



Treatment of Preeclampsia Symptoms through Modulation of Bcl-2 and Beclin-1 Homeostasis Using Kopyor Coconut Water

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Abstract

Background: Preeclampsia (PE) is a significant contributor to maternal and perinatal morbidity and mortality, especially in low-income countries. The condition, characterized by hypertension and proteinuria after 20 weeks of gestation, has complex and poorly understood pathophysiological mechanisms, primarily involving placental dysfunction. Recent studies suggest that autophagy and apoptosis play crucial roles in PE progression. This study investigates the potential therapeutic effects of Kopyor coconut water (KCW) on PE, focusing on its mineral content and impact on placental autophagy and apoptosis. **Methods:** Female Wistar rats were induced with PE using L-NAME, a nitric oxide synthase inhibitor, and divided into five groups, including controls and treatments with low-dose aspirin (LDA) and KCW. The mineral content of KCW was analyzed using Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES). Placental levels of Beclin-1 and Bcl-2 were measured to assess autophagy and apoptosis. Blood pressure and proteinuria were monitored, and pregnancy outcomes were evaluated. **Results:** KCW contained significant levels of potassium, calcium, sodium, magnesium, and phosphorus, essential for cellular

functions and homeostasis. In L-NAME-induced PE rats, KCW and LDA treatments significantly reduced systolic blood pressure and proteinuria. Placental analysis showed that KCW treatment increased Beclin-1 levels and decreased Bcl-2 levels, indicating enhanced autophagy and reduced apoptosis. Additionally, KCW improved pregnancy outcomes, including the number of live fetuses, without significantly affecting placental weight. **Conclusion:** KCW's mineral-rich composition effectively modulates placental autophagy and apoptosis, reducing PE symptoms and improving pregnancy outcomes in L-NAME-induced PE rats. These findings suggest that KCW could be a promising nutritional therapy for managing and preventing PE, warranting further research in human studies.

Keywords: Preeclampsia, Preeclampsia, Kopyor Coconut Water, Autophagy, Apoptosis, L-NAME, Bcl-2, Beclin-1, Proteinuria

1. Introduction

Preeclampsia is one of leading causes of maternal morbidity and mortality worldwide (Rana et al., 2019). Preeclampsia (PE) is an important cause of maternal and perinatal mortality worldwide, accounts for 10% to 15% of direct maternal deaths, and 99% of these deaths are in low-income countries (ACOG, 2020). Preeclampsia/eclampsia is characterized by a blood pressure (BP) $\geq 140/90$ mm Hg after 20 weeks' gestation in a woman whose

Significance | Kopyor Coconut Water showed potential in reducing preeclampsia symptoms by modulating autophagy and apoptosis, suggesting therapeutic benefits.

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normal BP previously, and has proteinuria ≥ 0.3 gram in 24-h urine specimen (Bouter & Duvekot, 2020). Preeclampsia's underlying mechanisms are still not completely understood, investigations are still ongoing to determine the molecular pathways underlying this disorder (Wu et al., 2015). One of the key theories regarding the pathogenesis of PE points to the placenta as the primary site of the disorder. Specifically, the trophoblastic invasion occurs on the uterine spiral arteries, which is essential for proper placental development and function (Rana et al., 2019).

Placental autophagy, an intracellular mechanism breaking down damaged or defective cell components in bulk, is essential for maintaining cellular homeostasis throughout healthy pregnancies, which is necessary for the development of the embryo (Gong & Kim, 2014). Autophagy in the placenta plays a crucial role in cell survival and development, contributing to the maintenance of cell homeostasis and the differentiation and infiltration activity of trophoblasts (Rezeck Nunes et al., 2019). Studies of autophagy in preeclampsia showed conflicting roles of this homeostatic mechanism on preeclampsia development and progression (Nakashima et al., 2020). The interaction between beclin1 and the bcl-2 family of proteins plays a crucial role in regulating autophagy and apoptosis (Marquez & Xu, 2012). Bcl-2 is a member of the Bcl-2 family of proteins, which plays a crucial role in regulating cell survival and apoptosis. Bcl-2 can inhibit apoptosis by binding to Beclin1, a key regulator of autophagy, thus preventing the formation of autophagosomes and inhibiting the autophagy process. This interaction is essential for maintaining cellular homeostasis and preventing excessive autophagy, leading to cell death (Wan et al., 2024).

Low-dose aspirin has been used during pregnancy most commonly to prevent or delay the onset of preeclampsia (Chaemsaihong et al., 2020). Preventive Services Task Force (USPSTF) has recommended low-dose aspirin prophylaxis at 81 mg/day. According to this recommendations, low-dose aspirin should be started between weeks 12 and 28 of pregnancy, ideally before weeks 16, and continued every day until delivery. (Chaemsaihong et al., 2020). This is attributed to the characteristic of aspirin as a non-steroidal anti-inflammatory medication, which functions by blocking the cyclooxygenase (COX) pathway (Gatford et al., 2020). However, its use should be carefully managed, especially in the second half of pregnancy, to mitigate the risk of peripartum bleeding (Golyanovskyi, 2021). Many bioactive natural products contain chemicals that have been utilized therapeutically or prophylactically to prevent or treat various ailments. Using natural products has the benefit that they are typically well-tolerated and have few adverse effects. (Cragg & Pezzuto, 2016).

Herbal medicine, such as black cumin (*nigella sativa*), is another therapy option for PE. In a study, the best dose to lower AT1-AA placenta levels and raise placental ET-1 expression in a

preeclampsia mice model was 1000 mg/kg body weight/day. (Rahma et al., 2017). The most prevalent component of *Nigella sativa* seeds' volatile oil, thymoquinone (TQ), has been investigated for possible protection against angiotensin II (Ang II)-induced cardiac damage. (Zhang et al., 2022). However, some people who drink high black cumin cause nausea, especially when black cumin is taken orally in high doses or in concentrated forms like oil (Karimi et al., 2019). Another natural functional food which is used to reduce high blood pressure is coconut water (Bhagya et al., 2012), reduced oxidative stress induced by isoproterenol-induced myocardial infarction (Prathapan & Rajamohan, 2011), reduced inflammation (Rao & Najam, 2016) and tender coconut water (TCW) lessens the hepatocyte damage brought on by increased inflammatory cytokine production and nitric oxide generation, as well as proinflammatory gene expression. (Lakshmanan et al., 2020).

A coconut tree, known as a tree of life, is a tropical plant distributed in tropical and subtropical countries and every part of the coconut tree, and has beneficial effects on human life (Zhao et al., 2018). In general, one coconut fruit contains 300 ml water with pH 3.5 – 6.1, depending on variety, maturity, and climate. Interestingly, young coconut water has very close composition to isotonic fluid, which is suitable for replacement of body fluid (Prades et al., 2012) due to high amino acids and minerals (Zulaikhah, 2019). Minerals are essential for the control and operation of autophagy, a cellular mechanism that helps break down and recycle cellular constituents. To preserve cellular homeostasis and respond to dietary stress, autophagy is necessary. (Cornelius & Wallace, 2020). Minerals tightly control it, especially those with functional roles like arginine, leucine, glutamine, and methionine, which affect autophagy through signal transduction pathways (C. Liu et al., 2021). In addition, the researchs on kopyor coconut water (KCW) which is rich in minerals on the autophagy process in model-like rat PE are currently limited.

Research on pregnant women have firm limitations due to ethical issues, thus, using experimental animals *rattus norvegicus* because they have good adaptability to life in a laboratory environment and are genetically similar to humans, so it is hoped that they can be used as a comparison for PE in humans. According to previous studies, nitric oxide (NO) inhibition in rats model results in a PE-like state (Korokin et al., 2020). Because the clinical characteristics of PE women and rats treated with NG-nitro-arginine-methyl-ester (L-NAME) are comparable, PE has been induced in rats with this nitric oxide synthase (NOS) inhibitor (Raofi et al., 2020)

2. Materials and Methods

2.1 Materials

The materials used in this study included KCW of the Puan Kalianda variety provided by a farmer at Tanjung Anom village,

Kalianda district, South Lampung Regency, Lampung Province, Indonesia. KCW was prepared for chemical analysis at PT Saraswanti Indo Genetech (SIG), following the previous procedure stated in the press publication. Initially, female Wistar rats (*Rattus norvegicus*) were provided by Laboratorium Penelitian dan Pengujian Terpadu (LPPT) 4 UGM University Jogjakarta Province. L-NAME (Cas. No: 51298-62-5), including aspirin (Cas-No.: 50-78-2. 1.2), were purchased from Sigma, St. Louis, Missouri, USA. Furthermore, proteinuria (Cat. No FY- RA 4983) was bought from Eiyue Biological Company, China. Beclin-1 (Cat No. RK03528) was bought from ABclonal, Company Inc., United Kingdom. Reagen B-cell lymphoma 2 (Bcl-2) (Rat Cat No E1880Rat) was purchased from Bioassay Technology Laboratory, China.

2.2 Methods

2.2.1 Quantification of Minerals using the ICP-OES method

Minerals in the KCW used an Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) (ARCOS FHE12, SPECTRO, Germany), which followed the manufacturer's instructions. A series of standard minerals, yttrium and KCW were dissolved in double distilled water and mixed well with HNO₃ and HCl acid solutions for 15 minutes. The dissolved samples were filtered using filter paper into a fresh tube and then were measured using the ICP-OES to determine the intensity (Szkudzińska et al., 2017). Metal and mineral contents were calculated using a standard curve with the following formula:

$$\text{Metals Minerals (ppm, mg/L, mg/Kg)} = \frac{ASpl - a}{b} \times V \times fp$$

Note:

- Aspl = Response (area) of the analyte in the sample
- A = Intercept of the standard calibration curve
- b = Slope of the standard calibration curve
- V = Final volume of test solution (mL)
- Fp = Dilution factor
- Wspl = Test portion weighing weight (gram)
- Vspl = Pipetting volume of test portion (mL)

2.2.2 Research design of animal experiment.

This research study was an in-vivo experiment with pre-posttests control group design except beclin1 and bcl-2 placental levels. The number of female rats used in this study was calculated using the G-power software, was downloaded from https://www.gpower.com/Menu/OE_Menu.htm. Female Wistar rats were eligible for this study that aged 6-8 weeks old and weighed 180-200 g. Before development of pregnant Wistar rats model with PE, every five female rats were mated with one male wistar rat in the same cages, which aged 8-12 weeks old and weighed 250- 350 g. Rat pregnancy was determined by examining the presence of copulatory plug in the vagina or sperm through vagina swab, which was observed under a light microscope with 100x magnification (Cora et al., 2015). Once female rats became

pregnant, they were induced by providing drinking water containing 0.75 mg/mL L-NAME from 4 to 19 Gestational days (GDs). Pregnant rats were then divided randomly into five different groups:

- I. PC: Pregnant control rats (PC) without L-NAME treatment, n = 7.
- II. PE: Pregnant rats received L-NAME treatment from GD4 to GD19, n = 7.
- III. PE + aspirin: Pregnant rats received L-NAME treatment from GD4 to GD19 and aspirin treatment from GD4 to GD19, n = 7.
- IV. PE + KCW 2ml/200gBW: Pregnant rats received L-NAME treatment from GD4 to GD19 and KCW 2ml/200gBW treatment from GD4 to GD19, n = 7.
- V. PE + KCW 3 ml/200gBW: Pregnant rats received L-NAME treatment from GD4 to GD19 and KCW 3 ml/200gBW treatment from GD4 to GD19, n = 7.

Administration of aspirin (1.5 mg/kg BW/day) or KCW was given for 15 consecutive days. The protocol of this research study was approved by the Research Ethics Committee, Faculty of Medicine Universitas Sebelas Maret (UNS) with 301/UNS/27.06.9.1/TU.00/2022 number and 01 November 2022.

2.2.3 Measurements of placenta Bcl-2 and Beclin-1 levels.

A total amount of 0.1 gr placenta were smoothed with cold conditions, mixed 0.9 ml PBS until homogeneous, samples were centrifuged at 5000 rpm for 5 minutes. Collected placenta was stored at -20°C before further analysis. Placenta Beclin-1 and Bcl-2 levels were measured using the protocol from the manufacturers. Absorbance values of standards and samples were spectrophotometrically measured at 450 nm.

2.2.4 Urine analysis and blood pressure measurement

Rats were kept in separate metabolic cages for 24 hours, made by Tecniplast in Italy, and on GD4, GD12, and GD19, urine output was measured. The BP-2000 Blood Pressure Analysis System (Visitech Systems, Inc., Apex, NC, USA) was then used to perform a non-invasive tail-cuff method of measuring mean arterial pressure (MAP) on GD7, GD13, and GD18. All female Wistar rats were conditioned to 38°C in preparation for the measurement.

2.3 Statistical analysis

All data were presented as mean ± standard deviasi (SD). Tukey's post hoc test was used in conjunction with one-way analysis of variance (ANOVA) to assess group comparisons. An ANOVA with repeated measurements and a Bonferroni post hoc was used to evaluate group differences. GraphPad Prism software version 9.1.1 (GraphPad Software, San Diego, CA, USA) was used to illustrate the statistical analysis and graphs, and p-value < 0.05 was showed statistically significant.

3. Results

3.1 Eight important minerals were found in the KCW

There were eight minerals detected in the KCW samples, but the Cu (copper) mineral was not detected in the KCW sample (Table 1). The KCW contained the highest levels of K (Potassium) (230.69 mg/100g), followed by Ca (Calcium) (21.44 mg/100g), Na (Sodium) (13.86 mg/100g), Mg (Magnesium) (10.74 mg/100g), and P (Potassium) (4.48 mg/100g). On the other hand, the KCW contained low levels of Fe (iron) = 1.32 mg/100g, Mn (manganese) = 0.221 mg/100g and Zn (Zinc) = 0.10 mg/100g.

3.2 KCW nutrition therapy activated autophagy and apoptosis in placenta L-NAME-induced PE rats.

The impact of KCW nutrition therapy on placenta Bcl-2 levels and placental Beclin-1 in L-NAME-induced PE rats is showed in Figure 1 a and b. The Bcl-2 level in the L-Name treated groups were lower than those in the PC group (6.21 ± 0.80) and a significant difference was present among the PE (4.78 ± 0.98). While the L-name induction in the figure 3 shows that the PE group has the lowers Bcl-2 level and significant difference when compared the PE+LDA (5.50 ± 1.78), PE+2mlKCW (5.21 ± 0.98), PE+3mlKCW (6.6 ± 1.08).

The Beclin-1 level in the L-Name treated groups were higher than those in the PC group (2.13 ± 0.2) and a significantly difference was present among the PE (5.88 ± 0.68). While the L-name induction in the figure 3 shows that the PE group has the higher Beclin-1 level and significant difference when compared the PE+LDA (2.87 ± 0.88), PE+2mlKCW (3.61 ± 0.78), PE+3mlKCW (3.06 ± 0.18).

3.3 KCW nutrition therapy declined MAP and urinary protein level in L-NAME induced PE rats

Pregnant rats' SBP measured on GD4, GD13, and GD19 illustrates Figures 2a. Based on GD4, there was no significant variation in the baseline SBP and proteinuria levels across the groups, as illustrated in Figures 2a and b. Compared to Group PC, SBP of female Wistar rats was significantly elevated after the treatment of L-NAME on GD12, which KCW and aspirin downregulated. The results showed that 3 ml of KCW influenced SBP and proteinuria in PE rats' model. KCW nutrition therapy showed a stronger ability in the reduction of SBP in PE rats. As seen in Figure 2b, proteinuria was also seen in GD4, GD12, and GD19 in each group. PE+3 ml of KCW and aspirin medication downregulated the elevated level of proteinuria following L-NAME treatment. Figure 1b illustrates how KCW nutrition therapy and aspirin were more effective in reducing proteinuria in PE rats based on SBP. Therefore, KCW nutrition therapy enhanced the effect of reducing MBW in L-NAME-induced PE rat's model. Comparing the PE+2ml KCW and PE+3ml KCW treatment groups to the control group from GD 12 to GD 20, the maternal daily weight gain during the dosage period was considerably lower. Compared to the other groups, the group that was given 3ml KCW experienced a significant decrease in overall maternal weight gain.

3.4 The impact of KCW mineral therapy on the course of pregnancy in PE rats induced by L-NAME

The impact of KCW and aspirin therapy on the secondary outcomes of PE pregnancy was further investigated. As shown in table 2, the number of live fetuses showed significant differences between PC, PE, KCW nutrition therapy, and aspirin. However, there was no difference in placental weights in normal pregnant rats with or without KCW nutrition therapy and aspirin. As shown in table 2, average fetus weights were not significantly decreased in L-NAME administrated rats. These results suggested that KCW improved the number of live fetus pregnancy outcomes in PE rats.

4. Discussion

In this study, there are several important results. The KCW was measured using the ICP-OES method contained eight essential minerals. However, the Cu mineral was not detected in the KCW sample. KCW down-regulated the decreased placental Bcl-2 levels, and increased placenta Beclin-1 level after L-NAME therapy. Furthermore, the KCW reduced systolic blood pressure, proteinuria, and maintained weight in pregnant rats. In addition, the KCW reduced the occurrence of IUGR and resorption of rat fetuses.

Minerals, such as K, Ca, Na and Mg are essential micronutrients for maintenance of human body functions and physiological processes, including cellular metabolism, antioxidant, anti-inflammation, modulation of enzyme activities and regulation of gene expression and protein synthesis (Y. Liu et al., 2023). Our results indicated that the KCW contained the highest levels of K (230.69 mg/100g), Ca (21.44 mg/100g), Na (13.86 mg/100g), and Mg (10.74 mg/100g). Compared to other varieties such as wulung coconut water which contains 560.03 mg/L Na, 146.16mg/L Mg and 8.76mg/L P, however the KCW has similar contains to green coconut water with 290.86 mg/L K, 94.43mg/L P and 74.24mg/l Mg (Zulaikhah, 2019). In the clinical study, 440 inward patients who had a higher daily intake of Ca, Mg, P, Cu, Fe, Mn, and Zn during pregnancy is inversely associated with PE development (Houston, 2011). Supplementation of 540 mg/day K tablet for 4 weeks in 52 with established or newly diagnosed mild to moderate essential hypertension patients of Department of Internal Medicine of the University of Pisa reduced systolic and diastolic blood pressure (Franzoni et al., 2005). A recent study also reported that 678 women with PE higher risk in South Africa, Zimbabwe and Argentina who were treated with 500 mg/day Ca tablet for 12 weeks had lower blood pressure than that of 677 women without Ca treatment (Hofmeyr et al., 2018). Sixty Iranian pregnant women with age 12-14 weeks pregnancy and low serum Mg levels (< 1.9 mg/dL) who received 200 mg of Mg tablet/day for one month and 100 mg of Mg tablet/day until the end pregnancy had lower risks of PE, retarded growth and preterm birth than that control groups

Table 1. Quantification of mineral levels in the KCW sample using the ICP-OES method

Minerals	Unit	Concentration
Potassium (K)	mg / 100 g	230.69
Magnesium (Mg)	mg / 100 g	10.74
Manganese (Mn)	mg / 100 g	0.221
Sodium (Na)	mg / 100 g	13.86
Phosphorus (P)	mg / 100 g	4.480
Zinc (Zn)	mg / 100 g	0.10
Iron (Fe)	mg / 100 g	1.32
Calcium (Ca)	mg / 100 g	21.44
Copper (Cu)	mg/kg	ND

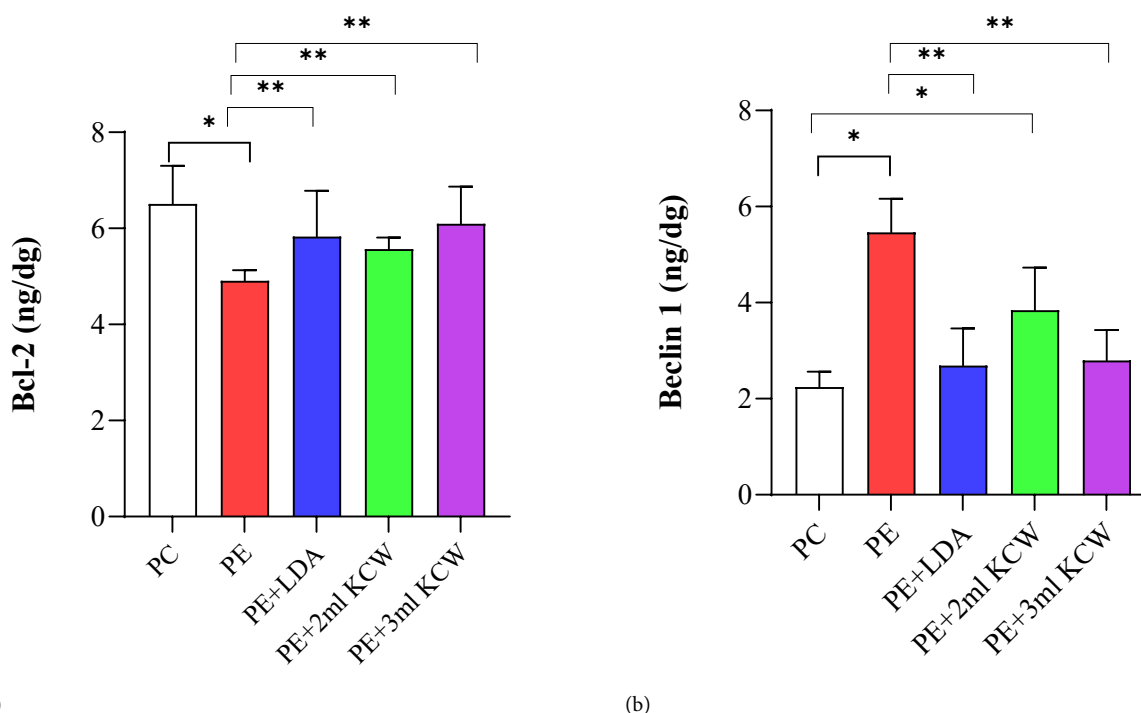


Figure 1. The effect of KCW nutrition therapy activated autophagy in placenta L-NAME induced PE rats. Placental BCL-2 level (a) and placenta beclin-1 level (b) were calculated in other groups on GD 20. Data placental Bcl-2 and Beclin-1 were shown as mean ± SD. * ANOVA test significant and post hoc Tukey p < 0.05 vs PC group. ** p < 0.05 vs PE group.

Table 2. Effects of KCW treatment in rats during pregnancy on indices of fetal growth and development

Group	Placental weight (g)	Implantation size (n)	Resorbed and stillborn fetuses	Number of live fetuses	Fetal weight (g)	Crown-rump length (cm)
PC	0.62±0.12	10.9±1.2	0.12±0.56	14±2.3	3.43±0.51	3.47±0.47
PE	0.61±0.08	10.3±1.05	3.21±0.34*	7±3.4*	3.23±0.59	3.09±0.56
PE+aspirin	0.60±0.05	11.4±0.89	0.56±0.41	11±3.1**	3.01±0.61	3.23±0.87
PE+KCW2ml/200gBW	0.56±0.07	10.8±0.91	0.45±0.75	10±2.5	3.13±0.34	3.45±0.57
PE+KCW3ml/200gBW	0.52±0.05	11.8±1.03	0.76±0.34	12±2.9**	2.97±0.51	3.58±0.91

Note:

Data are the mean ± SD (n = 7 pregnant rat).

*P < 0.05 compared with the control group.

**P < 0.05 compared with the control group (one-way ANOVA followed by a Tukey multiple comparison test or by the Kruskal-Wallis when the data were not normally distributed).

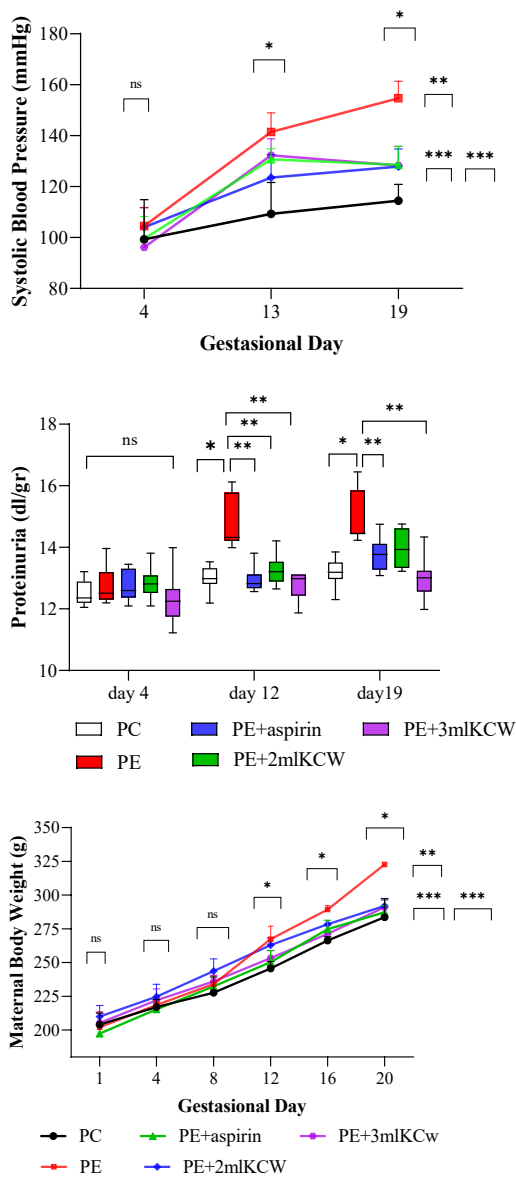


Figure 2. Wistar pregnant rats develop PE-like symptoms in response to KCW. Pregnant rats were given L-Name (in induced group), 1,5 mg mg/kg aspirin or KCW on GD 4 to GD 19 were measured and displayed as the mean ± SD . Systolic blood pressure (SBP), proteinuria and maternal body weight (MBW) are presented in (a), (b) and (c), respectively. All data are expressed as the mean ± SD. ns p> 0.05, *P < 0.05 repeated ANOVA, ** p < 0.05 Bonferroni test significant vs, PC group *** p< 0.05 Bonferroni test significant vs PE group

(Zarean & Tarjan, 2017). Thus, the KCW provides essential minerals that is an important role in maintenance of blood pressure. Therefore, the KCW may become a nutrition therapy for PE management. The Bcl-2 type of proteins, including Bcl-2 itself, plays an important role in regulating apoptosis (Xu & Qin, 2020). In the current study, rats were given L-NAME to cause pathophysiological alterations and symptoms resembling those of PE. Additionally, in the L-NAME-induced PE rat model, the level of Bcl-2 dropped while Beclin-1 increased. In PE+2 and 3 ml KCW groups, there were significant differences between PE groups. However, LDA and KCW administration partially restored Bcl-2 and Beclin-1 level. A recent study also reported that 20 pregnant rats induce 50 mg/kg/day LName, and decrease Bcl2 expression (Guo et al., 2022). Therefore, by blocking mitochondrial apoptosis and autophagy, we were able to confirm that aspirin and KCW were a promising treatment in human PE and L-NAME-induced PE rat models.

The symptoms of preeclampsia is high blood pressure, proteinuria, or other signs of the kidneys or other organ damages. As expected, the increased SBP and proteinuria in the L-NAME-induced PE rat model were reversed by KCW therapy. Further data indicated that in the general normotensive population, PE+LDA, PE+2 ml KCW and PE+3ml KCW could all effectively lower SBP (Manivannan et al., 2018). This research is in line with research conducted by Bhagya, 2012, where 24 Male Sprague-Dawley rats given 4ml/100gBW for 42 were able to reduce SBP (Bhagya et al., 2012). This study also reported preliminary findings that KCW consumption can reduce proteinuria and maintain stable weight gain in pregnant rats.

This study also examined the outcomes of these pregnancies (Table 2). Prenatal-induced L-name exposure did not significantly affect placental weight, implantation size of fetal weight and CRL (p values >0.05). However, the living sample fetuses were significantly reduced in rats from the PE+ group compared to the control group (P <0.05). The PE group resulted in considerably more prenatal losses (due either to resorption and/or stillbirth) (P <0.05). In conclusion, in L-NAME-induced PE rats, the researchers identified the impact of KCW on the progress of pregnancy. The improved rat survival rate resulted from KCW therapy. In the PE rat model, neither the two doses nor aspirin therapy affected placental weight. The researchers have shown that KCW could increase the impact of several distinct preeclamptic symptoms, including proteinuria, SBP, MBW, and autophagia. However, placental hyphatology PE was not examined in this study. It is shown that placental vascular and villous lesions, as well as aberrant trophoblast invasion, were linked to PE. (Schiffer et al., 2018). The high mineral content in KCW is able to improve pregnancy outcomes. A deficiency in calcium can lead to conditions like preeclampsia and low birth weight. Iron deficiency during pregnancy can lead to preterm birth

and low birth weight adequate magnesium intake during pregnancy can help reduce the risk of preterm labor and preeclampsia.

To further confirm the effect of KCW, the histopathological features in the placenta of L-NAME-induced preeclampsia rats should be observed.

5. Conclusion

In summary, the minerals in coconut water variety Kopyor (*Cocos nucifera* L var. Kopyor) inhibit apoptosis and autophagy in the placenta by reducing homeostasis Beclin1 and Bcl-2, increasing autophagy and decreasing apoptosis. This study showed that KCW nutrition therapy may improve the effects of prevention and therapy in rats with L-NAME-induced PE. These results may offer a new approach to treating and preventing PE in humans.

Author contributions

F.F, S.S, D.I, S.S, I.N, conceptualized, prepared draft, data curation wrote, reviewed, and edited the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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