ACTA ABP BIOCHIMICA POLONICA

Vol. 70, No 1/2023
131–135
https://doi.org/10.18388/abp.2020_6331

Regular paper

Resveratrol inhibits multiple organ injury in preeclampsia rat model

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Objective: **To investigate the effects of resveratrol on multiple organ injury and energy metabolism and its possible mechanism in preeclampsia model. Methods**: **A total of 45 clean-grade female adults Sprague Dawley (SD) rats (weight 270–320 g) were randomly divided into three groups: a control group, preeclampsia group (PE), and Preeclampsia with resveratrol treatment group (RE). Preeclampsia was induced in rats by administering 200 mg/kg/day L-NAME. Expression levels of TNF-α and IL-6 in the lungs and kidney tissues were analysed by ELISA, while the activity of superoxide dismutase (SOD) and malondialdehyde (MDA) was determined by biochemical assays. The levels of lactic acid and pyruvate were detected using biochemical assays, while the epinephrine level in the kidney and heart tissues was determined by the ELISA method. Reverse transcription polymerase chain reaction and the western blotting were used to detect the expression of pyruvate dehydrogenase kinase 4 (PDK4) in the myocardial tissues. Results**: **We found that resveratrol treatment inhibited the levels of IL-6, TNF-α, and MDA in the lungs and kidney tissues, while the SOD activity was increased. Treatment with resveratrol reduced the levels of lactic acid, pyruvate, and epinephrine in the kidney and heart tissues. Furthermore, resveratrol treatment significantly increases the expression of PDK4 myocardial tissues in RE group compared to PE group. Conclusion**: **Resveratrol may inhibit the release of tissue inflammatory factors, regulate the body's energy metabolism, and ultimately protect tissue damage caused during Preeclampsia.**

Key words: preeclampsia, multiple organ injury, resveratrol, inflammatory factors, proteinuria

Received: 21 April, 2022; revised: 03 August, 2022; accepted: 21 October, 2022; available on-line: 03 February, 2023

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Acknowledgements of Financial Support: This study was supported by the Scientific research project plan of Shanghai Health Commission (No: 202140091), Establishment of preeclampsia-eclampsia cohort database (Clinical Research Plan of SHDC, No: SHDC2020CR6021), the interdisciplinary program of Shanghai Jiao Tong University (No: ZH2018ZDA31)
Abbreviations: COX-2, Cyclic oxygenase; HGF, Hepatocyte growth factor; ICAM-1, Intercellular Cell Adhesion Molecule; IGF-1, Insulin-like growth factor; IL, Interleukin; JNK, Jun N-terminal kinase; L-NAME, N(gamma)-nitro-L-arginine methyl ester; MAPK, Mitogen-Activated Protein Kinase; MMP, Matrix metalloproteinases; NOS, Nitric oxide synthase; PCOS, Polycystic ovarian syndrome; PDC, Pyruvate dehydrogenase complex; ROS, Reactive Oxygen Species; SBP, Systolic blood pressure; SD, Sprague Dawley; TGF-ß, Transforming growth factor; TNF-a, Tumour necrosis factor

INTRODUCTION

Pregnancy is associated with many complications like polycystic ovarian syndrome (PCOS), Dysmenorrhea and Preeclampsia. Among them, Preeclampsia is a very fatal and multifactorial disorder and is strongly associated with other entities such as hypertension and proteinuria that can occur within 20 weeks of gestation (Ding *et al*., 2017). According to the World Health Organization (WHO), only 10% of pregnant women suffer from preeclampsia but the mortality rate associated with the disease can be as high as involving one-seventh of the affected women (Say *et al*., 2014). The pathogenesis of preeclampsia associated with pregnancy is due to limited perfusion of the placenta causing hypoxia and subsequently apoptosis. The affected placenta in turn causes an increased oxidative stress, leading to the release of the various inflammatory mediators and anti-angiogenic proteins (Roberts & Escudero, 2012). The increased blood pressure demands the need for application of anti-hypertensive drugs, namely Labetalol, Nifedipine and Hydralazine. Compared to other drugs, Nifedepine is safer due to less side effects related to the maternal or fetal development (including control of arterial pressure and maintenance of urine output) (Zuo *et al*., 2021; Childress & Katz, 1994). Antihypertensive drugs are effective, but some adjuncts can provide additional effects. There are expectations from adjuncts to modify the destructive processes in the body. Among the adjuncts, resveratrol (potent inhibitor of the nuclear factor kappa B-NF-ϰB) could prove to be an adjunct to current therapy of preeclampsia. It was found that RE has the capacity to lower the blood pressure along with several other beneficial effects related to promotion of healing and modulation of inflammatory mechanisms (Novakovic *et al*., 2022).

The origin of resveratrol is purely natural as it is found exclusively in selected products such as red wine, grapes, peanuts, and in limited types of plants. In 1939, RE was extracted for the first time from Veratrumgrandiflorum and was later, found in dried roots of *Polygonum cuspidatum*. Initially, resveratrol was utilized for the treatment of injuries but later used for to manage various cardiovascular diseases (Novakovic *et al*., 2022). Resveratrol was initially used to treat injuries but later was also utilized for the management of the cardiovascular diseases (Novakovic *et al*., 2022). Resveratrol has the capability to repress the p38-Mitogen-Activated Protein Kinase (MAPK)/NF-ϰB pathway and produce several Reactive Oxygen Species (ROS) such as anti-angiogenic molecule (FMS-like tyrosine kinase 1 and sFlt-1) through which, it

mediates anti-inflammatory and anti-oxidative stress activities (Zuo *et al*., 2021; Novakovic *et al*., 2022).

The evidence present in the past literature shows that resveratrol can also suppress various factors such as Transforming growth factor (TGF-β), Matrix metalloproteinases (MMP), Cyclic oxygenase (COX-2), Tumour necrosis factor (TNF-α), Interleukins (IL-1β and IL-6), and Intercellular Cell Adhesion Molecule (ICAM-1). The effects of resveratrol can be broadly classified into two major mechanisms. The first one is the p50/p65 mechanism that controls the signaling cascade IKKBα/I ϰBα and activator protein-1 complex of MAPK/ERK/p38/c-Jun N-terminal kinase (JNK) (Wang *et al*., 2017). Second mechanism is the inhibition of the p65 subunit translocation but it is based on the experimental model of hepatocarcinogenesis. Basically, resveratrol leads to decrease in two processes namely – phosphorylation (both IϰB and normal) and acetylation (Chavez *et al*., 2008). Further reduction of IϰB phosphorylation leads to variation in p65 protein levels, causing resveratrol-induced apoptosis. Resveratrol also mediate mi-RNAs by suppressing miR-21 expression and inhibition of the NF-ϰB.

Studies have shown some beneficial effects of resveratrol in complicated pregnancies associated with gestational diabetes, malnutrition/obesity, any teratogen exposure or placental insufficiency) (Zielinsky & Busato, 2013). It resulted in improvement of sub-optimal fetal development. Even in the treatment of polycystic ovarian syndrome, this product is providing synergistic effects with metformin through *via* SIRT1 and AMPK activation (Pan *et al*., 2016). It is probably the inherent properties of RE (including the anti-inflammatory and anticancerous capability) which enable it to be a treatment modality for endometriosis. It was found that resveratrol has the potential to discourage the process of invasion, adhesion, and angiogenesis of endometria-related lesions, thereby, slowing the process of inflammation and oxidative stress (Vian *et al*., 2018). Even with the involvement of eutopic endometrial stromal cells, resveratrol could definitely, cause several valuable effects by altering the gene expression and inhibiting the insulin-like growth factor (IGF-1) and hepatocyte growth factor (HGF) (Taguchi *et al*., 2016).

The inhibitory effects of resveratrol can prove to be a useful tool for the management of cancers and chronic diseases. Like in diabetes mellitus type 1, resveratrol has been shown to attenuate testicular apoptosis while in terms of respiratory diseases, there is inhibition of LPS-induced inhibition on SIRT1 expression (Novakovic *et al*., 2022; Pan *et al*., 2016). In addition to them, there is repression of activation effects of LPS on MAPKs and NF-ϰB activation also. Due to the inhibition of inflammatory responses leading to a complete perfusion, the healing of kidney is also promoted. Colorectal cancer is another example associated with induction of apoptosis and resveratrol provides suppression of NF-ϰB activation and finally relief to the devastating condition (Chavez *et al*., 2008). Similarly for Thyroid and breast cancer, resveratrol shows marked improvement by inhibiting the NF-ϰB/p65 signaling in which levels of IL-6 and Cyclooxygenase (COX-20) are also affected. Lastly, it induces pancreatic apoptosis so it is also proven to be helpful in prevention of pancreatic cancer.

The NF-ϰB plays a mighty part during the treatment of preeclampsia by exhibiting the inflammatory factors. The benefits of resveratrol along with proven clinical studies are useful in managing many clinical problems. These can range from chronic diseases like Diabetes mellitus, Respiratory diseases, Hypertension, Reproductive problems and lastly, various types of cancers. It has both modulatory and attenuated effects. No doubt we have a variety of medications for all of the above mentioned critical conditions, yet the beneficial effects of resveratrol cannot be matched easily. Hence, resveratrol can be assumed to be a good adjunct for the prevention of complications and therapies of the human diseases including preeclampsia. The present study aims to explore the possible role of resveratrol in inhibiting multiple organ injury in preeclampsia rat model.

MATERIAL AND METHODS

Animal preparation and grouping

A total of 45 healthy female adults Sprague Dawley (SD) rats (weight 270–320 g and aged 2–3 months) and were provided by the Experimental Animal Center of the Shanghai Jiao Tong University (China). The animals were maintained in fully ventilated rooms with free access to pellet diet and fresh water. The photoperiod used for keeping animals was 12 h day and 12 h night cycle. Standard institutional ethical guidelines were followed in performing various experimental procedures on the rats. The rats were divided into three groups: the control group (n=15), Preeclampsia group (PE) (n=15), and Preeclampsia with Resveratrol treatment (RE) group (n=15). The animals received humane care in compliance with the principles of laboratory animal care.

Induction of the animal model

To induce preeclampsia, nitric oxide synthase (NOS) inhibitor namely N(gamma)-nitro-L-arginine methyl ester (L-NAME) (obtained from Sigma-Aldrich) at the dose of 200 mg/kg/day was administered to the rats. Resveratrol, dissolved in distilled water were given to rats at the doses of 20 mg/kg/day orally by oral gavage for 4 weeks. Systolic blood pressure (SBP) was monitored continuously through the experimental period by using a blood pressure recorder using tail-cuff method. The protein level in urine (proteinuria) was measured by the Coomassie blue method.

After completion of experimental periods, rats were sacrificed using pentobarbital sodium anesthesia. The livers, kidneys and hearts were collected rapidly and prepared for mRNA and protein extraction.

TNF-α, IL-6, MDA, and SOD detection

In accordance with the instructions on the operating kits, enzyme-linked immunoassay (ELISA) (SOLARBIO, China) was used to detect TNF-α and IL-6 in the kidney and myocardial tissues, the xanthine oxidase method (Sun *et al*., 1988) was used to detect the content and activity of SOD, and the thiobarbiturates method (Draper *et al*., 1993) was used to determine the MDA content. The SOD and MDA content in the lung and kidney tissues were calculated according to the formula and Coomassie Brilliant Blue detect protein content.

Detection of lactic acid, pyruvate, and epinephrine levels

In accordance with the instructions on the operating kits, biochemical methods were used to detect lactic acid and pyruvate levels, and ELISA was used to detect epinephrine levels in the heart and kidney tissues.

Reverse transcription polymerase chain reaction (RT-PCR)

RNA from tissues were obtained using TRIzol method and then reversed to cDNA with RT Kit. Quantitative PCR was carried out using SYBRGreen (Takara) with appropriate primers designed by Primer 5.0 according to the conditions, including an initial step of 10 minute in 95°C, and then 40 cycles of amplification, which includes 10 s in 95°C, 20 s in 55°C and 25 s in 72°C. Quantification was determined by $2^{-\Delta\Delta CT}$ (Livak & Schmittgen, 2001). The internal control used was GAPDH.

Western blot

The tissue was treated with RIPA lysis buffer for the isolation of total cellular proteins. Following, the protein concentrations were determined with Bradford method. From each sample, 45 μg of proteins were loaded and run on SDS-PAGE gels which were processed for blotting to PVDF membranes followed by exposure to primary and secondary antibodies and finally the protein bands of interest were visualized with the help of efficient chemilumniscence reagent. Primary antibodies were directed against PDK4. The GAPDH gene was used as internal control. Primary antibody treatment was followed by secondary antibody treatment overnight at 4°C. Finally, enhanced chemiluminescence (ECL) reagent was used to detect the protein signals.

Statistical analysis

Values presented in the study are the mean of three biological replicates ± S.D., calculated from atleast three experimental replicas. ANOVA, Student's *t*-test and Duncan's test were used to estimate the significance of the statistical difference between two/among many data points. The at $p<0.05$ was considered as statistically significant difference.

RESULTS

Resveratrol Ameliorated Hypertension and Proteinuria in Preeclampsia group (PRE)

The control group (saline) exhibited stable SBP throughout experimental period. However, in the PRE rats, we observed significantly increased SBP. Interestingly, in (RE) group, a reverse effect was observed compared to the PE group.

Furthermore, the PRE group exhibited enhanced proteinuria, a clinical marker of renal malfunction) associated with PRE compared to control group. Interestingly, in (RE) group, a reverse effect on proteinuria was observed compared to the PE group.

TNF-α and IL-6 expression level

The expression of the inflammatory factor TNF-α in the kidney and myocardial tissues was lower in the control group than in the other two groups. The TNF-α expression in the kidney and myocardial tissues in the (PE) group increased significantly and was significantly lower in the (RE) group than in the LPS group ($P<0.05$). The concentration of IL-6 was higher in the (PE) than in the control group ($P<0.05$), but the administration of Resveratrol downregulated IL-6 production ($P<0.05$; see Fig. 1).

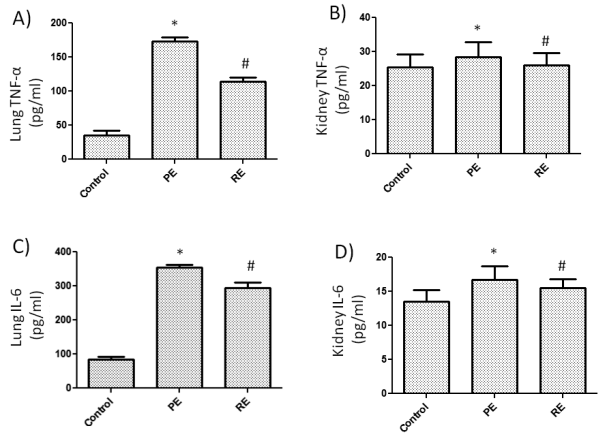

Figure 1. The expression of TNF-α and IL-6 in the lung and kidney tissues of rats.
*$P<0.05$ for comparison with the corresponding tissue of the control group, and #$P<0.05$ for comparison with the corresponding tissue of the preeclampsia group.

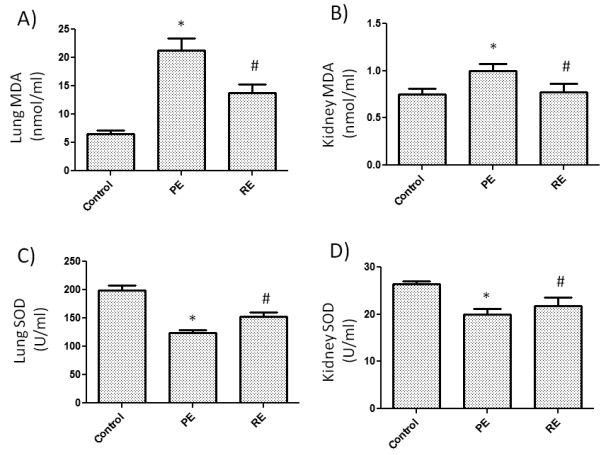

Figure 2. Malondialdehyde and superoxide dismutase levels in the lung and kidney tissues of rats.
*$P<0.05$ for comparison with the corresponding tissue of the control group, and #$P<0.05$ for comparison with the corresponding tissue of the preeclampsia group.

MDA and SOD levels

When compared with the control group, the MDA level was higher ($P<0.05$), and the SOD level was significantly lower in the (PE) group ($P<0.05$). When compared with the (PE) group, the MDA level was significantly lower ($P<0.05$), and the SOD level was higher in the (RE) group ($P>0.05$) (see Fig. 2).

Lactic acid, pyruvate, and epinephrine expression in the heart and kidney tissues

In order to study the effect of Resveratrol on organ metabolic damage induced by preeclampsia, the lactic acid, pyruvate, and epinephrine levels were measured in the heart and kidney tissues.

Lactic acid expression: The lactic acid level in the PE group was significantly higher than the control group ($P<0.05$), but there was no significant difference in this level between the RE group and the control group.

Pyruvate expression: The pyruvate level in the PE group was significantly higher than the control group

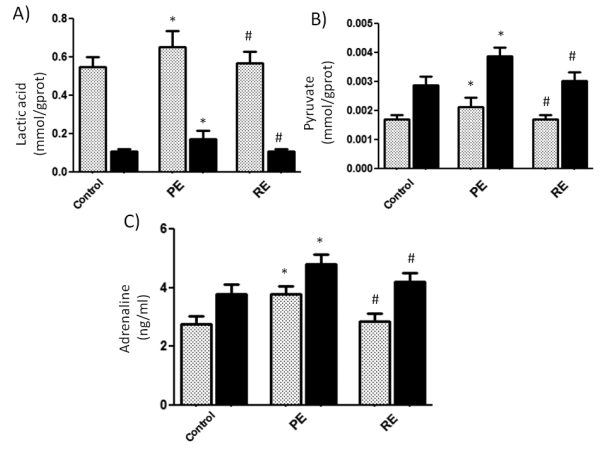

Figure 3. Lactic acid, pyruvate, and epinephrine expression in the heart and kidney tissues of rats.
*P<0.05 for comparison with the corresponding tissue of the control group, and #P<0.05 for comparison with the corresponding tissue of the preeclampsia group.

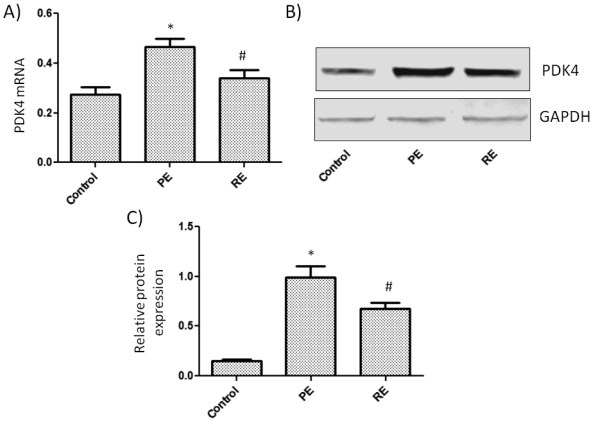

Figure 4. Pyruvate dehydrogenase kinase 4 expression in the myocardial tissue of rats.
*P<0.05 for comparison with the corresponding tissue of the control group, and #P<0.05 for comparison with the corresponding tissue of the preeclampsia group.

(P<0.05), but administration of Resveratrol downregulated the pyruvate level (P<0.05).

Epinephrine expression: The epinephrine level in the PE group was significantly higher than the control group (P<0.05), but administration of Resveratrol downregulated the pyruvate level (P<0.05; see Fig. 3).

PDK4 expression in the heart tissue

The mRNA and protein expression levels of PDK4 were highest in the PE group compared to control. It was significantly lowered in the RE group than in the PE group (P<0.05; see Fig. 4).

DISCUSSION

In the present study, the effects of Resveratrol on inflammatory cytokines and the energy metabolism disorder were evaluated in a preeclampsia rat model. We observed that Resveratrol had protective effects, as evidenced by the suppression of the expression and release of inflammatory cytokines and the regulation of energy metabolic indicators in preeclampsia rats.

Systemic inflammation plays a key role in the occurrence and development of multiple organ injury (Menden *et al.*, 2015). Endotoxin activates macrophages and monocytes, leading to an inflammatory cascade in which large quantities of inflammatory mediators, such as interleukins and TNF-α, are produced and released. Inflammatory mediators cause damage to alveolar epithelial cells, pulmonary capillary epithelial cells, and renal endothelial cells, leading to the progression of injury. Several cytokines have been implicated in the pathogenesis of preeclampsia (Conrad & Benyo, 1997). TNF-α is an important initiating factor that mediates endotoxic shock, systemic inflammatory response syndrome, and organ injury (Susantitaphong *et al.*, 2013). TNF-α damages lysosomes; causes enzymes to leak; promotes the migration of leukocytes to the site of inflammation; induces endothelial cells and macrophages to synthesize and release IL-1, IL-6, IL-8, superoxide, and lysosome; and promotes inflammation, the metabolism of arachidonic acid, the production of lipid mediators, and the formation of microthrombosis, which lead to lung and kidney damage. IL-6 is also an important inflammatory factor that is secreted in large quantities in the lungs and blood of patients with multiple organ injury. IL-6 levels in patients with multiple organ injury are significantly higher than in healthy people and can reflect the degree of lung tissue damage. IL-6 participates in the differentiation and infiltration of macrophages, which can induce the production of adhesion molecules by activating the expression of complement and C-reactive protein, vascular endothelial cells, and lymphocytes and participate in the acute phase response of lung and kidney injury (Hattar *et al.*, 2001). Therefore, inhibiting the production of cytokines is an effective means of treating inflammatory diseases. This study showed that during preeclampsia, a significant increase in the levels of TNF-α and IL-6 in lung and kidney tissues, and Resveratrol can reduce multiple organ dysfunction caused by preeclampsia by reducing the levels of the pro-inflammatory factors TNF-α and IL-6.

At the onset and during the development of preeclampsia, redox damage caused by oxygen free radicals is one of the important causes of multiple organ dysfunction (Gupte & Wagh, 2014). In preeclampsia, many oxygen free radicals attack the polyunsaturated fatty acids in the biofilm, triggering lipid peroxidation and forming a large quantity of the lipid peroxidation product MDA. MDA is lipid peroxide and a marker of oxidative stress and antioxidant status. MDA levels can reflect the severity of the attack of oxygen free radicals on the body. SOD is a natural scavenger of oxygen free radicals in organisms and can scavenge superoxide anions and free radicals to protect cells from damage. SOD levels can indirectly reflect the body's ability to scavenge oxygen free radicals, and maintains body's oxidation and antioxidant balance. The combined detection of SOD and MDA can accurately reflect the oxidative stress state and represent the degree of tissue damage.

This study found that when compared with the control group, MDA levels in the lung and kidney tissues of the Preeclampsia group (PR) group were significantly higher and SOD levels were significantly lower, suggesting that Preeclampsia caused oxidative stress damage to these tissues. Resveratrol can increase SOD levels and reduce MDA levels, suggesting that Resveratrol can reduce the production of oxygen free radicals, improve the body's antioxidant capacity, and inhibit the oxidative stress damage caused by Preeclampsia.

Hyperlactic acidemia is considered to be a sign of oxygen debt, systemic hypoxia, and anaerobic metabolism. Elevated lactic acid levels represent an energy metabolism disorder, and decreased levels of lactic acid signify

an improvement in tissue hypoxia and energy metabolism (Husain *et al*., 2003). Pyruvate is the direct and sole precursor of lactic acid, the end product of glycolysis, and the starter of the tricarboxylic acid cycle. Elevated pyruvate levels may be a consequence of reduced oxygen delivery (ischemic hypoxia) and reflect mitochondrial dysfunction (Hajjej *et al*., 2017). Both lactic acid and pyruvate are the products of glucose metabolism and abnormalities can reflect a disorder in energy metabolism.

Myocardial dysfunction is a common complication of Preeclampsia (Melchiorre *et al*., 2012). PDK4 is a key enzyme that regulates the pyruvate dehydrogenase complex (PDC). In some cases, the overexpression of PDK4 can lead to PDC inactivation, mitochondrial dysfunction, and negative health consequences (Jeon *et al*., 2021). Energy metabolism disorder is one of the important causes of myocardial damage in Preeclampsia (Hu *et al*., 2022). This study found that when compared with the control group, the lactic acid and pyruvate levels and the PDK4 gene and protein expression in the myocardial tissue were significantly higher in the Preeclampsia group, which suggests that Preeclampsia leads to increased anaerobic glycolysis in the heart and kidney tissues, causes glucose metabolism disorders, and results in the accumulation of lactic acid and pyruvate, which aggravate heart and kidney dysfunction. The results demonstrated that Resveratrol downregulated the excessive expression of the PDK4 and reduced the content of lactic acid and pyruvate in the heart and kidney tissues. Therefore, Resveratrol can reduce heart and kidney dysfunction induced by preeclampsia by regulating energy metabolism.

In the present study, we deduced that Resveratrol could decrease the exaggerated inflammatory response during preeclampsia conditions. Therefore, Resveratrol may be advantageous as a potential therapeutic agent for patients with preeclampsia.

CONCLUSIONS

In summary, Resveratrol can protect against multiple organ injury caused by preeclampsia by reducing the expression of anti-inflammatory cytokines and through the anti-oxidative stress pathway. Resveratrol can also inhibit the body's stress response, improve energy metabolism, and protect the heart tissue from preeclampsia. Therefore, Resveratrol is worthy of further investigation as a potential intervention strategy for preeclampsia in preeclampsia. Further studies are required to elucidate the precise mechanism of its protective action.

Declarations

Conflict of interest. The authors declare no conflict of interest.

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