly soluble fms-like tyrosine kinase-1 (sFlt-1), along with alterations in proangiogenic factors such as placental growth factor (PlGF)[5-8]. Elevated sFlt-1 acts as a decoy receptor for vascular endothelial growth factor (VEGF) and PlGF, reducing angiogenic signaling and impairing endothelial integrity, while excessive ROS promotes lipid peroxidation reflected by increased malondialdehyde (MDA), a reliable marker of oxidative cellular damage[9-11].

This angiogenic imbalance—elevated sFlt-1 with reduced PlGF—together with oxidative stress is now regarded as a central, interconnected hallmark of preeclampsia, and the sFlt-1/PlGF ratio has become a valuable biomarker for diagnosis, prognosis, and disease monitoring[12-14]. MDA, sFlt-1, and PlGF were selected as the primary biomarkers for this review because they represent, respectively, the oxidative, antiangiogenic, and proangiogenic arms of this shared pathogenic pathway and are the outcomes most consistently reported across experimental preeclampsia studies, making cross-study comparison feasible. Because oxidative stress and angiogenic imbalance are closely interconnected, natural compounds with antioxidant, anti-inflammatory, and proangiogenic properties—rich in flavonoids, polyphenols, isoflavones, and other phytochemicals—have attracted growing interest as potential adjunctive therapies[15-17]. Recent studies using Nω-nitro-L-arginine methyl ester (L-NAME)-induced preeclamptic rodent models have reported that compounds such as *Astragalus* spp., pomegranate juice, soybean tempeh extract, olive leaf extract, *Cosmos caudatus*, *Nigella sativa*, *Puerariae lobatae* Radix, and young coconut water can modulate MDA, sFlt-1, and PlGF/VEGF levels and improve placental morphology, blood pressure, and fetal outcomes[5-11,16-19].

Despite this growing body of evidence, previous reviews have generally focused on antioxidant activity or herbal therapy in isolation, without integrating findings on oxidative stress biomarkers, antiangiogenic factors, and proangiogenic factors within a single framework; to date, no narrative review has specifically synthesized evidence on the effects of natural compounds on MDA, sFlt-1, and PlGF together, which represents the specific knowledge gap this review addresses[18,20]. This review therefore aims to synthesize current experimental evidence on how natural compounds influence these three biomarkers and their underlying molecular mechanisms, in order to clarify their therapeutic potential as adjunctive strategies for preeclampsia and to identify priorities for future translational and clinical research.

Materials and Methods

Study Design

This study was conducted as a narrative review to synthesize current evidence regarding the effects of natural compounds on oxidative stress, angiogenic biomarkers, and endothelial dysfunction in experimental preeclampsia models[21]. The review was developed following the principles of the Scale for the Assessment of Narrative Review Articles to

ensure methodological transparency, scientific rigor, and comprehensive reporting[22].

Although a structured and transparent search process, including predefined eligibility criteria and a systematic search strategy, was applied to reduce selection bias, this review does not include meta-analysis, dual independent screening, or a formal risk-of-bias synthesis, and should therefore be understood as a narrative review employing a systematic search component rather than a full systematic review.

Search Strategy

A comprehensive literature search was conducted to identify experimental studies that investigated the effects of natural compounds on oxidative stress, angiogenic biomarkers, and endothelial dysfunction in animal models of preeclampsia. Electronic databases, including PubMed, Scopus, ScienceDirect, and Web of Science, were systematically searched for articles published between January 2016 and March 2026. The search strategy combined medical subject headings (MeSH) and free text terms related to preeclampsia, natural compounds, oxidative stress, angiogenic biomarkers, and animal models. Boolean operators (AND, OR) were applied to maximize search sensitivity and specificity. Manual searches of reference lists from eligible studies were also performed to identify additional relevant articles. The literature search was conducted systematically to improve transparency; however, the review was synthesized narratively rather than following the full methodology of a systematic review. The complete search strategy, including databases, keywords, Boolean operators, and inclusion parameters, is summarized in Table 1.

The complete electronic search strategy applied to each database is provided to ensure transparency. The PubMed search string used was: ("preeclampsia"[MeSH] OR "pre-eclampsia") AND ("natural compounds" OR "phytochemicals" OR "plant extract" OR "antioxidants") AND ("oxidative stress" OR "malondialdehyde" OR "sFlt-1" OR "PlGF" OR "angiogenic") AND ("rat" OR "mice" OR "animal model").Equivalent field-tagged syntax, adapted to each platform's indexing structure, was applied to Scopus (TITLE-ABS-KEY), ScienceDirect, and Web of Science (topic search), using the same three concept blocks (condition AND intervention AND outcome or model) combined with the Boolean operators shown above.

Eligibility Criteria

Studies were included in this review if they fulfilled the following criteria:

1. Original experimental studies involving animal models of preeclampsia;
2. Studies investigating natural compounds, plant-derived bioactive substances, or natural antioxidants;
3. Articles evaluating at least one biomarker associated with oxidative stress or endothelial dysfunction, including sFlt-1, MDA, endothelial nitric oxide synthase (eNOS), VEGF, PlGF, NO, or inflammatory mediators;
4. Studies published in peer-reviewed journals;
5. Articles written in English.

Table 1. Literature search strategy

Component	Description
Study design	Narrative review focusing on the effects of natural compounds as adjuvant therapy for preeclampsia in experimental animal models
Databases used	PubMed, Scopus, ScienceDirect, and Web of Science
Search period	Articles published between 2016 and 2026 were included in the search process
Search approach	Systematic electronic database searching complemented by manual screening of reference lists
Keywords/MeSH terms	"Preeclampsia," "pre-eclampsia," "natural compounds," "natural products," "phytochemicals," "plant extracts," "antioxidants," "oxidative stress," "malondialdehyde," "MDA," "soluble fms-like tyrosine kinase-1," "sFlt-1," "placental growth factor," "PlGF," "angiogenic biomarkers," "endothelial dysfunction," "mice model," "rat model," and "experimental preeclampsia"
Boolean operators	Boolean operators "AND" and "OR" were applied to combine keywords and optimize database searching
Example search syntax	("preeclampsia" AND "natural compounds" AND "oxidative stress") OR ("sFlt-1" AND "MDA" AND "PlGF" AND "experimental preeclampsia")
Additional search method	Manual screening of reference lists from eligible studies was conducted to identify additional relevant articles
Language restriction	Only articles published in English were included
Study type included	Experimental animal studies involving mice or rat models of preeclampsia
Primary outcomes	Biomarker modulation including sFlt-1, MDA, PlGF, VEGF, nitric oxide, and oxidative stress indicators

MeSH: Medical subject headings, sFlt-1: Soluble fms-like tyrosine kinase-1, PlGF: Placental growth factor, MDA: Malondialdehyde, VEGF: Vascular endothelial growth factor

The exclusion criteria included:
1. Clinical studies involving human participants;
2. Review articles, conference abstracts, editorials, and case reports;
3. Studies without biomarker evaluation;
4. Articles with incomplete methodological descriptions or unavailable full text.

Study Selection Process

The study selection process was conducted in several stages. Initially, all retrieved articles were imported into a reference management system to identify and remove duplicate records[23]. Subsequently, titles and abstracts were screened according to the eligibility criteria. A full-text assessment was performed to determine final study inclusion. Studies considered relevant were further evaluated for methodological suitability and biomarker reporting consistency.

Data Extraction

Data extraction was performed using a modified Joanna Briggs Institute (JBI)-based extraction framework developed specifically for experimental preeclampsia studies. The extracted variables included author(s) and publication year; country of study; experimental animal model; method of preeclampsia induction; type of natural compound; dosage and intervention duration; biomarker outcomes (sFlt-1, MDA, PlGF, eNOS, VEGF, NO); laboratory examination methods; mechanistic pathways; and main findings and conclusions. The extraction framework was expanded to emphasize oxidative stress and angiogenic biomarkers in order to strengthen mechanistic interpretation across studies.

Quality Appraisal

Methodological quality assessment was conducted descriptively using the JBI critical appraisal framework for experimental studies. The appraisal considered study randomization, intervention consistency, outcome measurement reliability, biomarker assessment methods, and clarity of statistical analysis[24]. Quality assessment was performed to improve interpretative rigor and minimize potential bias in evidence synthesis.
The detailed results of the JBI appraisal for each included study are summarized in Table 1.1, rather than reported only as a general statement, to allow readers to assess the methodological strength underlying each biomarker finding.

Data Synthesis

Data synthesis was conducted narratively, through thematic grouping based on biomarker mechanisms and therapeutic effects of natural compounds. The findings were categorized into several major themes, including antioxidant activity, angiogenic modulation, endothelial protection, and anti-inflammatory mechanisms. A comparative analysis of studies was performed to identify patterns of biomarker changes associated with various natural compounds.

Ethical Consideration

Since this study was based exclusively on previously published literature and did not involve human participants or experimental animal interventions conducted by the authors, ethical approval was not required.

Table 1.1. Summary of Joanna Briggs Institute (JBI) critical appraisal results (JBI Critical Appraisal Checklist for Randomized Controlled Trials, 13 items)

Author (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	Yes/11	% Yes
Zhu et al.[5]	Y	U	U	NA	U	U	U	NA	Y	Y	Y	Y	Y	6/11	54.5%
Kerdsuknirund et al.[6]	U	U	Y	NA	U	U	U	NA	Y	Y	Y	Y	Y	6/11	54.5%
Yang et al.[8]	Y	U	U	NA	U	U	U	NA	Y	Y	Y	Y	Y	6/11	54.5%
Fitriana et al.[16]	Y	U	Y	NA	U	U	U	NA	Y	Y	Y	Y	Y	7/11	63.6%
Sulistianingsih et al.[11]	U	U	U	NA	U	U	U	NA	Y	Y	Y	Y	Y	5/11	45.5%
Kurniasari et al.[10]	Y	U	Y	NA	U	U	U	NA	Y	Y	Y	Y	Y	7/11	63.6%
Huang et al.[7]	Y	U	Y	NA	U	U	Y	NA	Y	Y	Y	Y	Y	8/11	72.7%
Marpaung et al.[17]	U	U	U	NA	U	U	U	NA	Y	Y	Y	Y	Y	5/11	45.5%
Anggraini et al.[9]	Y	U	U	NA	U	U	U	NA	Y	Y	Y	Y	Y	6/11	54.5%

JBI Checklist items for Randomized Controlled Trials: 1=true randomization used for group assignment; 2=allocation concealment; 3=treatment groups similar at baseline; 4=participants blind to treatment assignment; 5=those delivering treatment blind to assignment; 6=outcome assessors blind to assignment; 7=treatment groups treated identically other than the intervention; 8=follow-up complete/differences adequately described and analyzed; 9=participants analyzed in the groups to which they were randomized; 10=outcomes measured in the same way across groups; 11=outcomes measured in a reliable way; 12=appropriate statistical analysis used; 13=trial design appropriate for the topic, with deviations accounted for in analysis. Y=yes; U=unclear (not explicitly reported in the source article); NA=not applicable to the animal-experimental design of the included studies (items 4 and 8). The "Yes/11" and "% Yes" columns denote the proportion of applicable items (11 of 13; items 4 and 8 excluded) rated 'yes' for each study; these values summarize methodological quality for transparency and were not used as an exclusion criterion in this narrative review

Results

Characteristics of Included Studies

A total of 9 experimental studies investigating the effects of natural compounds on preeclampsia models were included in this narrative review. The studies were published between 2016 and 2026 and predominantly used rat and mouse models induced by lipopolysaccharide, reduced uterine perfusion pressure, NO synthase inhibition, and placental hypoxia. Most interventions involved plant-derived bioactive compounds with antioxidant, anti-inflammatory, and endothelial-protective properties.

The majority of the included studies evaluated oxidative stress biomarkers, particularly MDA, eNOS, and sFlt-1. Additional biomarkers included VEGF, PlGF, NO, tumor necrosis factor-alpha (TNF-α), and interleukin-6.

JBI-based Data Extraction of Included Studies

The detailed characteristics, interventions, and biomarker findings of each included study are presented in Table 2.

Across the nine included studies, all natural compounds demonstrated beneficial effects on key biomarkers associated with the pathophysiology of preeclampsia, particularly markers of angiogenic imbalance and oxidative stress. Most studies used L-NAME-induced preeclamptic rat models and evaluated biomarkers, such as sFlt-1, PlGF, MDA, ROS, and inflammatory mediators. Astragalus-based interventions consistently reduced circulating sFlt-1 levels, increased PlGF expression and were accompanied by reductions in oxidative stress markers, including MDA and ROS, as well as improvements in endothelial function and fetal outcomes. Similar findings were reported for pomegranate juice, soybean tempeh extract, *Cosmos caudatus* extract, *Nigella sativa*, olive leaf extract, and young kopyor coconut water, all of which significantly attenuated oxidative stress and decreased expression of antiangiogenic factors. Several interventions also improved placental morphology, renal function, blood pressure, and proteinuria. In addition, *Puerariae lobatae* Radix enhanced VEGF and PlGF expression, suggesting restoration of angiogenic signaling and placental vascular integrity. Overall, the findings indicate that natural compounds may exert protective effects in preeclampsia by reducing oxidative stress, suppressing sFlt-1 overexpression, restoring angiogenic balance, and improving maternal and fetal outcomes.

The included studies consistently demonstrated that natural compounds exert beneficial effects on both oxidative stress and angiogenic dysregulation, two central mechanisms in the pathogenesis of preeclampsia. Most interventions, including *Astragalus* injection, *Astragalus membranaceus*, soybean tempeh extract, *Cosmos caudatus* extract, olive leaf extract, pomegranate juice, and *Nigella sativa*, significantly reduced circulating sFlt-1 levels, indicating attenuation of anti-angiogenic activity. Several studies also have reported improvements in pro-angiogenic signaling, as evidenced by increased PlGF expression following administration of *Astragalus*-based therapies, and enhanced PlGF and/or VEGF expression after treatment with *Puerariae lobatae* Radix. Regarding oxidative stress, reductions in MDA and ROS levels were consistently observed, particularly following treatments with *Astragalus* injection, *Astragalus membranaceus*, soybean tempeh extract, *Cosmos caudatus* extract, and olive leaf extract. Furthermore, *Astragalus membranaceus* increased the activities of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), while the young kopyor coconut water reduced placental oxidative injury. Collectively, these findings suggest that natural compounds may ameliorate experimental preeclampsia through dual mechanisms involving suppression of oxidative stress and restoration of angiogenic balance, ultimately contributing to improved placental function and maternal-fetal outcomes. These integrated effects of natural compounds on oxidative stress and angiogenic biomarkers are summarized in Table 3.

Comparative Synthesis Across Studies

When compared across studies, most interventions were tested in L-NAME-induced Wistar or Sprague-Dawley rat models with treatment initiated in mid-to-late gestation (approximately GD 7-20), providing reasonable consistency in the experimental platform used to evaluate biomarker response. However, considerable heterogeneity was observed in dosage (ranging from 200 mg/kg BW to 2000 mg/kg BW), treatment duration, and the specific biomarker panel reported: MDA and sFlt-1 were assessed in the majority of studies, whereas PlGF was assessed in the studies by Zhu et al.[5], Yang et al.[8], and Huang et al.[7], whereas VEGF was assessed only in the study by Huang et al.[7]. Methodological detail also varied, with some studies [e.g., Zhu et al.[5], Sulistianingsih et al.[11]] reporting more comprehensive biomarker panels and statistical detail than others [e.g., Marpaung et al.[17]], which focused narrowly on inflammatory markers. This heterogeneity limits direct pooling of effect sizes across studies, but it does not undermine the qualitative consistency of the overall pattern: interventions that reduced oxidative stress markers also tended to reduce sFlt-1, which supports a shared upstream mechanism that links oxidative and antiangiogenic pathways across diverse natural compounds and experimental models.

Discussion

This narrative review synthesizes evidence from nine experimental studies investigating the effects of natural compounds on oxidative stress and angiogenic biomarkers in preeclampsia models. Rather than restating these findings in detail here, the sections below focus on interpreting their biological plausibility, critically comparing evidence across studies, and outlining the resulting limitations-in line with the Results section presented above.

Oxidative Stress Biomarkers

Oxidative stress is recognized as a central mechanism in the development of preeclampsia[1]. Inadequate trophoblast invasion and impaired spiral artery remodeling result in placental ischemia and hypoxia, leading to excessive production of ROS[25]. This process promotes lipid peroxidation and cellular injury, reflected by increased MDA concentrations[26].

In the present review, most studies reported significant reductions in MDA following administration of Astragalus spp., soybean tempeh extract, Cosmos caudatus extract, olive leaf extract, and young kopyor coconut water[5,8-11,16]. These findings suggest that natural compounds effectively mitigate oxidative damage in preeclamptic pregnancies.

Table 2. Characteristics and biomarker findings of included experimental studies

Author (year)	Experimental model	Natural compound	Dose and duration	Biomarkers assessed	Main biomarker findings
Zhu et al.[5]	L-NAME-induced preeclamptic Sprague-Dawley rats	Astragalus injection	0.024 mL/g BW/ day during PE induction	sFlt-1, PlGF, MDA, ROS, NO	Decreased sFlt-1, MDA, and ROS; increased PlGF and NO; improved angiogenesis and endothelial function
Kerdsuknirund et al.[6]	L-NAME-induced pregnant rats	Pomegranate juice	Low-, medium-, and high-dose administration (GD 7-20)	sFlt-1, placental histology	Reduced sFlt-1, blood pressure, and proteinuria; improved placental morphology in a dose-dependent manner
Yang et al.[8]	L-NAME-induced preeclamptic rats	*Astragalus membranaceus*	Oral administration during PE induction	sFlt-1, PlGF, MDA, SOD, GSH-Px	Reduced sFlt-1 and MDA; increased PlGF and antioxidant enzyme activity; improved fetal outcomes
Fitriana et al.[16]	Early-onset preeclampsia rat model induced by L-NAME	Young kopyor coconut water	2-3 mL/200 g BW (GD 4-19)	Oxidative stress markers, eNOS	Reduced placental hypoxia and oxidative stress; increased eNOS expression and vascularization
Sulistianingsih et al.[11]	L-NAME-induced Sprague-Dawley rats	Soybean tempeh extract	400 mg/kg BW/day	MDA, sFlt-1, NT-proBNP, Angiotensin II	Significantly reduced MDA and sFlt-1; improved cardiovascular function, placental health, and fetal outcomes
Kurniasari et al.[10]	L-NAME-induced preeclamptic rats	*Cosmos caudatus* (Kenikir) extract	200 mg/kg BW	MDA, IL-6, sFlt-1	Reduced MDA, IL-6, and sFlt-1; improved renal function and reduced glomerulosclerosis
Huang et al.[7]	L-NAME-induced preeclamptic rats	*Puerariae lobatae* Radix	Puerarin-equivalent 72 mg/kg BW	VEGF, PlGF	Increased VEGF and PlGF expression; improved placental barrier integrity and reduced hypertension
Marpaung et al.[17]	Preeclamptic pregnant rat model	*Nigella sativa*	500 and 2000 mg/ kg BW	TNF-α, IL-2, sFlt-1	Significantly reduced inflammatory cytokines and sFlt-1 expression
Anggraini et al.[9]	L-NAME-induced Wistar rat model	OLE	200 mg/kg BW alone or combined with nifedipine (GD 7-20)	MDA, sFlt-1, NGAL, creatinine	Markedly reduced MDA and sFlt-1; improved renal function, proteinuria, and blood pressure

L-NAME: Nω-nitro-L-arginine methyl ester, BW: Body weight, PE: Preeclampsia, GD: Gestational day, sFlt-1: Soluble fms-like tyrosine kinase-1, PlGF: Placental growth factor, MDA: Malondialdehyde, ROS: Reactive oxygen species, NO: Nitric oxide, SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase, eNOS: Endothelial nitric oxide synthase, NT-proBNP: N-terminal pro-B-type natriuretic peptide, IL: Interleukin, VEGF: Vascular endothelial growth factor, TNF-α: Tumor necrosis factor-alpha, OLE: Olive leaf extract, NGAL: Neutrophil gelatinase-associated lipocalin

Oxidative stress ↓ → MDA ↓

The observed antioxidant effects are consistent with previous experimental and clinical studies demonstrating that phytochemicals rich in flavonoids, polyphenols, and phenolic acids enhance endogenous antioxidant defenses[27]. Polyphenolic compounds can directly scavenge ROS while simultaneously activating antioxidant enzymes such as SOD, catalase, and GSH-Px[28]. Notably, Astragalus membranaceus increased both SOD and GSH-Px activities, supporting the hypothesis that natural compounds exert protective effects through activation of cellular antioxidant systems[8]. These findings align with current theories suggesting that a reduction in oxidative stress may interrupt the progression from placental ischemia to systemic endothelial and vascular injury in preeclampsia.

Angiogenic Biomarkers: sFlt-1

Angiogenic imbalance is considered a hallmark of preeclampsia[29]. Elevated sFlt-1 acts as a circulating anti-angiogenic factor by binding VEGF and PlGF, thereby limiting their biological activity[30]. Excessive sFlt-1 production contributes to placental vascular dysfunction, maternal hypertension, and proteinuria.

sFlt-1 ↓ → VEGF ↑

Most studies included in this review demonstrated significant reductions in sFlt-1 following treatment with *Astragalus* spp., pomegranate juice, soybean tempeh extract, *Cosmos caudatus*, olive leaf extract, and *Nigella sativa*[5,6,8-11,17]. These findings are consistent with previous reports showing that anti-inflammatory and antioxidant interventions may suppress placental sFlt-1 release under hypoxic conditions. Experimental evidence suggests that oxidative stress and inflammatory mediators such as TNF-α stimulate sFlt-1 production; therefore, reduction of oxidative and inflammatory signaling may indirectly restore angiogenic balance. The consistent decrease in sFlt-1 observed across studies supports the potential role of natural compounds in targeting one of the key molecular drivers of preeclampsia.

PlGF Pathway and Placental Angiogenesis

PlGF is a critical regulator of placental angiogenesis and vascular development[31]. Reduced circulating PlGF is frequently observed in women with preeclampsia and is associated with impaired placental perfusion and adverse pregnancy outcomes. In this review, *Astragalus* spp. and

Table 3. Integrated effects of natural compounds on oxidative stress and angiogenic biomarkers in experimental preeclampsia models

Natural compound	Oxidative stress biomarkers (MDA/ROS)	Anti-angiogenic marker (sFlt-1)	Pro-angiogenic marker (PlGF/VEGF)	Overall biological effect
Astragalus injection	↓ MDA, ↓ ROS	↓ sFlt-1	↑ PlGF	Reduced oxidative stress and restored angiogenic balance
Astragalus membranaceus	↓ MDA, ↑ SOD, ↑ GSH-Px	↓ sFlt-1	↑ PlGF	Enhanced antioxidant capacity and placental angiogenesis
Young kopyor coconut water	Reduced placental oxidative injury	Not assessed	Not assessed	Reduced oxidative damage in placental tissue
Soybean tempeh extract	↓ MDA	↓ sFlt-1	Not assessed	Improved oxidative status and angiogenic profile
Cosmos caudatus extract	↓ MDA, ↓ IL-6	↓ sFlt-1	Not assessed	Antioxidant and anti-inflammatory effects
Olive leaf extract	↓ MDA	↓ sFlt-1	Not assessed	Reduced oxidative stress and anti-angiogenic activity
Pomegranate juice	Beneficial effect on oxidative stress-related parameters	↓ sFlt-1	Not assessed	Improved placental health and angiogenic regulation
Nigella sativa	Reduced inflammatory-oxidative response (↓ TNF-α, ↓ IL-2)	↓ sFlt-1	Not assessed	Modulated inflammation and angiogenic imbalance
Puerariae lobatae Radix	Not directly assessed	Not reported	↑ PlGF, ↑ VEGF	Enhanced placental angiogenesis and vascular development
Overall findings	**Consistent reduction in MDA and oxidative stress-related markers**	**Consistent reduction in sFlt-1 levels**	**Increased PlGF and/or VEGF expression in studies evaluating angiogenic pathways**	**Natural compounds improved oxidative balance and angiogenic regulation in experimental preeclampsia**

MDA: Malondialdehyde, ROS: Reactive oxygen species, sFlt-1: Soluble fms-like tyrosine kinase-1, PlGF: Placental growth factor, VEGF: Vascular endothelial growth factor, SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha

Puerariae lobatae Radix significantly increased PlGF expression, while *Puerariae lobatae* Radix also enhanced VEGF levels[5,7]. These findings indicate restoration of pro-angiogenic signaling pathways that are typically suppressed in preeclampsia.

PlGF ↑ → Placental Angiogenesis ↑

The observed increase in PlGF is biologically plausible because several plant-derived bioactive compounds have been shown to improve placental vascular remodeling through modulation of hypoxia-related and angiogenic signaling pathways[32]. Increased PlGF availability may counteract the anti-angiogenic effects of sFlt-1, thereby promoting endothelial cell proliferation, vascular growth, and placental perfusion. Similar findings have been reported in experimental studies demonstrating that restoration of the VEGF-PlGF axis improves placental development and reduces disease severity[29]. Therefore, enhancement of PlGF-mediated angiogenesis represents a promising therapeutic mechanism through which natural compounds may improve maternal and fetal outcomes.

Mechanisms of Natural Compounds in Preeclampsia

The findings of this review, as illustrated in Figure 1, suggest that oxidative stress and angiogenic imbalance are closely interrelated in the pathogenesis of preeclampsia. Placental ischemia stimulates ROS production, which subsequently increases inflammatory signaling and the release of anti-angiogenic factors. Elevated sFlt-1 further suppresses PlGF and/or VEGF activity, resulting in impaired placental vascularization and disease progression. The natural compounds evaluated in this review appear to interrupt this pathogenic cascade at multiple levels by reducing oxidative stress, suppressing sFlt-1 production, and enhancing pro-angiogenic signaling. Such multimodal actions may explain the consistent therapeutic benefits observed across experimental studies.

Critical Synthesis and Translational Considerations

Beyond the overall pattern of biomarker improvement, important differences across studies deserve critical consideration. Compounds evaluated in shorter-duration, later-gestation models (e.g., pomegranate juice, olive leaf extract) predominantly produced reductions in blood pressure and sFlt-1 without directly assessing PlGF or VEGF; by contrast, compounds tested with a broader biomarker panel and earlier intervention (e.g., *Astragalus* spp., *Puerariae lobatae* Radix) provided more complete evidence of pro-angiogenic restoration. This suggests that the apparent consistency of benefit across natural compounds may partly

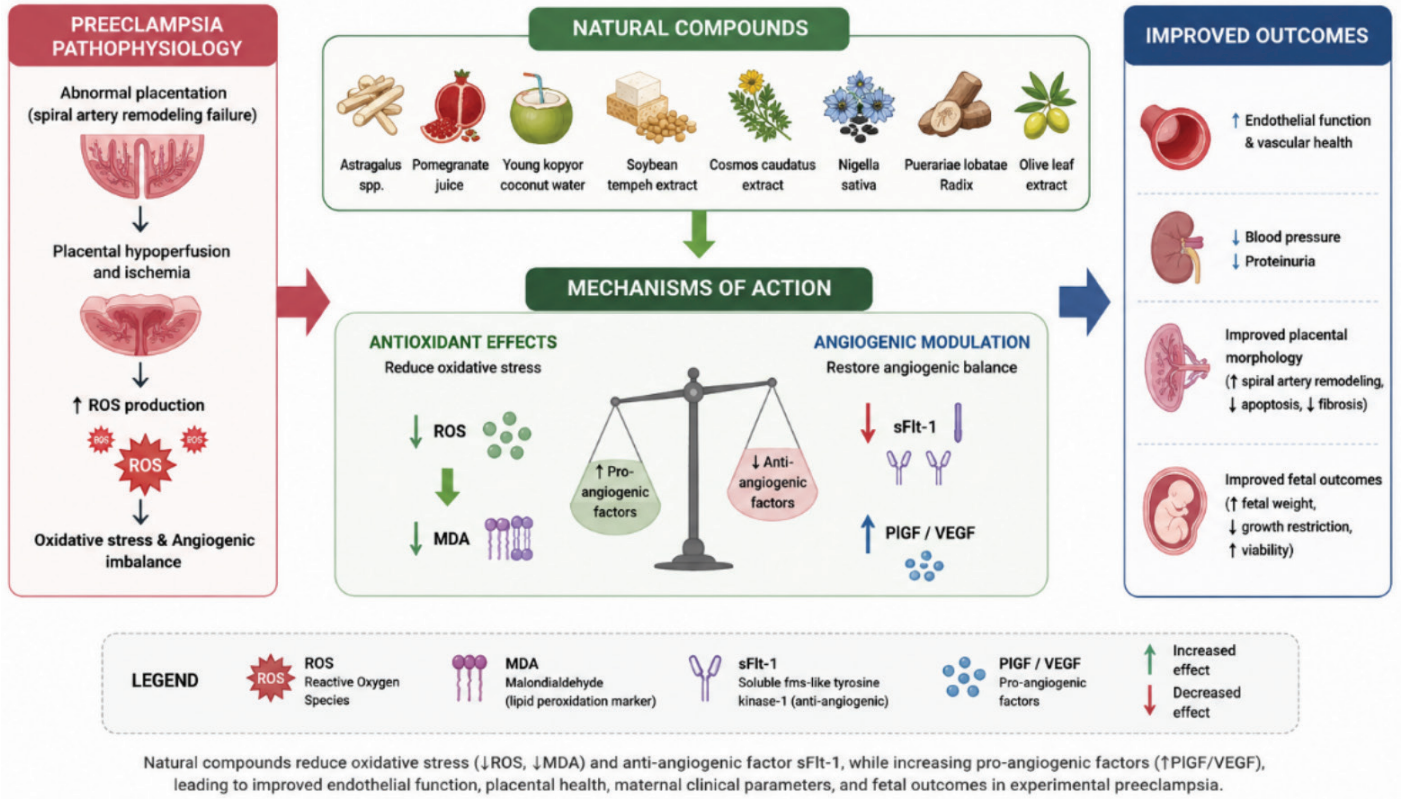

Figure 1. Mechanisms of natural compounds in preeclampsia

MDA: Malondialdehyde, ROS: Reactive oxygen species, sFlt-1: Soluble fms-like tyrosine kinase-1, PlGF: Placental growth factor, VEGF: Vascular endothelial growth factor

reflect differences in the biomarkers measured, rather than uniformly equivalent biological efficacy. Moreover, because L-NAME-induced hypertension models primarily reflect NO deficiency rather than the immunological and trophoblastic abnormalities underlying human preeclampsia, mechanistic conclusions drawn from this model should be extrapolated to human disease with caution.

Future Directions

Future research should focus on standardizing experimental protocols, including animal models, intervention dosages, and biomarker measurements. Additional studies are needed to investigate the effects of natural compounds on PlGF signaling and other angiogenic pathways because evidence in this area remains limited. Furthermore, mechanistic studies exploring molecular targets such as Nrf2/Keap1, HIF-1α, VEGF/PlGF signaling, and inflammatory pathways may provide deeper insights into therapeutic mechanisms. Ultimately, well-designed clinical trials are required to determine whether the promising findings observed in experimental models can be translated into safe and effective adjunctive therapies for women with preeclampsia.

Study Limitations

Several limitations should be considered when interpreting these findings. First, all included studies were conducted in animal models, the majority using L-NAME-induced preeclampsia models, which may not fully replicate the complexity of preeclampsia in humans. Second, substantial heterogeneity existed in intervention types, dosages, treatment durations, and biomarker assessment methods. Third, only a limited number of studies evaluated PlGF directly, whereas MDA and sFlt-1 were assessed more frequently. Finally, differences in experimental design and reporting standards limited direct comparison across studies.

Because only English-language articles were included and no formal assessment of publication bias was performed, language bias and selective reporting of predominantly positive findings cannot be excluded. As with any narrative review, study selection and interpretation may also carry a degree of subjectivity that is not fully mitigated by the structured search strategy employed. Most importantly, none of the included studies evaluated these natural compounds in human pregnancies; the complete absence of clinical-phase data constitutes a major factor limiting the strength and clinical applicability of the conclusions drawn from this review.

Conclusion

This narrative review synthesized evidence from nine experimental studies evaluating the effects of natural compounds on oxidative stress and angiogenic biomarkers in preeclampsia models. The findings consistently demonstrated that natural compounds attenuated oxidative stress by reducing MDA levels and enhancing endogenous antioxidant defenses. In addition, most interventions significantly decreased sFlt-1, a key anti-angiogenic factor implicated in the pathogenesis of preeclampsia. Several compounds, particularly *Astragalus* spp. and *Puerariae lobatae* Radix, also increased the expression of PlGF and/or VEGF, indicating restoration of pro-angiogenic signaling pathways and improvement in placental vascular development. Collectively, these findings suggest that natural compounds may target multiple interconnected mechanisms underlying preeclampsia, including oxidative stress, angiogenic imbalance, and placental dysfunction. The simultaneous reduction of MDA and sFlt-1, together with enhancement of PlGF-mediated angiogenesis, highlights their potential as adjuvant therapies for preeclampsia. However, the current evidence is limited to experimental animal studies with considerable methodological heterogeneity. Therefore, further mechanistic investigations and well-designed clinical trials are required to validate the efficacy, safety, optimal dosage, and translational applicability of these natural compounds in human pregnancies complicated by preeclampsia.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A.P., N.P., Concept: N.A.P., S.S., D.H.H., Design: N.A.P., N.P., S.S., D.H.H., Data Collection or Processing: N.A.P., Analysis or Interpretation: N.A.P., N.P., S.S., D.H.H., Literature Search: N.A.P., Writing: N.A.P., N.P., S.S., D.H.H.

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References

1. Santulli G, Kansakar U, Varzideh F. Epidemiology and pathophysiology of preeclampsia: new mechanistic insights. Hypertension. 2025;82:800-3.
2. Martini C, Saeed Z, Simeone P, Palma S, Ricci M, Arata A, et al. Preeclampsia: insights into pathophysiological mechanisms and preventive strategies. Am J Prev Cardiol. 2025;23:101054.
3. Mészáros B, Kukor Z, Valent S. Recent advances in the prevention and screening of preeclampsia. J Clin Med. 2023;12:6020.
4. Torres-Torres J, Espino-Y-Sosa S, Martinez-Portilla R, Borboa-Olivares H, Estrada-Gutierrez G, Acevedo-Gallegos S, et al. A narrative review on the pathophysiology of preeclampsia. Int J Mol Sci. 2024;25:7569.
5. Zhu Q, Wu X, Long Q, Liu R. Mechanism of astragalus injection to relieve symptoms of preeclampsia rat model by inhibiting MMP-9/sFlt-1/TNF-α. Altern Ther Health Med. 2023;29:125-31.

6. Kerdsuknirund S, Thaeomor A, Kupittayanant P, Khunkaewla P, Chanlun S, Srisawat R, et al. Pomegranate juice alleviates preeclampsia symptoms in an L-NAME-induced rat model: a dose-dependent study. Nutrients. 2025;17:1143.
7. Huang L, Liu Z, Wu P, Yue X, Lian Z, He P, et al. *Puerariae lobatae* radix alleviates pre-eclampsia by remodeling gut microbiota and protecting the gut and placental barriers. Nutrients. 2022;14:5025.
8. Yang L, Hao H, Zhang X, Ren X, Xu M, Zhang N, et al. The protective influence of Astragalus on rat models of preeclampsia. PLoS One. 2025;20:e0337583.
9. Anggraini Y, Soetrisno S, Wasita B, Cilmiaty R. Effects of olive leaf extract and nifedipine, alone and in combination, on blood pressure, neutrophil gelatinase-associated lipocalin, malondialdehyde, and creatinine levels in an Nω-nitro-L-arginine methyl ester-induced rat model of preeclampsia. Pharmacia. 2024;71:1-11.
10. Kurniasari D, Soetrisno S, Prayitno A, Wasita B, Dirgahayu P, Cilmiaty R, et al. Effects of Kenikir (*C. caudatus Kunth*) extract on biomarker and renal functionin apreeclamptic rat model study. Trends Sci. 2026;23:11792.
11. Sulistianingsih A, Soetrisno, Prayitno A, Cilmiaty R, Wasita B, Widyaningsih V, et al. Soybean tempeh extract on improving oxidative stress, angiogenic, cardiovascular dysfunction, and fetal outcome in arat model of preeclampsia. Trends Sci. 2026;23:11240.
12. Tătaru-Copos A, Huniadi AC, Negrini RG, Popescu MI, Trif P, Murvai GF, et al. sFlt-1/PlGF ratio as a central biomarker for preeclampsia and perinatal outcomes: a multisystem retrospective cohort study. J Clin Med. 2026;15:1990.
13. Irby MN, Hsu CD, Winget V, Srinivasan SA, Goyal R. Present status of sFLT1 and PlGF as diagnostic and therapeutic targets for preeclampsia. J Matern Fetal Neonatal Med. 2026;39:2648178.
14. Junaid MAL. Oxidative stress and nutrient imbalance in pre-eclampsia: the roles of homocysteine and vitamin B12. J Pioneer Med Sci. 2025;14:108-14.
15. Altanam SY, Darwish N, Bakillah A. Exploring the interplay of antioxidants, inflammation, and oxidative stress: mechanisms, therapeutic potential, and clinical implications. Diseases. 2025;13:309.
16. Fitriana F, Sulistyowati S, Indarto D, Soetrisno S, Nurwati I, Widyaningsih V. Effect of kopyor coconut water on early-onset preeclampsia-like impairments in rats induced by L-nitro-arginine methyl ester. Pharmacia. 2024;71:1-11.
17. Marpaung J, Siregar MFG, Sitepu M, Bachtiar A. Black cumin (Nigella sativa) effect on expression of TNF-α, IL-2, and sFlt-1 IN preeclamptic model rats. Int J Curr Pharm Res. 2020;12:78-86.
18. Fitriana F, Soetrisno S, Sulistyowati S, Indarto D. Evaluation of placental bed uterine in L-NAME-induced early-onset preeclampsia (EO-PE) like the rat model. Turk J Obstet Gynecol. 2024;21:180-9.
19. Li Pomi F, Gammeri L, Borgia F, Di Gioacchino M, Gangemi S. Oxidative stress and skin diseases: the role of lipid peroxidation. Antioxidants. 2025;14:555.
20. Jaisankar D, Ramamoorthy S, Ramasamy J. Therapeutic potential of flavonoid-enriched Chinese medicinal herbs in atherosclerosis, hypertension, myocardial infarction, and heart failure. Pharmacol Res Mod Chin Med. 2025;17:100701.
21. Gregory AT, Denniss AR. An introduction to writing narrative and systematic reviews - tasks, tips and traps for aspiring authors. Heart Lung Circ. 2018;27:893-8.
22. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5.
23. Hammer B, Virgili E, Bilotta F. Evidence-based literature review: de-duplication a cornerstone for quality. World J Methodol. 2023;13:390-8.
24. Hilton M. JBI critical appraisal checklist for systematic reviews and research syntheses (product review). J Can Health Libr Assoc. 2024;45.
25. Laskowska M, Bednarek A, Stworowski M. The etiopathogenesis of preeclampsia: where do we stand now? J Clin Med. 2025;14:7992.
26. Haro Girón S, Monserrat Sanz J, Ortega MA, Garcia-Montero C, Fraile-Martínez O, Gómez-Lahoz AM, et al. Prognostic value of malondialdehyde (MDA) in the temporal progression of chronic spinal cord injury. J Pers Med. 2023;13:626.
27. Ahmad Z, Rauf A, Orhan IE, Mubarak MS, Akram Z, Islam MR, et al. Antioxidant potential of polyphenolic compounds, sources, extraction, purification and characterization techniques: a focused review. Food Sci Nutr. 2025;13:e71259.
28. Buenfil-Chi TJ, Mercado-Uribe H, Sierra-Valdez FJ. ROS-specific neutralization of bioactive compounds: an optical approach. ACS Omega. 2025;10:26857-70.
29. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. Am J Obstet Gynecol. 2022;226:S1019-34.
30. Papapanagiotou A, Daskalaki MA, Gargalionis AN, Margoni A, Domali A, Daskalakis G, et al. The role of angiogenetic factors in preeclampsia. Int J Mol Sci. 2025;26:10431.
31. Bolunduț AC, Mureşan XM, Sufleţel RT, Mocan LP, Pîrv S, Şuşman S, et al. Placental pathology and placental growth factor (PlGF)/vascular endothelial growth factor receptor-1 (VEGFR-1) pathway expression evaluation in fetal congenital heart defects. Life (Basel). 2025;15:837.
32. Warrington JP, Palei AT, Cunningham MW, Amaral LM, editors. The pathophysiology of preeclampsia and eclampsia. Basel: MDPI; 2023.