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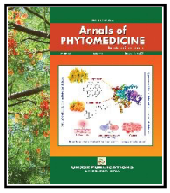

Original Article : Open Access

Natural therapeutic agent *Asparagus racemosus* (Willd.) ameliorates oxidative stress and sterile inflammation through TLR4/NF-κB interaction in pre-eclampsia

Sheema Wazib, Yashesvi Ambardar, Sayeed Ahmad*, Sher Afghan, Huma Quasimi and Md. Iqbal Alam◆

Department of Physiology, Hamdard Institute of Medical Sciences and Research, New Delhi-110062, India
**Department of Pharmacognosy and Phytochemistry, Jamia Hamdard, NewDelhi-110062, India*

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Abstract

Pre-eclampsia (PE) is a severe pregnancy complication characterised by hypertension and proteinuria, leading to significant maternal and neonatal risks. Its complex pathophysiology, involving reduced nitric oxide (NO) levels and heightened inflammation, makes treatment challenging. This study explores the potential of *Asparagus racemosus* Willd. (AR), commonly known as Shatavari, in modulating NO levels and alleviating PE-related complications. An N (G)-Nitro-l-arginine methyl ester (L-NAME)-induced PE model was used to assess key cardiovascular parameters, including systolic and diastolic blood pressure, mean arterial pressure, and heart rate on gestational day 20. ELISA was performed to quantify reactive oxygen species (ROS), NO levels, and inflammatory markers (NF-κB, TLR4 in plasma and vWF in plasma and placental tissues). Phytochemical analysis of AR extract was conducted using thin-layer chromatography (TLC) and high-performance thin-layer chromatography (HPTLC). L-NAME induced a significant increase in blood pressure, ROS and inflammatory markers and a decrease in NO levels in the PE model, indicating systemic inflammation and oxidative stress. Elevated levels of NF-κB, TLR4 and vWF were observed in both plasma and placental tissue of PE, which were significantly corrected by AR treatment ($p<0.05$). TLC analysis confirmed the presence of saponins, glycosides, and phenolic compounds in AR extract, supporting its antioxidant and anti-inflammatory potential. PE is driven by oxidative stress, inflammation, and vascular dysfunction. This study highlights the therapeutic potential of *A. racemosus* in mitigating these pathological changes, making it a promising candidate for PE management.

1. Introduction

A pregnancy complication known as pre-eclampsia (PE) is represented by elevated blood pressure and indications of harm to other organ systems, most frequently the kidneys and liver (Liberis *et al.*, 2016). This syndrome affects 3% to 14% of pregnancies globally and 5% to 8% worldwide. PE kills approximately 76,000 maternal and 500,000 fetuses annually (Khan *et al*., 2006). The onset of hypertension confirms the condition during the latter half of pregnancy and the presence of protein in the urine. Furthermore, fetal growth restriction is a method to diagnose pre-eclampsia; in the absence of proteinuria, new-onset liver dysfunction, the brain, kidneys, red blood cellsand platelets are used to analyze the condition. HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) is a severe sign of pre-eclampsia that is linked to higher risks of maternal morbidity and mortality (Committee on Practice Bulletins-Obstetrics, 2019; Lowe *et al.*, 2009 ; Brown *et al.*, 2018). Pre-eclampsia is a high-risk medical condition that disproportionately affects disadvantaged regions worldwide. While the specific causes may differ, research suggests that pre-eclampsia is linked to other conditions such as obesity, nulliparity, having several pregnancies, or having a family history of pre-eclampsia (Washington *et al.*, 2018). Despite extensive and prolonged study efforts, the cause of pre-eclampsia is still obscure; its underlying mechanisms are yet to be understood and require further investigation and intervention. The existing understanding affirms that the main pathological event is the impairment of the structure and function of the endothelial cells during the development of the placental blood vessels at the time of implantation (Kudo *et al.*, 2003). The complex aetiology and potential for catastrophic consequences of pre-eclampsia make it a significant concern in obstetrics. A wide variety of maternal characteristics and preexisting diseases can be considered risk factors. There is a need for further research to enhance early identification and management methods to treat pre-eclampsia, as the predictive accuracy of the established biomarkers and risk variables is different (Kim *et al*., 2013; Andrew and Patel, 2016). The process of a normal pregnancy is characterised by a set of consecutive chronological events, which include inflammation during implantation, inflammation during gestation, and inflammation during parturition. Maternal uterine endometrial signals facilitate the infiltration of fetaltrophoblasts into the uterine decidua during the implantation process (Cheng and Sharma, 2016). For the mother to accept the fetal trophoblast as a semi-allogeneic product, she must recognize the newly emerging embryo as an immunological “self”. This assumes the primary function of the mother’s innate immune system (Goldman-Wohl; Yagel, 2009; Madhukaran *et al.*, 2016; Redman and Sargent, 2008). Disturbances at this stage may enhance pre-eclampsia risk and explain its higher prevalence in women with unexplained subfertility or recurrent miscarriage (Trogstad *et al.*, 2009). Symptoms of pre-eclampsia typically subside following

Corresponding author: Dr. Md. Iqbal Alam
Professor and Head, Department of Physiology, Hamdard Institute of Medical Sciences and Research, New Delhi-110062, India
E-mail: iqbalasc@yahoo.com
Tel.: +91-9953971178

delivery, which is the only "cure" for the condition.India is a hub for traditional medicine, with Ayurveda, Unani and Siddha offering diverse treatments. There is a growing need for standardized, effective herbal drugs, requiring advanced analysis and evaluation of medicinal plants.

In Indian traditional medicine, *Asparagus adscendens*, *Chlorophytum arundinaceum* and AR are used to treat immunological diseases linked to stress and to improve overall health. The results indicate that these plants may aid in the management of stress and inflammatory disorders. Kanwar and Bhutani (2010) conducted and investigation to assess the effectiveness of some plant infusions in acting as potential antioxidants for obstetrics by studying their interactions with free radicals. *A. racemosus*, specifically its roots, are utilized to treat women who have inflammation in their genital organs, hormonal imbalances, premenstrual syndrome, polycystic ovary syndrome, infertility, a higher chance of miscarriage, and menopause (Alok *et al.*, 2013; Pandey *et al.*, 2018). In Ayurveda, *A. racemosus* is classified as a "rasayana," recognized for its adaptogenic characteristics that assist the body in acclimating to various stressors (Rajni *et al.,* 2023). Shatavari is a term that means "one who has a having 100 husbands has been considered acceptable by many." It is regarded as both a general tonic and a tonic for the female reproductive system. Shatavari can be translated as "hundred spouses," suggesting its capacity to enhance fertility and life. In Ayurveda, this herb is referred to as the "Queen of herbs" because of its ability to enhance feelings of love and devotion. This herb is extremely efficient in addressing issues about female reproduction (Sharma and Dash, 2003; Atreya, 1999). Additionally, plant-derived compounds continue to be a valuable resource in modern pharmacology, helping to create novel and efficient therapies for a range of health issues. Phytocons-tituents isolated from *A. racemosus* exhibits significant pharmacolo-gical properties, as shown in Table 1.

Table 1: Phytoconstituents and their respective biological effects

S. No.	Phytoconstituents of *A. racemosus*	Biological activities	References
1.	Racemosol and rhamnose	Antiparkinosonian	Smita *et al.*, 2017
2.	Sarsasapogenin	Neuroprotective	Bagchi *et al.*, 2017
3.	Racemofuran, racemosol and sparagamine A	Anti-amyloidogenic	Kashyap *et al.*, 2020
4.	Flavonoids	Antioxidant	Wiboonpun *et al.*, 2004
5.	Asparoside-C, and asparagamine-F	Antiepileptic	Shastry *et al.*, 2015
6.	Shatavarin IV	Anticancer	Mitra *et al.*, 2012
7.	2 → 1 linked fructo-oligosaccharides	Immunomodulatory	Thakur *et al.*, 2012

Shatavari is the primary rejuvenating tonic in Ayurveda for females, whereas Withania is the equivalent tonic for males (Rathore and Karkare, 2021). *A. racemosus,* a member of the family Asparagaceae, is commonly referred to as Shatavari. It is a widely recognized medicinal plant in Ayurveda and is particularly helpful in the treatment of disorders like internal heat, seet-veeryam, somrogam, Madhurrasam, Madhurvipakam, and chronic fever (Gogte, 2000; Frawley, 1997). The Charak Samhita, authored by Charak, and the Ashtang Hridyam, authored by Vagbhata, are the primary writings on Ayurvedic medicine. *A. racemosus* is an ingredient and the formulae used to treat women's health disorders (Srikantha, 1997). AR is a widely recognized Ayurvedic rasayana that serves to slow the ageing process, grows longer life, strengthens the immune system, enhances cognitive performance, increases vigor, and gives the body more vitality. Additionally, it is utilized in the treatment of neurological diseases, dyspepsia, tumours, inflammation, neuropathy, and hepatopathy (Sharma, 2001). A study of ancient classical Ayurvedic literature has identified many therapeutic properties associated with the root of AR. It has been specifically advised for cases of impending abortion and as a galactagogue. The root of AR possesses numerous properties, such as being bitter-sweet, cooling, a nervine tonic, constipating, galactagogue, aphrodisiac, diuretic, rejuvenating, carminative, stomachic and antibacterial. It may be useful for treating mental disorders, indigestion, diarrhea, dysentery, tumors, inflammation, excessive thirst, neuropathy, liver disorders, cough, bronchitis, hyperacidity, and infectious diseases. This study summarises the pharmacological characteristics of AR root extract studied and published. *A. racemosus* has steroidal saponins (Shatavarins I-IV) as its main active ingredient in the roots. Shatavarin IV inhibits Core-2 GlcNAc-transferase in cell-free experiments and modulates particular immunocompromised animals' T-dependent antigens (Kamat *et al.*, 2000). In summary, AR is a plant with significant medicinal value, supported by various bioactive compounds. Despite its widespread traditional use, further scientific research is necessary to substantiate some of the claimed health benefits. Conservation strategies are critical to ensure the sustainability of this valuable species (Kohli *et al.*, 2023). However, the plant was found safe during pregnancy and lactation (Bhandary *et al.*, 2017). Considering these factors, the present study evaluated whether the plant extract of *A. racemosus* might improve the pathophysiology of pre-eclampsia. We observed hemodynamic parameters, inflammation response, angiogenic factors and pregnancy outcomes in an L-NAME-induced animal model of PE with or without treatment of *A. racemosus*.

Additionally, thin layer chromatography (TLC) plays a key role in separating herbal components, aiding in the identification of bioactive compounds. High-performance, thin-layer chromatography (HPTLC) is an advanced method used for compound analysis, quality control and adulterant detection. It allows simultaneous analysis of multiple samples with minimal solvent use, making it an efficient technique for quantifying chemical constituents in extracts. In the present study, HPTLC was employed to analyze the phytochemical composition of *A. racemosus* extract, ensuring standardization and purity of the bioactive components.

Based on these considerations, the present study evaluated whether *A. racemosus* extract could improve the pathophysiology of pre-

eclampsia. We examined hemodynamic parameters, inflammatory responses, oxidative stress markers and pregnancy outcomes in an L-NAME-induced animal model of PE, with and without *A. racemosus* treatment.

2. Materials and Methods

2.1 Animals

Healthy Wistar rats (Female) weighing 180-210 g (10-12 weeks) were obtained from Hamdard University's central animal house in New Delhi. Each cage contained four rats. The animals were kept in polypropylene cages. The study was performed in the Department of Physiology, Central Research Lab, HIMSR. Every experiment was conducted in compliance with the guidelines set forth by the Institutional Animal Ethics Committee (IAEC) after obtaining approval from the IAEC of Jamia Hamdard with Protocol Number 2077. Healthy malewistar rats were obtained for mating (mating ratio = 2 female: 1 male) and were kept at 22 ± 3°C is the room temperature, with a 12 h light/dark cycle and examined then ext morning for the vaginal plug. The pregnancy was confirmed after the detection of the presence of sperm in vaginal smears. The day on which sperm was detected was designated as gestational day 0 (GD 0) (Yugesh *et al.*, 2023). They had free access to water and food *ad libitum*. After confirmation of pregnancy, eachrat was weighed and placed in an individual metabolic cage after randomizing into groups. An animal model of PE was developed using N(G)-Nitro-l-arginine methyl ester (L-NAME) at a dose of 125 mg/kg/day, subcutaneously (s.c.) (Quasimi *et al.*, 2024 ; Zhu *et al.*, 2017). Our study aimed to investigate the medicinal effect of plant *A. racemosus* protection against L-NAME induced PE animal model, while different doses were examined to assess the regulatory pathways and their interactions. Following perfusion, organs were harvested. After being separated from the blood by centrifugation at 3500 rpm, the plasma was kept at -20°C until it was needed. Following collection, one portion of the placenta and heart was immediately snap-frozen in nitrogen gas until it could be processed further, while the other portion was preserved in 10% formalin so that it could be sectioned for additional examination.

2.2 Treatment groups and surgical procedure

After the development of the animal model and issuance of animals, four groups of seven rats each were created from the rats. Group I (Pregnant control; PC) animals were on at constituent pellet diet and water *ad libitum*. Group II (PE) consisted of pregnant rats that were given a normal pellet diet and L-NAME (125 mg/kg/day, subcutaneously (s.c.) from days 13 to 20 of pregnancy. Group III (PE + labetolol) included pregnant rats fed a normal pellet diet along with L-NAME (Catalog No. # N5751-25G, Switzerland) and labetalol 3 mg/kg (Catalog No # L1011- 5G, Sigma ALDRICH, USA) from days 13 to 20 and Group IV (PE +*A. racemosus*) animals were fed a normal pellet diet, administered L-NAME, and treated with *A. racemosus* (200 mg/kg/day) from the 14th day until delivery.

2.3 Plant source

The roots of *A. racemosus* (Shatavari) were procured from Universal Biotech, Lal Kuan, and verified by a taxonomist at the Department of Botany, Jamia Hamdard, New Delhi, India. The Voucher Specimen HIMSR/PHY/2024/003 number has been taken and the sample is preserved for future reference. The roots were thoroughly washed with water, shade-dried for eight days until completely moisture-free, and then pulverized for further analysis.

2.4 Preparation of methanolic extract

Methanolic extract preparation: 500 ml of methanol was used to extract 30 g of powdered *A. racemosus* throughout 12 cycles. In a vacuum, the extracts were put through a Rotary evaporator (R-300, Büchi, Switzerland), and the solvent was eliminated until the extracts were dry (50°C, 218 mbar) (Pandiyan *et al.*, 2022). Then, the different doses of *A. racemosus* were standardized in our lab.The prepared extract was standardized by screening and chromatographic fingerprinting analysis concerning the methods reported by Rab *et al.* (2020); Parveen *et al.* (2019). Initial screening for phytochemicals of methonolic extract revealed the saponins, steroidal glycosides, phenols, and flavonoids as a major components, which have already been reported by *A. racemosus* (Zafar *et al.*, 2004).

2.5 Standardization using TLC and HPTLC

Chromatographic fingerprinting was performed using TLC on a silica gel G plate (Merck) for the separation of phytochemicals. The chromatographic process utilised asolvent mixture of toluene, ethyl acetate and formic acid (TEF). The methanolic extract was analysed using both TLC and HPTLC to obtain a detailed phytochemical profile. A silica gel G plate was used as the stationary phase and multiple distinct peaks were identified. The developed chromatographic spots were visualized under UV light at different wavelengths using an image documentation system (Kinco, Prolite DX, Aetron). To further confirm the presence of bioactive compounds, derivatization was performed, and the plate was treated with anisaldehyde reagent for chemical identification, as depicted in Figure 1.

2.6 Assessment of ECG

Rats in all groups received an intraperitoneal injection of a ketamine (75 mg/kg) and xylazine (10 mg/kg) cocktail to induce anaesthesia on the twentieth day of the experiment. The rats were then monitored by electrocardiography (ECG) recording. Each rat's front paw and hind leg dermal layers were fitted with ECG leads, which were then connected to the PowerLab Data Acquisition System (Chart 5.4.2, AD Instruments, Australia) to record the ECG for heart rate (HR) evaluation.

2.7 Measurement of hemodynamic parameters

On the same day after ECG recording, a polyethene catheter was inserted into the femoral artery or carotid artery and connected to a transducer for pressure (MLT0699-DC-06A) connected to a Power Lab Data Acquisition System (Lab Chart, version 8.1.8, AD Instruments, Colorado Springs, CO, USA) for measuring blood pressure (BP) levels. From the BP recording, the systolic, diastolic and mean blood pressure were analysed.

2.8 Preparation of tissue lysate

The target tissue placenta was dissected with sterile instruments on ice as rapidly as possible to avoid protease degradation and stored in microcentrifuge tubes with a circular bottom at -80 degrees Celsius. All placentas from each pregnant mother were included in the analysis. However, there were no significant variations between the intraplacental data within the group; the average of all intraplacental samples was calculated and used to represent each pregnant mother of a specific study group.Weighing was done on the frozen samples and for every 100 mg tissue sample, 1 ml of ice-cold Radio immuno precipitation assay buffer (RIPA buffer) (Lysis and Extraction Buffer

from Thermo Scientific, Catalog No # 89900),After adding 1µl of 100X Protease Inhibitor cocktail (PIC) (Sigma, Catalog No. P8849-1ML USA) and 0.5 ml of Phenyl Methane Sulfonyl Fluoride PMSF (Sigma, Catalog No. 329-98-6, USA), the mixture was homogenized using an electric homogenizer. Following homogenization, the prepared tissue lysate was centrifuged for 20 min at 4°C and 12,000 rpm. After being aspirated, the supernatant was moved to another tube that was kept on ice. In accordance with the manufacturer's instructions, this lysate was further processed for the enzyme-linked immunosorbent assay (ELISA).

2.9 Estimation of NO levels and oxidative stress markers

To evaluate the nitrosative and oxidative stress in PE, we performed ELISA markers such as nitric oxide (no) levels, assessment of lipid peroxidation by malondialdehyde (MDA) and superoxide dismutase enzyme (SOD) in the plasma and the tissue lysates of the placenta. Markers were done by using ELISA for MDA (Catalog No #: KTE100650, USA), superoxide dismutase (SOD) (Catalog No #: KTE101023, USA) and Nitric Oxide (NO) (Catalog No #: E-BC-K035-5, USA). The ELISA kits were obtained from R and D Elabsciences in the USA, and they were utilized following the manufacturer's directions.

2.10 Inflammatory markers

To determine the expression of inflammatory markers like NF-κB, ELISA was used (Catalog No # E-EL-R0674, USA), TLR4 (Catalog No # FN240329, USA) in plasma samples and vWF (Catalog No #: E-EL-R1079, USA) in both plasma and placental tissue. The ELISA kits were sourced from R and D elabsciences (USA) and were used in accordance with the manufacturer's instructions. These kits were designed to identify rat antibodies in the samples tested and no significant cross-reactivity or interference with analogous antibodies was observed.

2.11 Statistical analysis

GraphPad Prism, version 9 (GraphPad Software, LLC, San Diego, CA, USA), was used for drawing bar graphs and group data of hemodynamics, oxidative stress and inflammatory cytokines markers. The mean ± SEM was used to express the data. Tukey's test was used to determine the statistical significance. Every test had two tails. *p<0.05 were considered significant, and 95% confidence intervals were computed.

3. Results

3.1 Phytochemical screening of *A. racemosus*

On performing TLC using a Silica gel Gplate, yielding three distinct spots with Rf values of 0.35, 0.46 and 0.88. These spots were visualized under an image documentation system (Kinco, Prolite DX, Aetron) at 365 nm and 254 nm in manual mode. To confirm the presence of these compounds, the plate was further analyzed after derivatization by spraying with anisaldehyde reagent. Based on their Rf values, the identified phytochemicals indicate the potential antioxidant activity of the *A.racemosus* extract (Selvaraj *et al.*, 2019).

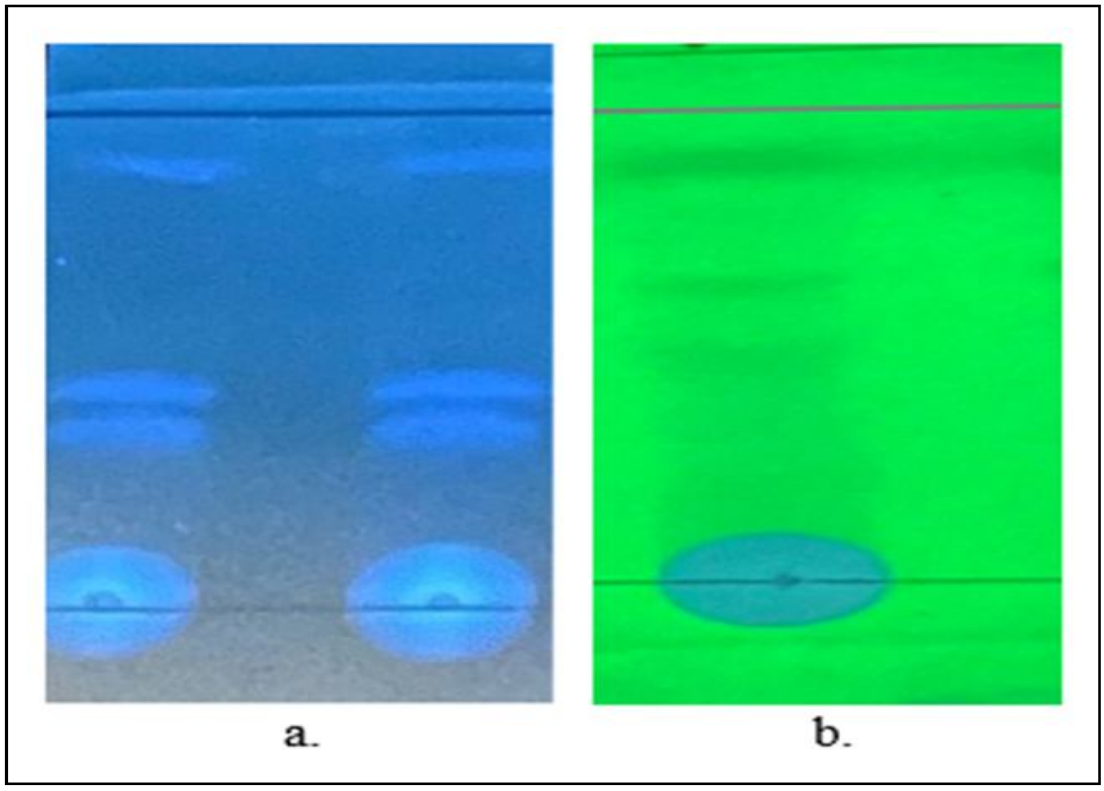

Figure 1: TLC analysis of *A. racemosus* root extract. (a) Visualisation under 365 nm UV light showing fluorescent phytochemicals. (b) Visualisation under 254 nm UV light highlights UV-absorbing compounds.

3.2 Determination of active phytochemicals in methanolic extract of *A. Racemosus*

Phytochemical analysis of *A. racemosus* methanolic extract revealed by HPTLC, showed bioactive compounds, including flavonoids, saponins, glycosides, phenolic compounds, and Shatavarin IV or kaempferol glycosides, as shown in Figure 2. These phytochemicals are well known for antioxidant, anti-inflammatory and vascular-protective properties, which may contribute to the therapeutic potential of AR. Their presence underscores the pharmacological significance of *A. racemosus*, highlighting its potential role in supporting endothelial function and maintaining vascular health, particularly in conditions such as pre-eclampsia.

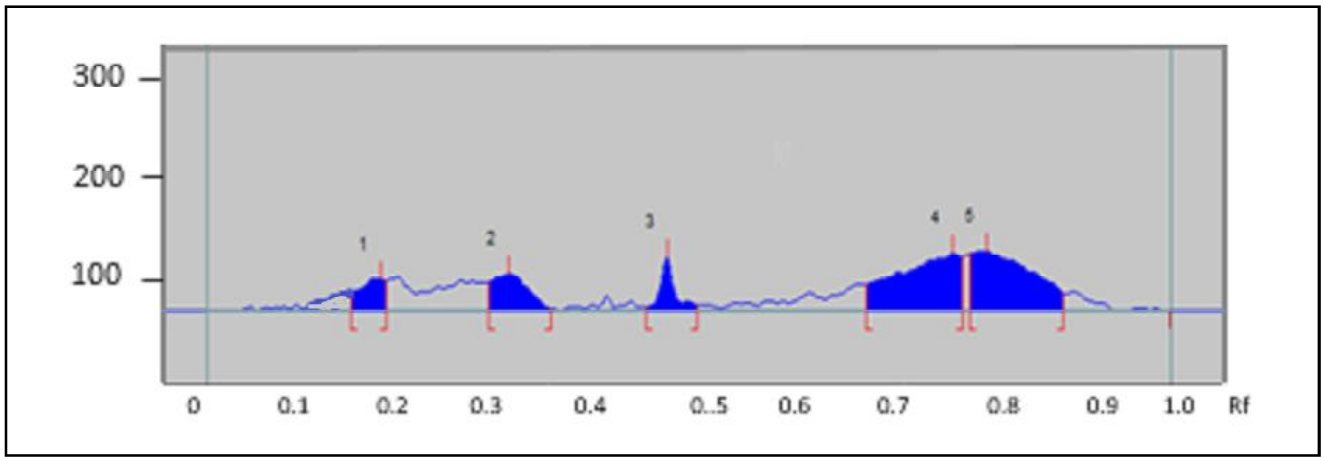

Figure 2: This high-performance, thin-layer chromatography (HPTLC) densitogram represents the separation of compounds based on their Rf (retention factor). The x-axis shows the Rf values (0.0-1.0), and the y-axis represents intensity. Peaks indicate detected compounds, with their heights corresponding to concentration.

The phytochemical analysis identified flavonoids, saponins, glycosides, phenolic compounds, and Shatavarin IV or kaempferol glycosides. These results suggest that the extract of *A.racemosus* may possess antioxidant properties, as depicted in Table 2.

Table 2: Represents the active phytochemical compounds with their assigned Rf values in *A. racemosus* methanolic extract

Peak No.	Rf values	Peak area	Assigned substances
1.	0.19	365.5	Flavonoids
2.	0.35	575.9	Saponins
3.	0.46	341.9	Glycosides
4.	0.73	1030.4	Phenolic compounds
5.	0.79	1559.3	Shatavarin IV or kaempferol glycosides

Table 3: Weight gain at parturition (g) in the Pregnant control (PC), Pre-eclampsia (PE), PE + labetolol (PEL), and PE + *A. racemosus* (PET) groups was analysed, fetal weight (g), crown-to-rump length (CRL) of the fetuses (cm), birth defects (%), fetal mortality (%), intrauterine growth restriction (IUGR) (%), proteinuria (mg/day), and maternal weight on gestational day 0 (g). For each group of seven animals, the data are shown as Mean ± SEM

S.No.	Phenotype	Pregnant control (PC)	Pre-eclampsia (PE)	PE + labetolol (PEL)	PE + AR (PET)
1.	Fetal weight (g)	7.6 ± 0.12	3.2 ± 0.22*	8.1 ± 0.1**	8.67 ± 0.23**
2.	CRL (cm)	5.60 ± 0.01	2.63 ± 0.12**	4.83 ± 0.4*	4.92 ± 0.01*
3.	Birth defect (%)	No defect	2.0 ± 0.5**	0.4 ± 0.4*	0.3 ± 0.4*
4.	Fetalmortality (%)	No mortality	2.6 ± 0.52	No mortality	No mortality
5.	IUGR (%)	No IUGR	40.5 ± 4.3	No IUGR	No IUGR
6.	Proteinuria (mg/day)	59.1 ± 1.12	120.8 ± 1.77*	66.3 ± 73*	62.32 ± 4.7*
7.	Weight on GD 0 (g)	205 ± 1.5	203 ± 2.8	207 ± 2.1	205 ± 1.8
8.	Weight gain at parturition (g)	33 ± 2.35	20.2 ± 3.12*	36 ± 1.5*	37 ± 0.55*

Statistical significance between the groups represented as *p significant at 5% probability and **p significant at 1% probability.

3.3 Characteristics of pups

The number of fetuses has been shown graphically. The pups across all four groups were normal; however, developmental abnormalities and mortality rates wereelevated significantly in the PE group (2 ± 0.57) compared to the PC group (0.0 ± 0.0). Moreover, there was a notable reduction in the rate of fetal abnormalities when pregnant female wistar rats were administered with AR (PET; 0.33 ± 0.21), as depicted in Figure 3.

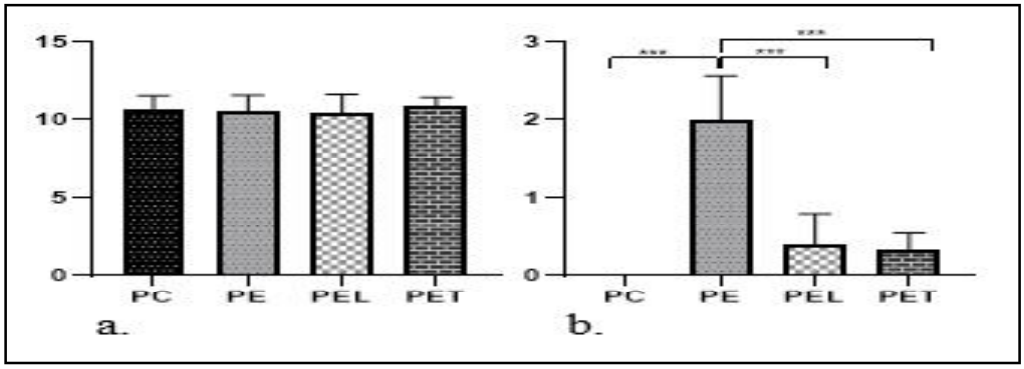

Figure 3: The bar graph shows a. number of fetuses, while ano-ther graph b. shows the num-ber of abnormal fetuses. The comparison was conducted across various groups (each group comprising 7 rats). The data was expressed as mean ± standard error of the Mean. A one-way analysis of variance (ANOVA) followed by Tukey's test revealed significant differences in abnormalities between the pre-eclampsia (PE) and Pregnant control (PC) groups (*p<0.05). Although some abnormalities were seen in the Pre-eclampsia + Labetalol (PEL) and Pre-eclampsia Treatment (PET) groups, these diffe-rences were not statistically significant compared to the PC group.

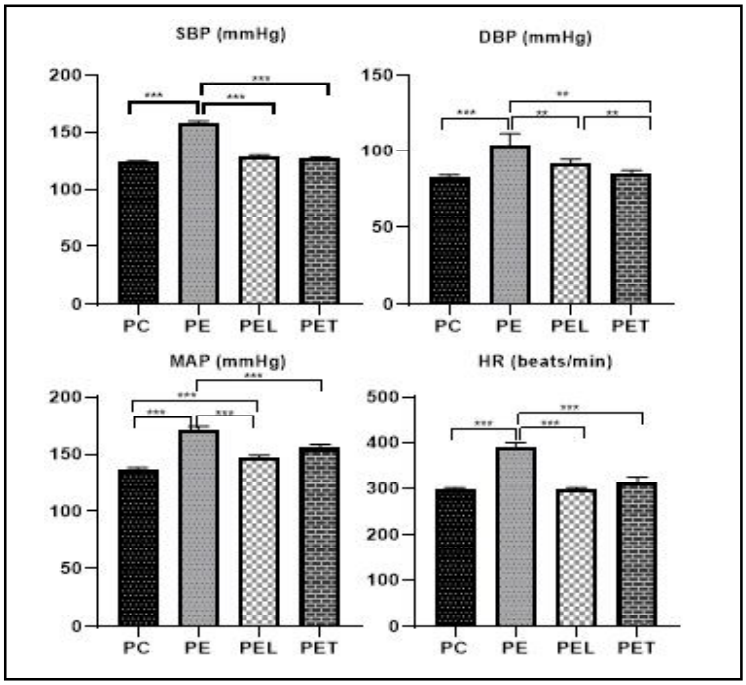

Figure 4: Hemodynamic parameter changes in the test and control groups (each consisting of seven rats). (a) SBP, or systolic blood pressure. (b) DBP, or diastolic blood pressure. (c) MAP, or mean arterial pressure. (d) HR, or heart rate. The mean ± standard error of the mean is how the data are displayed. The groups differed significantly according to one-way analysis of variance (ANOVA) and Tukey's test. When compared to PC and PEL (Pre-eclampsia + labetalol groups), there was a notable decline in the AR-treated PE (pre-eclampsia) treatment group. Statistical significance in the data among the group is shown as *p<0.05, **p<0.01 and *** p<0.001.

3.4 Hemodynamics

All hemodynamic parameters were notably elevated, as indicated by the significantly higher blood pressure in the PE group ($p^*< 0.05$) (SBP; 157 ± 2.2, DBP; 103 ± 3.24, and MAP; 171 ± 2.309) and (HR; 390 ± 9.24) as compared to Pregnant control (SBP; 123 ± 1.20, DBP; 82.67 ± 0.71, and MAP; 137 ± 1.5) and (HR; 297 ± 4.3). Treatment with AR in PE rats, *i.e.,* PET group (SBP; 126 ± 0.9, DBP; 85.1 ± 0.83, and MAP; 155.3 ± 3.29) and (HR; 314.5 ± 11.81) significantly improved the increased blood pressure as compared to study group treated with standard drug labetalol, *i.e.,* PEL group (SBP; 128.7 ± 0.98, DBP; 91.83 ± 1.1, MAP; 147.4 ± 2.06) and (HR; 297 ± 4.29) as shown in Figure 4.

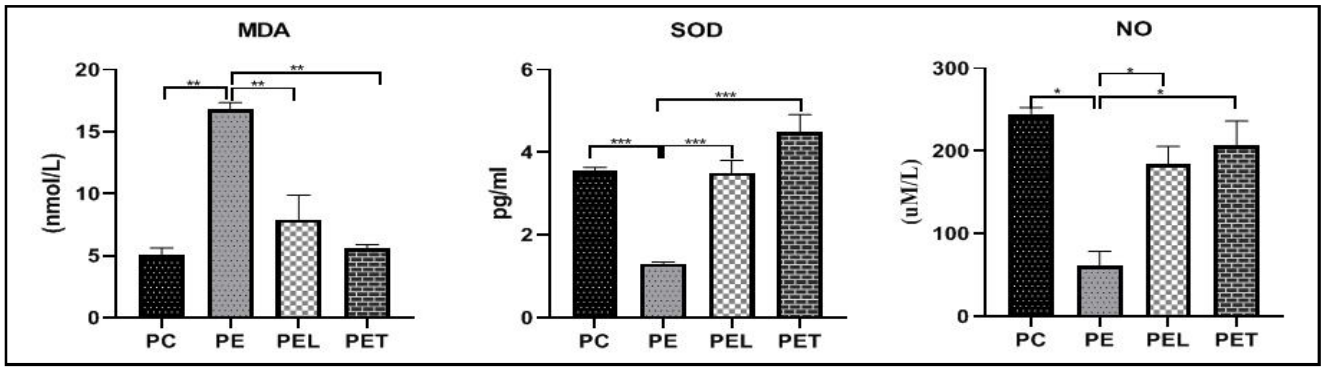

Figure 5: **In all the groups (7 each) oxidative stress level was evaluated in plasma. Malondialdehyde (MDA), superoxide dismutase (SOD), and nitric oxide (NO) levels were the three parameters that were measured. The data is represented as mean ± standard error of the mean (SEM). Significant differences between the groups were revealed by one-way analysis of variance (ANOVA) and Tukey's test. Statistical significance in the data among the group as *p<0.05, **p<0.01, ***p<0.001.**

3.5 Oxidative stress

In PE, there was a significant increase in plasma MDA (16.81 ± 0.54 vs. 5.05 ± 0.58) and significant decrease in SOD (1.31 ± 0.03 vs. 3.55 ± 0.07) and NO (61.7 ± 17 vs. 243 ± 9.01) levels in comparison to PC group. These results reflect a state of oxidative stress in PE rats. Treatment with AR (PET) significantly decreased plasma MDA (5.60 ± 0.30); significantly increased SOD (4.49 ± 0.416) and NO (207.4 ± 28.92) levels as compared to PE group.

Additionally, we compared the effect of AR treatment (PET) with standard drug labetalol, *i.e.,* PEL group (MDA; 7.935 ± 1.969, SOD; 3.505 ± 0.3076 and (NO; 184.6 ± 21.08) levels.These results indicate that due to reduced NO levels in pre-eclampsia, it exhibits vaso constriction, which leads to an increase in blood pressure shown in Figure 4.

3.6 Placental tissue oxidative stress

MDA and SOD levels in placental tissue samples significantly increased and NO levels significantly decreased in PE compared to PC and PEL groups, which is consistent with our findings in plasma. According to these findings, PE rats are experiencing oxidative stress. AR treatment significantly reduced plasma MDA levels.

Table 4: **The table presents the effects of pre-eclampsia and treatments on oxidative stress markers and antioxidants in different groups of pregnant rats in placental tissue. Malondialdehyde (MDA), a marker of lipid peroxidation, was significantly elevated in the PE group compared to the pregnant control group. Treatment with AR (PET) reduced MDA levels. Superoxide dismutase (SOD), an antioxidant enzyme, was decreased in the pre-eclampsia group compared to the control. AR treatment slightly increased SOD levels. Nitric oxide (NO) levels, essential for vascular function, were significantly lower in the pre-eclampsia group than in the control group. Treatment with AR increased NO levels. Values are expressed as mean ± standard error of the Mean (SEM).**

Markers	Pregnant control (PC)	Pre-eclampsia (PE)	PE + labetolol (PEL)	PE+AR (PET)
MDA	62.06 ± 0.18	157 ± 5.36**	79.8 ± 19.9*	54.6 ± 0.3*
SOD	3.702 ± 0.10	1.49 ± 0.06**	3.36 ± 0.630**	3.91 ± 0.42**
NO	312.4 ± 23.15	85.8 ± 12.81*	229 ± 33.8	239 ± 24.26*

Statistical significance between the groups represented as *p significant at 5% probability and **p significant at 1% probability.

3.7 Inflammatory markers

Pro-inflammatory cytokine vWF in plasma (2.27 ± 0.25) and placental tissue (2.9 ± 0.21)was significantly elevated (**p<0.001) in PE groups compared to PC plasma (1.04 ± 0.07) and placenta (1.37 ± 0.30). After treatment with AR, vWF levels reduced significantly (**p<0.001), reaching levels comparable to those PET (1.24 ± 0.35); plasma and 1.41 ± 0.31); placenta and PEL (1.05 ± 0.28); plasma and (1.55 ± 0.40); placental group, thus confirming the anti-inflammatory effects of vWF.

Similar to the vWF response in plasma of PE rats, the NF-κB (500.5 ± 0.35) and TLR4 (2.23 ± 0.33) levels were also increased significantly compared to PC group-NF-κB (110.6 ± 4.041) and TLR4 (0.833 ± 0.033). Treatment with AR in PE rats (PET) significantly reduced the levels of both NF-κB (135.7 ± 2.133) and TLR4 (0.93 ± 0.066) when compared to PE rats, as shown below in Figures 7a and b, respectively.

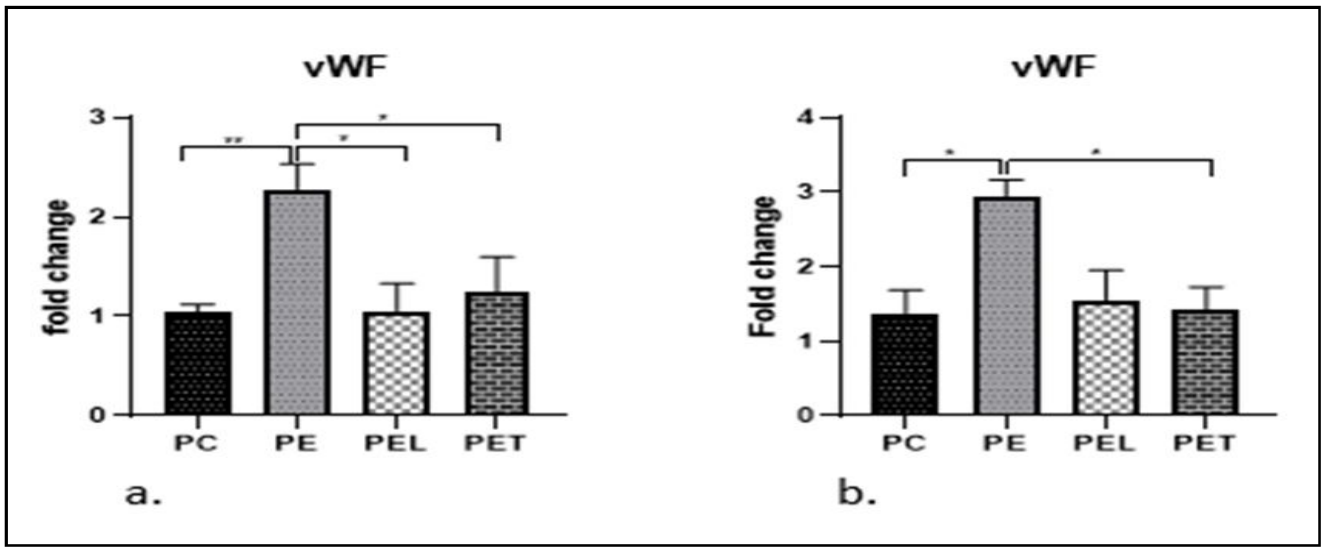

Figure 6: Expression of inflammatory cytokinesin plasma and placental samples collected after each treatment. Each group included 7 rats:a.vWF (Von Willebrand factor) in plasma and b. placenta. The data, shown as mean ± standard error of the Mean (SEM), were obtained from one experiment representative of four independent experiments performed in triplicate. One-way analysis of variance (ANOVA), followed by Tukey's test, revealed significant differences.

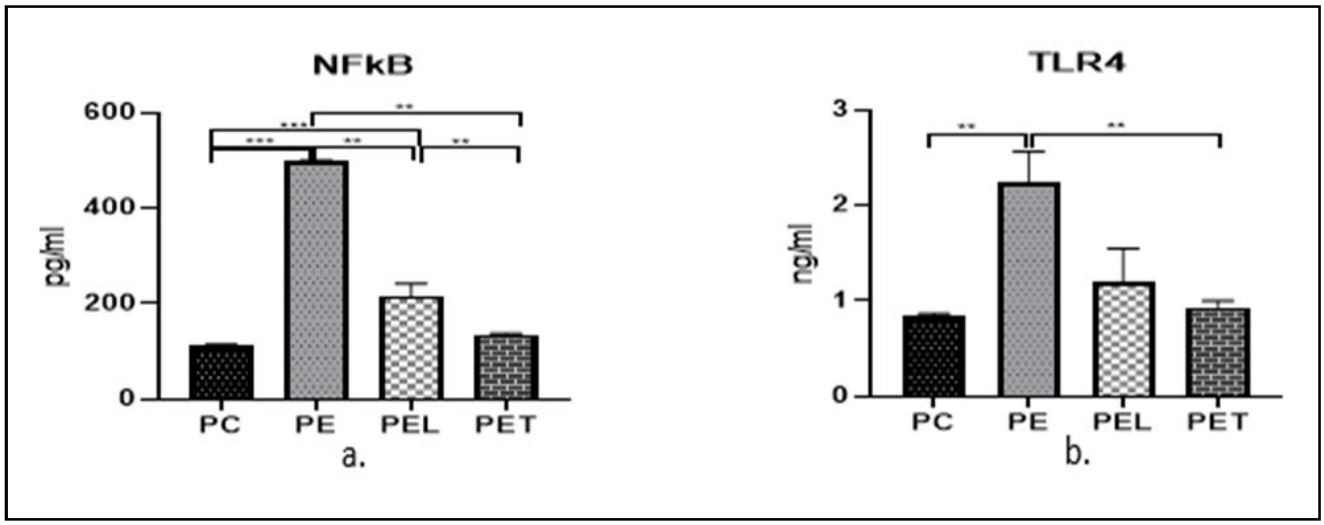

Figure 7: Expression of inflammatory a. NF-κB (nuclear factor kappa beta cell) and b. TLR4 (Toll-like receptor 4) in the plasma sample these results further confirm the anti-inflammatory effects of *A. racemosus*. The data, shown as mean ± standard error of the Mean (SEM), were obtained from one experiment representative of four independent experiments, all performed in triplicate. One-way analysis of variance (ANOVA), followed by Tukey's test, revealed significant differences.

4. Discussion

Herbal extracts are extensively researched for their medicinal properties, including anti-inflammatory, antimicrobial, and antioxidant activities, making them valuable for drug development. Our study highlights the crucial potential of *A. racemosus* as a natural therapeutic agent for mitigating the intricate interactions of various factors associated with pre-eclampsia. The findings suggest that AR could be a promising intervention for managing PE as it effectively reduces blood pressure, decreases oxidative stress and ameliorates inflammation while simultaneously enhancing endothelial function through increased nitric oxide (NO) levels. PE is a multi-faceted condition characterized by increased blood pressure, reduced NO levels, oxidative stress, and heightened inflammation (Palanisamy and Manian, 2012). On chromatographic analysis of crude *A. racemosus* extract, we determined the bands for assigned phytochemicals at Rf values of 0.35, 0.46 and 0.88 in the prepared AR methonolic root extract. According to Selvaraj *et al.* (2019), Saponins glycosides and phenolic substances present in *A. racemosus* are responsible for its antioxidant potential, as shown in figure 1 (Karimi *et al.*, 2024). Chromatographic profiling using thin-layer chromatography (TLC) and high-performance thin-layer chromatography (HPTLC) identified the presence of saponins, glycosides, and phenolic compounds in the *A. racemosus* extract, highlighting its potential antioxidant and anti-inflammatory properties. The HPTLC analysis displayed distinct peaks at Rf values of 0.19, 0.35, 0.46, 0.73 and 0.79, as illustrated in Figure 2,

confirming the presence of bioactive constituents within the extract. In this study, we observed the demographic data of the fetus and mother at the time of parturition, as shown in Table 3 and Figure 3. In previous literature, it has been well documented that among the most serious pregnancy problems, PE is a major contributor to maternal and neonatal morbidity and mortality (Poon *et al.*, 2019). Fetal growth stillbirth represents an important cause of fetal loss in late preterm infants. Increased perinatal mortality has been linked to pregnancies complicated by intrauterine growth restriction (IUGR), which is a pathological process of decreased fetal growth in PE (Backes *et al.*, 2011). The results are similar to our results in the animal model of PE but the novelty of our study is that we introduced AR in PE group and found improvement in crown-rump length, fetal weight, number of pups, fetal mortality rate, fetal birth defect incidence, intrauterine growth restriction (IUGR) incidence, presence and severity of proteinuria, and maternal weight at GD 0 and maternal weight gain at parturition.

One of the critical aspects of PE is the elevation of blood pressure, which poses significant risks to both the mother and the fetus. Our results indicate that AR significantly reduces systolic, diastolic, and mean arterial pressure, as shown in the graphical representation of Figures 4. This is particularly important, as prolonged hypertension can lead to severe complications, including placental abruption, organ dysfunction and adverse fetal outcomes (Camargo *et al.*, 2024). By reducing blood pressure, AR not only addresses a primary symptom of PE but also contributes to the overall stabilisation of maternal and fetal health.

Oxidative stress is the key contributor to the pathophysiology of PE (Hansson *et al.*, 2015). Consistent with the above, our findings also demonstrate that AR significantly reduces reactive oxygen species (ROS) levels, underscoring its potent antioxidant properties. The accumulation of ROS is known to lead to endothelial dysfunction and vascular damage, perpetuating the cycle of hypertension and inflammation in PE. By decreasing ROS levels, AR enhances endothelial NO bioavailability, as observed in many studies (Montezano and Touyz, 2014), which is critical for vasodilation and maintaining normal blood pressure. The enhancement in nitric oxide availability may mitigate the vascular rigidity frequently observed in pre-eclampsia, hence facilitating improved blood circulation and oxygen transport to the placenta and fetus. In such a situation, superoxides and free radicals generated by maternal oxidative stress may affect lipids, proteins, and nucleic acids, resulting in damage to placental cells, tissues, and organs. In this study, we report increased levels of MDA and decreased levels of the antioxidants SOD and NO in plasma Figure 5 and in placental tissue Table 4. The insufficiency of nitric oxide may initiate a series of physiological mechanisms in PE, including hypertension, elevated glomerular filtration rate, proteinuria and platelet dysfunction (Maged *et al.*, 2020). NO is a crucial factor in regulating placental blood flow. It is actively involved in cytotrophoblast endovascular invasion and placental development, owing to its distinctive angiogenic and vasculogenic characteristics. Consequently, oxidative stress significantly contributes to the pathogenesis of pre-eclampsia by modifying the oxidative state of the placenta.

The study further reveals that AR has a protective effect on endothelial dysfunction, as evidenced by the significant reduction in von Willebrand factor (vWF) levels, as shown in Figure 6a, a well-established marker of endothelial dysfunction. Elevated vWF levels are typically associated with endothelial injury and dysfunction, which are common features in pre-eclampsia (Wazib *et al.*, 2024). By lowering vWF levels in plasma and further validated by placental tissue, AR may play a crucial role in restoring endothelial health, thereby enhancing vascular function and reducing the risk of thrombotic events that can complicate PE.

Reports suggest that *A. racemosus* root extract has several pharmacological actions, such as antiulcer (Sairam *et al.*, 2003), antioxidant, antidiarrhoeal, antidiabetic, and immunomodulatory effects. Inflammation is a significant driver of the pathophysiology of pre-eclampsia and our study highlights AR's potential to modulate inflammatory pathways. We observed a substantial reduction in proinflammatory markers, specifically NF-κB and its receptor TLR4, in both plasma and tissue samples following AR treatment (Figures 7a and b.). The TLR4 - NF-κB signalling axis is particularly crucial in mediating the inflammatory response associated with pre-eclampsia, and by inhibiting this pathway, AR may help mitigate the inflammatory cascade that contributes to the development of PE.This anti-inflammatory effect not only aids in reducing the overall inflammatory burden but also promotes a more favourable environment for both maternal and fetal health (Gong *et al.*, 2016). The present investigation demonstrated that *A. racemosus* inhibited the synthesis of vWF, NF-κB and TLR4, reducing the plasma levels of these inflammatory molecules (Joshi *et al.*, 2022). In conjunction with the abnormal inflammatory response associated with pre-eclampsia, our findings indicate that AR may represent a promising approach for managing the condition by addressing the interconnected issues of hypertension, oxidative stress, and inflammation. The significant reductions in blood pressure, oxidative stress markers, and proinflammatory cytokines suggest that AR acts through multiple mechanisms to improve endothelial function and protect against the adverse effects of pre-eclampsia. As a natural therapeutic agent, AR represents a promising option for the development of effective treatments for pre-eclampsia, with the potential to improve outcomes for both mothers and their infants. Our study presents a novel and timely investigation into the therapeutic potential of *A. racemosus* in a preclinical model of pre-eclampsia, effectively bridging traditional medicine and modern biomedical research. The study is methodologically sound, employing a well-established L-NAME-induced model alongside detailed biochemical, hemodynamic, and histological analyses. The inclusion of both plasma and placental tissues enhances the depth of inflammatory and oxidative stress assessments. Data are presented through well-structured tables and informative figures, aiding in interpretation. Notably, the findings highlight the herb's ability to modulate key biomarkers related to endothelial dysfunction and inflammation. The discussion is insightful and well-contextualised within existing literature, and the study meets ethical and technical standards, supporting its scientific credibility and translational relevance.

5. Limitations of the study

It is limited to a preclinical model, and the findings may not fully translate to human physiology without further validation. The study does not identify the specific phytoconstituents of *A. racemosus* responsible for the observed effects. Future research focusing on isolating and characterising these active compounds will help clarify the precise mechanisms and identify the key bioactive constituents involved in their protective role against pre-eclampsia.

6. Conclusion

Our study demonstrates that *A. racemosus*, a natural therapeutic agent, effectively alleviates the complexities associated with pre-eclampsia (PE) by significantly reducing blood pressure and improving endothelial integrity, as evidenced by decreased levels of von Willebrand factor (vWF). AR possesses potent antioxidant properties, decreasing reactive oxygen species (ROS) and enhancing nitric oxide (NO) bioavailability, which are critical for maintaining vascular health. Furthermore, AR treatment significantly reduces pro-inflammatory markers such as NF-κB and its receptor TLR4, underscoring its ability to modulate inflammatory pathways linked to PE. These findings suggest that AR could serve as a valuable therapeutic avenue for managing pre-eclampsia, demonstrating its multifaceted effects on hypertension, oxidative stress, and inflammation.

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Author contributions

The research was conceived and planned by MIA, with MIA and SW contributing to the experimental design. SW,YA, SAF, and HQ conducted the experiments, while SA assisted in the determination of phytoconstituents in the plant extract. All authors have read and approved the final manuscript and declare no conflict of interest. Furthermore, the authors confirm that the manuscript has been approved for publication, with all data generated in-house and no involvement of a paper mill.

Conflict of interest

The authors declare no conflict of interest relevant to this article.

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