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# The effect of resveratrol in cardio-metabolic disorders during pregnancy and offspring outcomes: a review

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**Review**

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## Abstract

Resveratrol supplementation during pregnancy and lactation has been associated with a reduced risk of maternal obesity, gestational diabetes mellitus , and preeclampsia. In addition, emerging evidence has shown that maternal resveratrol supplementation diminishes cardio-metabolic disorders in offspring, highlighting its role in modulating adaptative responses involving phenotypical plasticity. Therefore, it is reasonable to infer that administration of resveratrol during pregnancy and lactation periods could be considered an important nutritional intervention to decrease the risk of maternal and offspring cardio-metabolic disorders. To highlight these new insights, this literature review will summarize the understanding emerging from experimental and clinical studies about resveratrol supplementation and its capacity to prevent or minimize maternal and offspring cardio-metabolic disorders.

## Introduction

Maternal cardio-metabolic disorders, including gestational diabetes mellitus (GDM) and hypertensive disorders, are reported risk factors for maternal and offspring mortality. In part, inappropriate nutrition (under or overnutrition) has been the leading cause of cardio-metabolic diseases during pregnancy.[1] Epidemiological evidence has demonstrated that metabolic disorders experienced *in utero* or during early life are a risk factor for developing cardio-metabolic disorders in offspring in later life. According to the developmental origins of adult health and disease (DOHaD) hypothesis, impairments in nutritional consumption during pregnancy and lactation can lead to an adverse adaptation *in utero,* impact fetal growth during critical windows of development, and increase the risk of cardio-metabolic disease in adulthood.[2-5]

Fetal exposure to maternal cardio-metabolic disorder increases the risk of obesity and type 2 diabetes in later life.[6] The pathophysiological mechanisms associated with perinatal cardio-metabolic disorders involve increased oxidative stress, the release of pro-inflammatory mediators, and impaired adipokine signaling.[1] Experimental evidence revealed that these disturbs increase oxidative stress-related factors, including 8-hydroxy-2-deoxyguanosine.[1] Furthermore, mitochondrial dysfunction leads to increased reactive oxygen species (ROS) production and oxidative stress that can damage biological molecules, cells, and tissues.[1] Therefore, antioxidant and anti-inflammatory interventions, such as polyphenols, can represent a potential intervention in treating maternal cardio-metabolic disorders and their harmful effects on offspring.

Emerging evidence has suggested that high maternal dietary intake of polyphenols, known for their antioxidant properties, was associated with a reduced risk of maternal obesity[7] and cardio-metabolic disorders, such as GDM,[8] preeclampsia.[9] Polyphenols are plant-derived secondary metabolites found naturally in a wide range of foods, including fruits, vegetables, cereals, and beverages such as red wine, coffee, cocoa, and tea,[10] which are divided into four main classes, including flavonoids, phenolic acids, stilbenes, and lignans.[11] Among the polyphenols present in foods, resveratrol has received increased interest due to its antioxidant and anti-inflammatory properties and evidence associating their intake with preventing non-communicable diseases.[12,13]

In this way, nutritional approaches with resveratrol during pregnancy and lactation periods could be considered an essential intervention to reduce the risk of maternal and offspring cardio-metabolic disorders.[14-16] In addition, it is pertinent to explore the effectiveness of early administration of resveratrol to prevent metabolic diseases in later life.

This review will highlight these new insights and present the effects of interventions with resveratrol on maternal metabolic disorders and their potential benefits on offspring health. We have focused on resveratrol because of its safety during pregnancy in preclinical studies.[17] In clinical conditions, resveratrol has been reported to be safe when used either alone or as a

combination therapy.[18] However, there are no data on the safety of resveratrol in clinical studies with pregnant women. The current literature review will focus on the emerging findings of experimental and clinical studies that used resveratrol supplementation to prevent or treat maternal and offspring cardio-metabolic disorders. To further investigate the effectiveness of this polyphenol source, we will focus on dosage, duration of treatment, the gestational timing of exposure, and the primary outcomes reported.

## Resveratrol

Resveratrol (3, 5, 4'-trihydroxy stilbene) belongs to the stilbenes class, being naturally present in many natural plants such as *Polygonum cuspidatum* and bark and seeds of grapes, wine, peanuts, blueberry, bilberry, and cranberry.[13,19-22] A growing body of evidence has indicated that resveratrol has a broad range of beneficial effects on human health,[23] including anti-hypertensive,[24] anti-inflammatory,[25] anti-obesity,[26] antidiabetic,[27] and antioxidant properties.[28]

Resveratrol can exist in two forms: the trans-resveratrol form, the most organic form, and the cis-resveratrol form, obtained by the action of light on the trans-resveratrol form.[29] This bioactive compound has low bioavailability and water solubility (less than 0.05 mg/mL). To improve their bioavailability, nanoparticles and nanostructures containing resveratrol have been developed.[30] Resveratrol metabolism consists of the activity of some metabolic processes, such as glucuronidation, sulfation, and microbial biotransformation, and can be influenced by different factors, such as dosage, duration of supplementation, species, sex, gender, and disease state.[31]

The dosage, duration, and time of intervention with resveratrol vary depending on the clinical condition. For example, a meta-analysis carried out with 17 randomized controlled trials (RCTs) suggested that the effect of resveratrol as an active compound to promote cardiovascular health mainly was when used in high daily doses (300 mg/d) in diabetes mellitus patients.[24] On the other hand, a meta-analysis performed with 28 RCTs suggested that resveratrol supplementation, particularly at the dosages of <500 mg $d^{-1}$ and for periods of more than three months, reduced body weight (BW), body mass index, and waist circumference, but not fat mass in subjects with obesity.[32] In the following sections, we will discuss the role of resveratrol during pregnancy and lactation to prevent maternal and offspring cardio-metabolic disorders: GDM, preeclampsia, and causative disorders, such as maternal protein restriction and maternal obesity.

## Treatment with resveratrol during pregnancy and lactation

Maternal supplementation with resveratrol has been used as a therapeutic agent for pregnancy complications in rodent models, such as preeclampsia,[33] GDM,[34] and fetal growth restriction (FGR).[35] Recently, the potential use of resveratrol in adverse human pregnancies has been under investigation.[36,37]

A recent systematic review evaluated the effects of resveratrol supplementation during pregnancy on maternal and offspring health outcomes in 31 studies of complicated pregnancies and suggested that resveratrol possesses epigenetic effects that can influence the placenta, fetal tissues, and organs during the gestational period. However, the different species, dosage, and administration routes of study have limited the interpretation of resveratrol supplementation's effectiveness in complicated pregnancy models.[38]

Some underlying mechanisms have been described to explain the beneficial effects of maternal intervention with resveratrol on the offspring. For example, it was shown that maternal resveratrol consumption could decrease inflammation and oxidative stress in placental and embryonic tissues.[39] In addition, it is reported that maternal resveratrol consumption reduces serum levels of leptin, a typical condition of obesity caused by increased resistance to the action of this hormone. Another potential mechanism is that maternal resveratrol consumption leads to epigenetic modulation, including methylation and acetylation processes, which regulate gene expression.[40] Among main epigenetic changes, resveratrol modulates histone H3 on lysine 9 (H3K9) methylation and acetylation in the zygotic pronuclei. Also, gestational resveratrol exposure induced breast cancer-1 (BRCA-1) promoter hypermethylation and decreased BRCA-1 expression in mammary tissue of rat offspring.

Concerning embryo and fetus outcomes, it was demonstrated that supplementation of maternal diets with resveratrol (4 g/kg diet) during pregnancy alleviated adverse effects in a rat model of severe hypoxia, suggesting that resveratrol can cross the placenta and act on the fetus.[41] Similar results were found in experimental models of preeclampsia, characterized by a dysfunctional placenta resulting from intermittent placental hypoxia and ischemic injury.[42] In this study, resveratrol treatment increased uterine artery blood flow and fetal oxygenation, increased antioxidant enzymes in the placenta, and reduced markers of endothelial dysfunction, enhancing placental and fetal weight.[42] Based on preclinical findings, it is suggested that resveratrol supplementation during pregnancy may be effective, safe, and confer benefits for the mother and also for the embryo and fetus. However, when administered during pregnancy, it remains unclear if resveratrol could trigger maladaptation of the placenta and induce adverse effects, highlighting the need for further studies to investigate potential adverse effects on placenta development caused by resveratrol during pregnancy.

The therapeutic potential of resveratrol was also evaluated after fetal damage induced by lipopolysaccharide (LPS) exposure. Dietary supplementation with resveratrol (120 mg of resveratrol per kg of rodent diet) given to the mother during pregnancy protected offspring against striatal dopaminergic deficits caused by in utero LPS exposure.[43] In addition, a recent study showed that resveratrol inhibited uterine myometrium contractility of human term pregnancy by modulating K+ channels, suggesting that resveratrol may attenuate the risk of premature delivery or fetal aggression at the end of gestation.[44]

Regarding the effects of resveratrol on the milk composition, it was demonstrated that dietary resveratrol supplementation (300 mg/kg) during gestational and lactating of sows improved lactose content in the colostrum and the milk fat content at day 21 of lactation. In addition, resveratrol supplementation on sows increased high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (LDL-C) in the plasma and partially improved the fat metabolism in adipose tissue of piglets.[45]

It was recently suggested that supplementation with 40 mg/kg of resveratrol during pregnancy and lactation could promote mammary gland cells proliferation and enhance the mammary gland antioxidant capacity through mitophagy activation. Moreover, administration of resveratrol increased the abundance of intestinal microbiota in pregnant mice, such as *Acidobacteri* at the phylum level, *Bacilales* at the order level, *Staphylococcaceae* at the family level, and *Staphylococcus* at the genus level.[46] Therefore, maternal supplementation with resveratrol plays a protective role on the fetus due to different

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**Table 1.** Preclinical studies using resveratrol in the treatment of models of GDM

| Reference | Model | Dose | Duration of treatment | Maternal outcomes | Embryonic, fetal, and neonatal outcomes |
|---|---|---|---|---|---|
| Singh, Kumar et al. 2011 | Rat | 100 mg/kg. | 10 d (during pregnancy). | Improved glucose and lipid profile during the gestation period. | ↓ Oxidative stress (normalized the LPO level, ↓GSH, SOD levels and activity, and HNE presence) in embryos; ↓ Apoptosis in embryos; Preventing embryonic development delay (improved weight of embryo, crown-rump length, and somite number). |
| Wang et al. 2019 | Rat | 20 mg/kg. | Protocol 1: On days 1, 4, 7, 10, 15, and 20 of pregnancy; Protocol 2: postnatal life (once every 3 d and continuously for 4 weeks). | ↑ mRNA expression of ERβ and SOD2 in the amygdala; ↓ Superoxide anion release and 3-nitrotyrosine formation. | Partially improved social recognition tests. |
| Yao, Wan et al. 2015 | Mice | 10 mg/kg. | 4 weeks (before pregnancy and 20 d during pregnancy). | ↓ Hyperglycemia and insulin resistance. | ↑ Fetal survival; ↑ Litter size; ↓ BW at birth. |
| Brawerman, Kereliuk et al. 2019 | Rat | 147 mg/kg. | Start at the beginning of the third trimester of pregnancy. | Improved glucose homeostasis and insulin secretion. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. |
| Zheng, Chen, 2021 | Mice | 0.2% | 2–3 weeks during gestation (until gestational day 18) | ↓ BW; ↓ Blood glucose levels; ↓ Insulin level; ↑ Expression of leptin and adiponectin. | The authors did not evaluate embryonic, fetal and neonatal outcomes. |
| Zhang et al. 2021 | Rat | 60, 120, and 240 mg/kg | 2 weeks (during gestation) | ↓ BW; ↓ Blood glucose levels; ↑ Insulin level; Improved lipid profile (decreased total cholesterol, TG, LDL-C, and increased HDL-C level); ↓ Leptin; ↑Adiponectin; ↓ Resistin. ↓ TNF-α, and IL-6 levels ↓ TNF-α, and IL-6 Levels in Plasma. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. |

metabolic and endocrine signals transmitted by the uterus from the placenta and breast milk.

## Effects of resveratrol treatment on maternal cardio-metabolic disorders and related-causative disorders

### *Resveratrol intervention on GDM in preclinical studies*

Different methods of perinatal supplementation of resveratrol attenuated the appearance of GDM (Table 1). Using a diabetic embryopathy model in rats, the intervention with resveratrol for 10 d (100 mg/kg) during pregnancy prevented oxidative stress and apoptosis in embryos and improved glucose and lipid profile of diabetic dams.[47] Considering these results, maternal resveratrol administration demonstrated antioxidant capacity to prevent embryonic malformations, including neural tube defects.

Recently, the role of resveratrol in maternal diabetes-induced autism spectrum disorder was investigated. Studies in rodents have demonstrated that maternal diabetes may induce autism-like behavior in offspring through hyperglycemia-mediated persistent oxidative stress and downregulation of estrogen receptor β (ERβ) and superoxide dismutase 2 (SOD2) in the amygdala. Conversely, treatment with resveratrol (20 mg/kg for four weeks after pregnancy and during pregnancy) reversed these effects through increased expression of ERβ and SOD2 in the amygdala. In addition, these responses were more effective in female rats,[48,49] which suggests that female offspring appear to be more responsive to resveratrol treatment than male offspring. A possible explanation is that basal ERβ expression in the amygdala is significantly higher in female rats compared to male rats.

Resveratrol treatment on the *db*/+ genetic GDM mouse model at the dose of 10 mg/kg 4 weeks before pregnancy and 20 d during pregnancy significantly alleviated hyperglycemia and insulin resistance in pregnant *db*/+ mice, as well as increased fetal survival and improved BW at birth.[50] Moreover, the study demonstrated that resveratrol treatment attenuated hyperglycemia and insulin resistance by enhancing adenosine monophosphate-activated protein kinase (AMPK) and reducing glucose-6-phosphatase activity in the liver in both pregnant *db*/+ mice and their offspring.[50] In consequence of these protective effects, supplementation with resveratrol attenuated adverse effects of GDM by improving reproductive outcomes, including increased litter size and BW at birth.

An experimental study verified that the daily treatment with resveratrol (147 mg/kg) at the beginning of the third trimester of pregnancy (onset of GDM development) and throughout lactation improved glucose homeostasis and insulin secretion in dams with GDM. In addition, maternal resveratrol supplementation attenuated obesity, prevented hepatic steatosis, and improved insulin sensitivity and islet dysfunction in male rat offspring.[51]

A study in mice identified that a 0.2% dose of resveratrol during 2–3 weeks of gestation induced maternal benefits. The main benefits were decreased bodyweight, plasma glucose, and increased leptin and adiponectin expression.[52] Similarly, a study testing different doses of resveratrol in rats (60, 120, and 240 mg/kg) during two weeks of pregnancy observed a decrease in BW, blood glucose levels, and an improvement in the lipid and inflammatory profile.[53]

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### Resveratrol intervention on maternal protein restriction in preclinical studies

During pregnancy, maternal protein restriction increases serum glucocorticoids and oxidative stress by generating ROS, leading to metabolic dysfunction in both mother and offspring.[54,55] The gestational protein restriction model is commonly used in studies in the DOHaD field. This model reflects the dietary inadequacies typically observed in underdeveloped and emerging countries. An early study demonstrated that maternal supplementation with resveratrol (at a dose of 20 mg/kg/d, from the first day of gestation until delivery) partially decreased maternal and placental oxidative stress biomarkers in *Wistar* rats subjected to protein restriction.[56] Additionally, the authors demonstrated that the liver oxidative stress in offspring from dams fed a low protein diet was diminished when dams received resveratrol supplementation during pregnancy.[56-58] However, we highlight that these effects need to be investigated in RCTs to confirm these findings in human studies.

### Resveratrol intervention on maternal obesity in preclinical studies

Evidence has shown that perinatal treatment with resveratrol can reduce maternal obesity and related symptoms (Table 2). Supplementation with resveratrol attenuated harmful effects of high-fat diet (HFD)-induced obesity, improving maternal conditions, and reducing adverse effects on offspring.[59] It is noteworthy that the HFD used in preclinical studies shows different fat percentages, ranging from 32% to 61.6%, and the caloric amount ranging from 3.80 kcal/g to 5.56 kcal/g. In addition, most studies used 50 g of fiber, 3 g of vitamins, and 50 to 54.50 g of minerals. Furthermore, the most used fat sources were lard and soybean oil.

The beneficial responses reported to resveratrol supplementation were strongly associated with antioxidant, anti-inflammatory properties, epigenetic changes, and modulation of gut microbiota. Among antioxidant properties, resveratrol decreased the synthesis of reactive oxygen and nitrogen species and increased endogenous antioxidant gene expression. Regarding anti-inflammatory capacity, resveratrol supplementation reduces the production of pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNFα), interleukins like one-beta and six (Il-1β and IL-6), the production of nitric oxide (NO), and the translocation of Nuclear Factor kappa-B (NF-κB). Considering epigenetic changes, resveratrol modulates methylation and acetylation of lysine 9 of histone H3 in zygotic pronuclei. These changes in zygotes may lead to more successful preimplantation embryo development. Additionally, resveratrol can affect gut microbiota and their metabolic products, such as short-chain fatty acids and intraluminal lipids, helpful in obesity.[60] Therefore, it has been suggested that resveratrol supplementation in early life triggered adaptative responses involving phenotypical plasticity and could be considered a reprogramming strategy against the development of obesity and related symptoms.[61]

It was shown that maternal HFD consumption during gestation and lactation has undesirable long-term effects on male offspring, resulting in obesity, hyperphagia, hyperleptinemia, and leptin resistance in adulthood. The daily chronic treatment with resveratrol (30 mg/kg) from 150 until 180 d of age reversed hyperleptinemia, reduced BW, and improved central leptin action in adult rats offspring from HFD dams.[62] Similarly, resveratrol supplementation (42 d during pregnancy and lactation) at a concentration of 0.2% promoted the browning of white adipose tissue and increased the thermogenic activity of brown adipose tissue, reduced adiposity, and improved insulin sensitivity in adulthood in mice subjected to HFD, demonstrating that maternal resveratrol supplementation had lasting beneficial effects on offspring metabolic health.[63]

Maternal resveratrol treatment of rats at a concentration of 50 mg/L of resveratrol in the water to drink before and during pregnancy and lactation (8 weeks) reduced retroperitoneal adiposity, improved leptin dysregulation by decreasing leptin/soluble leptin receptor (sOB-R) ratio, and reduced the gene expression of ATP citrate lyase (ACL) and acetyl-CoA carboxylase 2 of the retroperitoneal depot in male offspring exposed to prenatal HFD.[64] Another experimental study showed that exposure to a maternal HFD and a post-weaning HFD led to the most significant metabolic disruption in offspring and the daily treatment with resveratrol (at 10 mg/kg, for five weeks, before mating as well as during gestation and lactation) ameliorated metabolic syndrome by reduced BW, blood pressure, leptin, cholesterol, and triglyceride (TG) serum levels.[65] In addition, an early experimental study showed that the resveratrol supplementation (50 mg/L in drinking water) to pregnant rats dams during pregnancy and lactation attenuated offspring damage induced by HFD.[66] The main findings demonstrated that supplementation with resveratrol during the early stages of life decreased BW, adipose tissue, and serum leptin levels in pups with 21 d of postnatal life (P21), suggesting the protective effects of resveratrol observed in the offspring dependent on the maternal diet.[66] Analyzing if these metabolic changes are maintained in adulthood, these authors also found that maternal resveratrol intake reduced plasma cholesterol levels in adult offspring from HFD dams. In addition, resveratrol treatment during pregnancy and 21 d of lactation decreased visceral adipose tissue (VAT) in male offspring fed on a HFD and increased VAT depots in offspring from both sexes fed on a low-fat diet (LFD), suggesting that maternal resveratrol had long-lasting effects on metabolic health in offspring in a sex-specific manner with these effects being highly dependent on the maternal diet.[67] These findings suggest that resveratrol treatment on different developmental windows can exert a reprogramming strategy against obesity induced by maternal HFD consumption.

In pregnant Japanese macaques fed on a HFD, the addition of 0.37% of resveratrol in the diet between 3 months before the breeding and gestational day 130 resulted in 30% maternal weight loss and improved glucose tolerance, increased uterine artery volume blood flow, and decreased placental inflammation and liver TG deposition, demonstrating that resveratrol intake during pregnancy improves maternal, placental and fetal metabolic disturbances provoked by the HFD consumption.[68] Additionally, an early study showed that Western-style diet consumption during pregnancy impaired fetal islet capillary density and sympathetic islet innervation, suggesting a novel mechanism by which offspring are predisposed to developing type two diabetes mellitus in adulthood. Conversely, intervention with 0.37% of resveratrol in maternal diet between 3 months before the breeding and gestational day 130 restored the loss of fetal islet vascularity.[69]

Another study using the pregnant Japanese macaque reported that this maternal intervention with resveratrol before and throughout pregnancy increased placental docosahexaenoic acid uptake capacity, AMPK activation, and higher expression of multiple fatty acid transporters in the placenta, suggesting that resveratrol improves uterine and umbilical blood flow.[70]

The neuroprotective effects of resveratrol have also been investigated in offspring exposed to maternal obesity. For example, maternal HFD during pregnancy and lactation and a postnatal HFD promote the development of metabolic syndrome-related features, alter biochemical profiles in the dorsal hippocampus,

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**Table 2.** Preclinical studies using resveratrol in the treatment of models of maternal obesity

| Reference | Model | Dose | Duration of treatment | Maternal outcomes | Embryonic, fetal, and neonatal outcomes | Adulthood outcomes |
|---|---|---|---|---|---|---|
| Zou, Chen et al. 2017 | Mice | 0.2%. | During pregnancy and lactation (42 d). | ↓ BW; ↓ Fat accumulation; No differences in blood glucose levels; ↓ Serum insulin. | ↓BW; ↓WAT mass; ↑Thermogenic activity of BAT; ↓serum TG; ↓serum insulin. | ↓Adiposity; ↑Insulin sensitivity; ↑Energy expenditure. |
| Tsai, Tsai et al. 2020 | Rat | 50 mg/L. | 8 weeks (before, during pregnancy, and lactation). | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ BW; ↓ Retroperitoneal adiposity; No difference in blood glucose and TG concentration; ↓ Plasma leptin level; ↓ Leptin resistance; No difference in SIRT1 in retroperitoneal tissue; ↓The gene expression of ACL and ACC2. |
| Sheen, Yu et al. 2018 | Rat | 10 mg/kg. | 5 weeks (before mating and during gestation and lactation). | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ BW; ↓ Blood pressure; ↓ Blood glucose and serum insulin; ↓ Leptin, cholesterol, and TG serum levels. |
| Ros, Diaz et al. 2018 | Rat | 50 mg/L. | During pregnancy and lactation. | No difference in energy intake; No differences in glycemia or serum leptin levels; ↑ total cholesterol, LDL, and ↓ TG levels. | There is no difference in litter size; ↓ BW; ↓ Adipose tissue; ↓serum leptin levels. | The authors did not evaluate adulthood outcomes. |
| Ros, Diaz et al. 2020 | Rat | 50 mg/L. | During pregnancy and 21 d of lactation. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ Serum cholesterol level; ↓ VAT in male offspring |
| Roberts, Pound et al. 2014 | Pregnant Japanese macaques | 0.37%. | 12 weeks (before the breeding until gestational day 1). | Improved glucose tolerance; ↑ Uterine artery volume blood flow; ↓Placental inflammation and liver TG deposition | ↓ Lipid deposition in the fetal liver. | The authors did not evaluate adulthood outcomes. |
| Pound, Comstock et al. 2014 | Pregnant Japanese macaques. | 0.37%. | Before the breeding until gestational day 130. | The authors did not evaluate maternal outcomes. | Restored the loss of fetal islet vascularity. | The authors did not assess adulthood outcomes. |
| O'Tierney-Ginn, Roberts et al. 2015 | Pregnant Japanese macaques | 0.37%. | Before the breeding until gestational day 130. | The authors did not evaluate maternal outcomes. | ↑ Placental uptake of DHA; ↑ Placental AMPK activation; ↑ Expression of multiple fatty acid transporters in the placenta. | The authors did not assess adulthood outcomes. |
| Li, Yu et al. 2017 | Mice | The authors did not inform. | During the perinatal period, up to 4 months of age of the offspring. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ BW; Improved glucose tolerance; ↓ Blood pressure; Improved lipid profile; Restored the expression and regulation of SIRT1, phospho-ERK1/2, p66Shc, and BDNF in the hippocampus. |
| Huang, Huang et al. 2020 | Rat | 50 mg/L. | From the ages of 2 to 4 months. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ BW; ↓ Blood pressure; ↓ Retroperitoneal fat; No difference in blood glucose level; ↓ Leptin ↓ Gut microbiota dysbiosis. |
| Dolinsky, Rueda-Clausen et al. 2011 | Rat | 4 g/kg diet. | 9 weeks (starting at 3 weeks of age). | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | No difference in BW; No difference in body composition; ↓ Insulin resistance; ↓Hyperlipidemia |

(*Continued*)

**Table 2.** (*Continued*)

| Reference | Model | Dose | Duration of treatment | Maternal outcomes | Embryonic, fetal, and neonatal outcomes | Adulthood outcomes |
|---|---|---|---|---|---|---|
| Castro-Rodriguez et al. 2021 | Rat | 20 mg/kg/. | One month before mating and during gestation and lactation. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ BW; Female percentage of fat; No difference in serum glucose, TG, and cholesterol; Improved intestinal morphological parameters. |
| Serrano et al. 2021 | Mice | 2 mg/kg. | From day 2 to 20 of the age of postnatal life. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | Protection against HFD-induced lipid accumulation; ↑Muscular capacities for fat oxidation and mitochondria activity; ↓Capacity for lipogenesis in the liver. |
| Izquierdo et al. 2021 | Mice | 1 g/kg. | Throughout all study design. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ BW; ↓ Plasma leptin level; ↓ Reduced TG levels in the blood; ↓ Pro-inflammatory markers; ↑ BDNF levels; Improved cognitive function. |
| Hsu et al. 2020 | Rat | 50 mg/L. | Before the breeding until lactation. | The authors did not evaluate maternal outcomes. | Restored adiponectin and BDNF in the fetal brain. | ↓ BW; ↓Peripheral insulin resistance; Improved cognitive function. |

and lead to cognitive deficits in adult male offspring. Interestingly, treatment with resveratrol during the perinatal period up to 4 months of age of the offspring improved glucose tolerance and elevated blood pressure, partly rescued cognitive deficits, and also restored the expression and regulation of silent information regulator transcript 1 (SIRT1), phospho-ERK1/2, p66Shc and brain-derived neurotrophic factor (BDNF) in the hippocampus of mice.[71] However, the authors did not inform the dose and duration of treatment, making it challenging to interpret obtained findings. During pregnancy, maternal resveratrol treatment (50 mg/L in drinking water) was also reported to reduce BW, peripheral insulin resistance, blood pressure, and repaired hippocampal pAKT and BDNF in adult male offspring fed a HFD during pregnancy and postnatal period. These results indicate that supplementation with resveratrol attenuates metabolic disturbances and cognitive impairment in offspring exposed to maternal obesity.[72]

In addition, resveratrol intake in the drinking water (50 mg/L) from 2 to 4 months for offspring reduced gut microbiota dysbiosis induced in rats by prenatal and postnatal HFD exposure.[73] Additionally, in a combined prenatal hypoxia and postnatal HFD rat model, resveratrol supplementation (4 g/kg diet) for nine weeks, starting at three weeks of age, activated AMPK and attenuated insulin resistance and hyperlipidemia in male adult offspring, suggesting that early post-weaning resveratrol treatment between 3 and 12 week contributed to the improvement of the metabolic parameters in offspring born from pregnancies complicated by intrauterine growth restriction (IUGR).[74]

Resveratrol treatment at 20 g/kg started one month before mating, and throughout pregnancy and lactation, decreased bodyweight, fat percentage, and improved intestinal morphological parameters in adulthood offspring.[75] In addition, resveratrol treatment (2 mg/kg) from day 2 to 20 postnatal life in neonatal mice subjected to a HFD reduced lipid accumulation, increased muscular capacities for fat oxidation, and mitochondria activity through activation of the SIRT1-AMPK pathways.[76] Another recent study demonstrated that resveratrol treatment at 1 g/kg during the perinatal period triggered long-term responses, including reduced BW, blood leptin, and TG levels in neonatal mice, and improved inflammatory response profile and cognitive function in adulthood offspring.[77] Lastly, using 50 mg/L of resveratrol during the perinatal period, a loss in adiponectin and BDNF in the fetal brain was reported, as well as, long-term effects, including reduction of BW and peripheral insulin resistance, and improved cognitive function in adulthood offspring.[78]

## *Resveratrol intervention on models of complicated pregnancies, including preeclampsia*

Emerging evidence supports the idea that maternal intervention with resveratrol during pregnancy and lactation periods could serve as a reprogramming strategy to prevent models of complicated pregnancies, including preeclampsia (Table 3). Preeclampsia is a complication affecting pregnant women worldwide, which usually manifests as severe maternal hypertension and proteinuria.[79]

Maternal resveratrol supplementation (4 g/kg diet), from the first gestational day until postnatal day 21, prevented the development of hypertension in adult offspring and improved NO bioavailability in spontaneously hypertensive rats.[80] Another study demonstrated that maternal resveratrol supplementation at a dosage of 50 mg/L in drinking water during the entire pregnancy and lactation (a total of 6 weeks) alleviated programmed hypertension induced by combined maternal NG-nitro-L-arginine-methyl ester

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**Table 3.** Preclinical studies using resveratrol in the treatment of models of complicated pregnancies including preeclampsia

| Reference | Model | Dose | Duration of treatment | Maternal outcomes | Embryonic, fetal, and neonatal outcomes | Adulthood outcomes |
|---|---|---|---|---|---|---|
| Care, Sung et al. 2016 | Rat | 4 g/kg | From first gestational until postnatal day 21. | Improved NO bioavailability. | Growth restriction in the offspring by 3 weeks of age. | Prevented the development of hypertension. |
| Chen, Lin et al. 2019 | Rat | 50 mg/L | During the entire pregnancy and lactation | ↓ Programmed hypertension; Restored the *Firmicutes* to *Bacteroidetes* ratio. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ Systolic blood pressure and mean arterial pressure; ↑ Plasma GSH levels; Prevent the increase of *Firmicutes* to *Bacteroidetes* ratio. |
| Jia, Zhang et al. 2020 | Rat | 250 mg/kg | 4 weeks (from the 7th week until the 10th week of pregnancy). | ↓ Systolic and diastolic blood pressure. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | The authors did not assess adulthood outcomes. |
| Shah, Reyes et al. 2016 | Rat | 4 g/kg | For 9 weeks of postnatal life. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓Insulin resistance; Promoted cardiac; Recovery from I/R injury; ↓Superoxide levels. |
| Rueda-Clausen, Morton et al. 2012 | Rat | 4 g/kg | Between 3–12 weeks of postnatal age. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | Prevented the harmful cardiovascular effects; improved postischemic recovery in hearts from offspring born IUGR). |
| Tain, Lee et al. 2018 | Rat | 50 mg/L | From weaning to three months of age. | The authors did not evaluate maternal outcomes. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | ↓ Systolic blood pressure and diastolic blood pressure; ↓The *Firmicutes* to *Proteobacteria* ratio. |
| Zou, Zuo et al. 2014 | Rat | 20 mg/kg/d twice daily | Twice daily during the entire pregnancy. | ↓Oxidative stress injury; ↓ Systolic blood pressure. | No differences in litter size, external malformations, or birth weight of fetuses. | The authors did not evaluate adulthood outcomes. |
| Zou, Li et al. 2019 | Rat | 20 mg/kg/d | During pregnancy until gestational day 18.5. | ↓ Hypertension and proteinuria. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | The authors did not assess adulthood outcomes. |
| Moraloglu, Engin-Ustun et al. 2012 | Rat | 20mg/kg twice daily | During the entire pregnancy. | No difference in blood pressure, blood flows, and placental pathology parameters. | The authors did not evaluate embryonic, fetal, and neonatal outcomes. | The authors did not assess adulthood outcomes. |
| Poudel, Stanley et al. 2013 | Mice | 4 g/kg | During pregnancy (from gestational day 0.5 to 18.5). | ↑ In the uterine artery, blood flow velocity. | ↑ Fetal weight. | The authors did not evaluate adulthood outcomes. |

(L-NAME) treatment and postnatal HFD and restored the *Firmicutes* to *Bacteroidetes* (F/B) ratio in male adult offspring.[81]

In a hypertensive pregnant rat model, it was demonstrated that oral resveratrol supplementation (250 mg/kg/d) for four weeks (from the 7th week until the 10th week of pregnancy) significantly reduced systolic blood pressure, diastolic blood pressure, and mean arterial pressure on gestational days 7 and 14. In addition, it was shown that treatment effectively increases sodium excretion and serum NO levels. These findings indicated that resveratrol could be a promising candidate as a blood pressure-lowering agent for pregnancy-induced hypertension treatment.[82]

In pregnant Sprague Dawley rat model who submitted hypoxia (11% O2) from gestational day 15–21, it was shown that at 12 months of age, hypoxia in utero and HFD, offered during nine weeks, impaired metabolic and cardiac function in a sex-specific manner, indicating that male offspring was more susceptible to a manifestation of metabolic and cardiovascular disorders compared with their female counterparts. In addition, it was found that indices of cardiac oxidative stress after ischemia-reperfusion (I/R) injury were enhanced in both male and female rat offspring exposed to prenatal hypoxia. Resveratrol supplementation in the diet (4 g/kg) for nine weeks in postnatal life attenuated insulin resistance, recovered cardiac damage provoked by I/R injury, and attenuated superoxide levels, suggesting that early intervention with resveratrol could be a potential therapeutic approach to prevent the development of metabolic and cardiovascular diseases in adult male and female offspring.[83]

Furthermore, these authors demonstrated that postnatal resveratrol supplementation in diet (4 g/kg) for 18 weeks (from 13 to 21 weeks of age) could reduce heart damage by increasing cardiac p-AMPK and SOD2 levels in female IUGR offspring, but not in male IUGR offspring, suggesting that resveratrol treatment of adult IUGR offspring, improved cardiac function recovery in both sexes, however, the mechanisms involved were partially sex-specific and could be a strategy to counteract also the long-term oxidative damage induced by fetal hypoxia.[35]

Additionally, it has been demonstrated that postnatal resveratrol supplementation in diet (4 g/kg) between 3 and 12 weeks of age

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**Table 4.** Clinical studies using resveratrol in the treatment of cardio-metabolic disorders

| Reference | Type of study | Cardio-metabolic disorder | Dose | Duration of treatment | Maternal outcomes | Neonatal outcomes |
|---|---|---|---|---|---|---|
| Malvasi, Kosmas et al. 2017 | Clinical study (110 overweight pregnant women) | Maternal overweight | 80 mg of resveratrol combined with plus D-chiro-inositol and Myo-inositol | 30 or 60 d of supplementation during pregnancy | Improved the glucose levels, total cholesterol, LDL-C, and TG | The authors did not evaluate neonatal outcomes |
| Ding, Kang et al. 2017 | Clinical study (359 pregnant women with preeclampsia) | Preeclampsia | Capsules at a dose of 50 mg each, up to 5 dosages | During pregnancy | ↓ Time required to control blood pressure; ↑ The intervals between hypertensive crises | No neonatal adverse effects were observed |

prevented the harmful cardiovascular effects of HFD in male offspring exposed to prenatal hypoxia.[84] The study showed that postnatal resveratrol supplementation improved baseline heart rate and post-ischemic recovery in hearts from offspring born with IUGR.[84]

In male adult offspring exposed to combined maternal and post-weaning HFD was demonstrated that 0.5% resveratrol in drinking water between 2 and 4 months of age prevented hypertension through several underlying mechanisms, to cite: reduced oxidative stress in the kidney, mediating the renin-angiotensin system in favor of vasodilatation, restoration of nutrient-sensing pathways via increasing SIRT1, AMP-activated protein kinase 2 α (AMPK2 α), and peroxisome proliferator-activated receptor-gamma coactivator 1-α, and induction of autophagy.[85]

Similarly, it was demonstrated that early post-weaning intervention with resveratrol at a dosage of 50 mg/L in drinking water from weaning to three months of age reduced systolic blood pressure and diastolic blood pressure, as well as reduced the *Firmicutes* to *Proteobacteria* ratio; therefore, resveratrol therapy prevented the development of hypertension programmed by maternal and post-weaning high-fructose diet in male adult offspring. These results were linked to a reduction in renal oxidative stress, activation of several nutrient-sensing signals, and restoration of gut microbiota.[86]

It has been reported that resveratrol at a dosage of 20 mg/kg twice a day during pregnancy reduced oxidative stress injury in pregnant rats with preeclampsia.[87] Likewise, it was demonstrated that treatment with resveratrol (20 mg/kg/d) during pregnancy stimulated trophoblasts' invasive capability and reduced preeclampsia-related symptoms, including reduced hypertension and proteinuria. Thus, these data suggest that resveratrol could represent a therapeutic agent to prevent the occurrence and development of preeclampsia.[88]

A study using a rat model of preeclampsia that received an intervention with resveratrol at a dose of 20 mg/kg/d by gavage twice daily during the whole pregnancy did not demonstrate decreased blood pressure and did not result in a significant response in blood flows and placental pathology parameters.[33] On the other hand, in pregnant catechol-O-methyltransferase knockout mice that received a diet enriched with resveratrol (4 g/kg diet) during pregnancy (from gestational day 0.5 to 18.5) was observed an increase in uterine artery blood flow velocity and fetal weight, suggesting potential as a therapeutic strategy for preeclampsia and FGR.[89]

### *Resveratrol intervention on maternal cardio-metabolic disorders in clinical studies*

Although there is vast literature on the effect of resveratrol on maternal cardio-metabolic disorders in experimental studies, there is little data about maternal supplementation of resveratrol during the perinatal period in clinical, controlled, blind randomized trials (Table 4). The majority of clinical studies in the literature investigated the potential effects of resveratrol consumption during adult life on cardiovascular risk factors.[90]

Regarding GDM, resveratrol supplementation was tested in a study using human placenta, omental adipose tissue, and skeletal muscle obtained from non-obese women who delivered healthy, singleton infants at term. Then, tissues were subjected to a diabetic model using bacterial LPS, the synthetic viral dsRNA analogous polyinosinic-polycytidylic acid, and stimulated by pro-inflammatory cytokines (i.e., IL-1β, TNF-α). To determine the effects of resveratrol, collected tissues were incubated in 10 μg/ml LPS, 50 μg/ml poly(I: C), 10 ng/ml TNF-α, 5 ng/ml IL-1β with or without 200 μm resveratrol. It was demonstrated that resveratrol was able to decrease the expression and secretion of pro-inflammatory cytokines (IL-6, IL-1α, and IL-1β) and pro-inflammatory chemokines IL-8 and monocyte chemoattractant protein-1 (MCP-1) in the placenta and adipose tissue and increase insulin sensitivity in skeletal muscle, suggesting that resveratrol could be a useful preventative therapeutic for GDM.[91]

In a prospective, randomized, double-blinded, placebo-controlled clinical trial performed with 110 overweight pregnant women was demonstrated that intervention with 80 mg of resveratrol combined with plus D-chiro-inositol and Myo-inositol during pregnancy significantly improved the glucose levels, total cholesterol, LDL-C, and TG after 30 or 60 d of supplementation.[37] However, the authors did not report any effect of resveratrol in attenuating BW in overweight pregnant women. Therefore, further well-designed double-blind controlled human trials are needed to confirm the clinical efficacy of resveratrol in attenuating gestational overweight.

Few clinical studies investigated the role of resveratrol in preventing preeclampsia. An RCT performed with 359 pregnant women with preeclampsia who received resveratrol capsules at a dose of 50 mg each, up to five dosages, demonstrated that resveratrol supplementation was an effective adjuvant for the treatment of hypertensive symptoms in pregnant women treated with nifedipine anti-hypertensive.[36] According to this study, treatment with resveratrol attenuated time required to control blood pressure compared with the placebo group ($35.6 \pm 18.7$ vs. $51.1 \pm 22.4$). In addition, supplementation with resveratrol increased the intervals between hypertensive crises. To investigate the antioxidant properties of resveratrol, a *vitro* study was developed by analysis of plasma collected from 30 women with preeclampsia compared with healthy pregnant, treated or not by resveratrol.[92] The main

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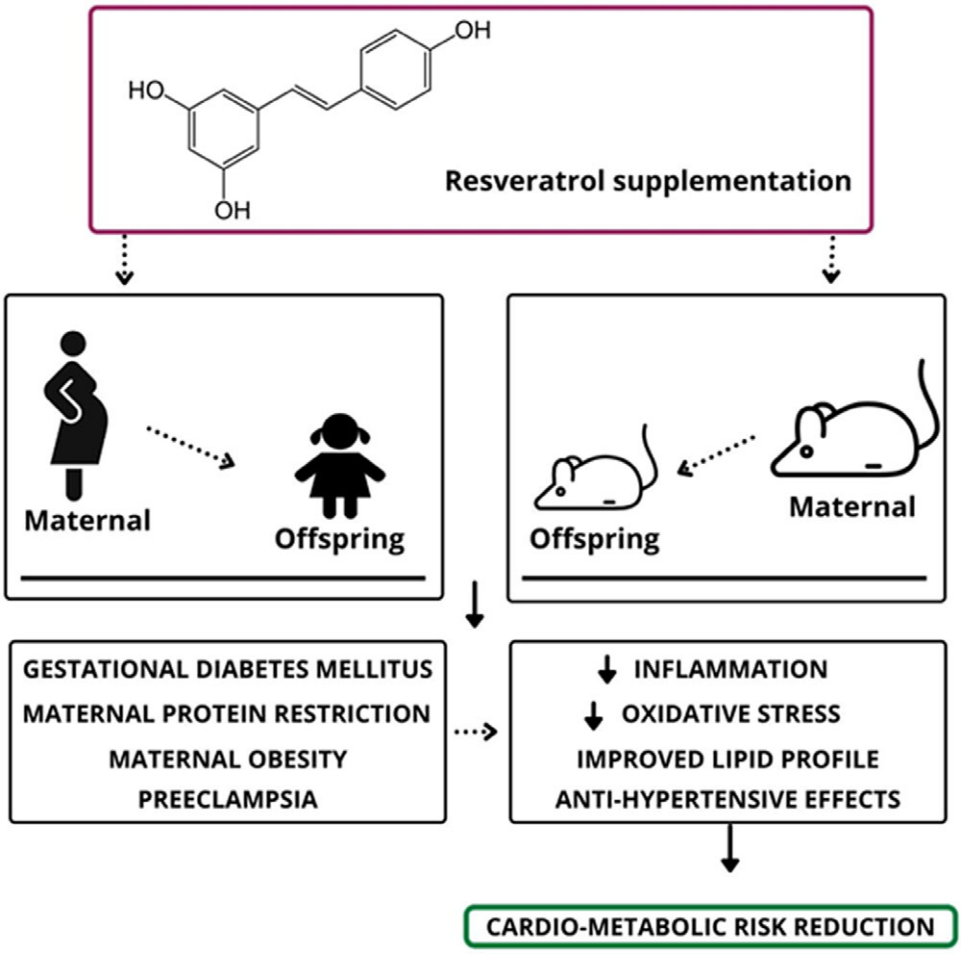


**Fig. 1.** Schematic drawing showing that maternal resveratrol supplementation reduces the risk of cardio-metabolic disorders, including gestational diabetes mellitus, malnutrition (protein restriction), maternal obesity, and preeclampsia.

findings showed that resveratrol improved the expression of genes and their related pathways associated with antioxidant defenses, such as increased expression of glutathione and nitrite levels. However, further clinical studies are needed to evaluate the effectiveness of resveratrol against preeclampsia disorder.

## Conclusion and prospects

Maternal supplementation with resveratrol can reduce the risk of cardio-metabolic disorders, including GDM, malnutrition (protein restriction), maternal obesity, and preeclampsia (Fig. 1). Preclinical studies showed that resveratrol administration might be an effective nutritional intervention to improve cardio-metabolic disorders in pregnancy and offspring outcomes. However, studies that evaluated the effectiveness of treatment with resveratrol during pregnancy and the early postnatal period show heterogeneities in terms of dose and duration of administration. Furthermore, there is a great lack of clinical data on the effectiveness of resveratrol in alleviating cardio-metabolic disorders during the perinatal period. Therefore, supplementation with resveratrol needs to be further investigated in randomized, double-blind, placebo-controlled trials to confirm these findings in human studies.

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## References

1. Agarwal P, Morriseau TS, Kereliuk SM, Doucette CA, Wicklow BA, Dolinsky VW. Maternal obesity, diabetes during pregnancy and epigenetic mechanisms that influence the developmental origins of cardiometabolic disease in the offspring. *Crit Rev Clin Lab Sci.* 2018; 55(2), 71–101.
2. Plagemann A, Harder T, Schellong K, Schulz S, Stupin JH. Early postnatal life as a critical time window for determination of long-term metabolic health. *Best Pract Res Clin Endocrinol Metab.* 2012; 26(5), 641–653.
3. Gluckman PD, Hanson MA. The developmental origins of the metabolic syndrome. *Trends Endocrinol Metab.* 2004; 15(4), 183–187.
4. Gluckman PD, Hanson MA, Beedle AS. Early life events and their consequences for later disease: a life history and evolutionary perspective. *Am J Hum Biol.* 2007; 19(1), 1–19.
5. Bateson P. Fetal experience and good adult design. *Int J Epidemiol.* 2001; 30(5), 928–934.
6. Fall CHD, Kumaran K. Metabolic programming in early life in humans. *Philos Trans R Soc Lond B Biol Sci.* 2019; 374(1770), 20180123.

https://doi.org/10.1017/S2040174422000332 Published online by Cambridge University Press

7. Zou T, Chen D, Yang Q, *et al.* Resveratrol supplementation of high-fat diet-fed pregnant mice promotes brown and beige adipocyte development and prevents obesity in male offspring. *J Physiol.* 2017; 595(5), 1547–1562.
8. Pham NM, Do VV, Lee AH. Polyphenol-rich foods and risk of gestational diabetes: a systematic review and meta-analysis. *European journal of clinical nutrition.* 2019; 73(5), 647–656.
9. Tenório MB, Ferreira RC, Moura FA, Bueno NB, Goulart MOF, Oliveira ACM. Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis.* 2018; 28(9), 865–876.
10. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.* 2009; 2(5), 270–278.
11. Perez-Jimenez J, Fezeu L, Touvier M, *et al.* Dietary intake of 337 polyphenols in French adults. *Am J Clin Nutr.* 2011; 93(6), 1220–1228.
12. Lacerda DC, Urquiza-Martinez MV, Manhaes-de-Castro R, *et al.* Metabolic and neurological consequences of the treatment with polyphenols: a systematic review in rodent models of noncommunicable diseases. *Nutr Neurosci.* 2021; 221, 1–17.
13. Dos Santos AS, de Albuquerque TMR, de Brito Alves JL, de Souza EL. Effects of quercetin and resveratrol on in vitro properties related to the functionality of potentially probiotic lactobacillus strains. *Front Microbiol.* 2019; 10, 2229.
14. Hahn M, Baierle M, Charao MF, *et al.* Polyphenol-rich food general and on pregnancy effects: a review. *Drug Chem Toxicol.* 2017; 40(3), 368–374.
15. Fogacci S, Fogacci F, Cicero AFG. Nutraceuticals and hypertensive disorders in pregnancy: the available clinical evidence. *Nutrients.* 2020; 12(2), 378.
16. Gao Q, Zhong C, Zhou X, *et al.* Inverse association of total polyphenols and flavonoids intake and the intake from fruits with the risk of gestational diabetes mellitus: a prospective cohort study. *Clin Nutr.* 2020; S0261-5614(20), 30290–30299.
17. Williams LD, Burdock GA, Edwards JA, Beck M, Bausch J. Safety studies conducted on high-purity trans-resveratrol in experimental animals. *Food Chem Toxicol.* 2009; 47(9), 2170–2182.
18. Singh AP, Singh R, Verma SS, *et al.* Health benefits of resveratrol: evidence from clinical studies. *Med Res Rev.* 2019; 39(5), 1851–1891.
19. Rangel-Huerta OD, Pastor-Villaescusa B, Aguilera CM, Gil A. A systematic review of the efficacy of bioactive compounds in cardiovascular disease: phenolic compounds. *Nutrients.* 2015; 7(7), 5177–5216.
20. Sanders TH, McMichael RW Jr., Hendrix KW. Occurrence of resveratrol in edible peanuts. *J Agric Food Chem.* 2000; 48(4), 1243–1246.
21. Vestergaard M, Ingmer H. Antibacterial and antifungal properties of resveratrol. *Int J Antimicrob Agents.* 2019; 53(6), 716–723.
22. Elshaer M, Chen Y, Wang XJ, Tang X. Resveratrol: an overview of its anticancer mechanisms. *Life Sci.* 2018; 207(7), 340–349.
23. Guo XF, Li JM, Tang J, Li D. Effects of resveratrol supplementation on risk factors of non-communicable diseases: a meta-analysis of randomized controlled trials. *Critic Rev Food Sci Nutr.* 2018; 58(17), 3016–3029.
24. Fogacci F, Tocci G, Presta V, Fratter A, Borghi C, Cicero AFG. Effect of resveratrol on blood pressure: a systematic review and meta-analysis of randomized, controlled, clinical trials. *Critic Rev Food Sci Nutr.* 2019; 59(10), 1605–1618.
25. Koushki M, Dashatan NA, Meshkani R. Effect of resveratrol supplementation on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Clin Ther.* 2018; 40(7), 1180–92 e5.
26. Tabrizi R, Tamtaji OR, Lankarani KB, *et al.* The effects of resveratrol intake on weight loss: a systematic review and meta-analysis of randomized controlled trials. *Critic Rev Food Sci Nutr.* 2020; 60(3), 375–390.
27. Zhu X, Wu C, Qiu S, Yuan X, Li L. Effects of resveratrol on glucose control and insulin sensitivity in subjects with type 2 diabetes: systematic review and meta-analysis. *Nutr Metab.* 2017; 14(1), 60.
28. Xia N, Daiber A, Förstermann U, Li H. Antioxidant effects of resveratrol in the cardiovascular system. *Br J Pharmacol.* 2017; 174(12), 1633–1646.
29. Delmas D, Cornebise C, Courtaut F, Xiao J, Aires V. New highlights of resveratrol: a review of properties against ocular diseases. *Int J Mol Sci.* 2021; 22(3), 1295.
30. de Vries K, Strydom M, Steenkamp V. A brief updated review of advances to enhance resveratrol's bioavailability. *Molecules.* 2021; 26(14), 4367.
31. Wang P, Sang S. Metabolism and pharmacokinetics of resveratrol and pterostilbene. *Biofactors.* 2018; 44(1), 16–25.
32. Mousavi SM, Milajerdi A, Sheikhi A, *et al.* Resveratrol supplementation significantly influences obesity measures: a systematic review and dose-response meta-analysis of randomized controlled trials. *Obes Rev.* 2019; 20(3), 487–498.
33. Moraloglu O, Engin-Ustun Y, Tonguc E, *et al.* The effect of resveratrol on blood pressure in a rat model of preeclampsia. *J Matern-Fetal Neonatal Med.* 2012; 25(6), 845–848.
34. Singh CK, Kumar A, Lavoie HA, Dipette DJ, Singh US. Diabetic complications in pregnancy: is resveratrol a solution? *Exp Biol Med.* 2013; 238(5), 482–490.
35. Shah A, Quon A, Morton JS, Davidge ST. Postnatal resveratrol supplementation improves cardiovascular function in male and female intrauterine growth restricted offspring. *Physiol Rep.* 2017; 5(2), e13109.
36. Ding J, Kang Y, Fan Y, Chen Q. Efficacy of resveratrol to supplement oral nifedipine treatment in pregnancy-induced preeclampsia. *Endocr Connect.* 2017; 6(8), 595–600.
37. Malvasi A, Kosmas I, Mynbaev OA, *et al.* Can trans resveratrol plus d-chiro-inositol and myo-inositol improve maternal metabolic profile in overweight pregnant patients? *La Clinica Ter.* 2017; 168(4), e240–e7.
38. Darby JRT, Mohd Dollah MHB, Regnault TRH, Williams MT, Morrison JL. Systematic review: impact of resveratrol exposure during pregnancy on maternal and fetal outcomes in animal models of human pregnancy complications - Are we ready for the clinic? *Pharmacol Res.* 2019; 144(672), 264–278.
39. Darby JRT, Saini BS, Soo JY, *et al.* Subcutaneous maternal resveratrol treatment increases uterine artery blood flow in the pregnant ewe and increases fetal but not cardiac growth. *J Physiol.* 2019; 597(20), 5063–5077.
40. Zheng S, Feng Q, Cheng J, Zheng J. Maternal resveratrol consumption and its programming effects on metabolic health in offspring mechanisms and potential implications. *Bioscience Rep.* 2018; 38(2), BSR20171741.
41. Bourque SL, Dolinsky VW, Dyck JR, Davidge ST. Maternal resveratrol treatment during pregnancy improves adverse fetal outcomes in a rat model of severe hypoxia. *Placenta.* 2012; 33(5), 449–452.
42. de Alwis N, Binder NK, Beard S, *et al.* Novel approaches to combat preeclampsia: from new drugs to innovative delivery. *Placenta.* 2020; 102(3), 10–16.
43. Rose KM, Parmar MS, Cavanaugh JE. Dietary supplementation with resveratrol protects against striatal dopaminergic deficits produced by in utero LPS exposure. *Brain Res.* 2014; 1573, 37–43.
44. Novaković R, Radunović N, Marković-Lipkovski J, *et al.* Effects of the polyphenol resveratrol on contractility of human term pregnant myometrium. *Mol Human Reprod.* 2015; 21(6), 545–551.
45. Sun S, Meng Q, Luo Z, Shi B, Bi C, Shan A. Effects of dietary resveratrol supplementation during gestation and lactation of sows on milk composition of sows and fat metabolism of sucking piglets. *J Anim Physiol Anim Nutr.* 2019; 103(3), 813–821.
46. Zha C, Xiao H, Song B, *et al.* Resveratrol promotes mammary cell proliferation and antioxidation capacity during pregnancy and lactation in mice. *J Appl Microbiol.* 2020; 130(2), 450–463.
47. Singh CK, Kumar A, Hitchcock DB, *et al.* Resveratrol prevents embryonic oxidative stress and apoptosis associated with diabetic embryopathy and improves glucose and lipid profile of diabetic dam. *Mol Nutr Food Res.* 2011; 55(8), 1186–1196.
48. Xie W, Ge X, Li L, *et al.* Resveratrol ameliorates prenatal progestin exposure-induced autism-like behavior through ERβ activation. *Mol Autism.* 2018; 9(1), 43.
49. Wang X, Lu J, Xie W, *et al.* Maternal diabetes induces autism-like behavior by hyperglycemia-mediated persistent oxidative stress and suppression of superoxide dismutase 2. *Proc Natl Acad Sci U S A.* 2019; 116(47), 23743–23752.
50. Yao L, Wan J, Li H, *et al.* Resveratrol relieves gestational diabetes mellitus in mice through activating AMPK. *Reprod Biol Endocrin.* 2015; 13(1), 118.
51. Brawerman GM, Kereliuk SM, Brar N, *et al.* Maternal resveratrol administration protects against gestational diabetes-induced glucose intolerance and islet dysfunction in the rat offspring. *J Physiol.* 2019; 597(16), 4175–4192.


https://doi.org/10.1017/S2040174422000332 Published online by Cambridge University Press

52. Zheng T, Chen H. Resveratrol ameliorates the glucose uptake and lipid metabolism in gestational diabetes mellitus mice and insulin-resistant adipocytes via miR-23a-3p/NOV axis. *Mol Immunol.* 2021; 137, 163–173.
53. Zhang G, Wang X, Ren B, Zhao Q, Zhang F. The effect of resveratrol on blood glucose and blood lipids in rats with gestational diabetes mellitus. *Evid Based Complement Alternat Med.* 2021; 2021, 1–7.
54. de Sousa SM, Braz GRF, Freitas CM, *et al.* Oxidative injuries induced by maternal low-protein diet in female brainstem. *Nutr Neurosci.* 2018; 21(8), 580–588.
55. Silva SCA, Braz GRF, do Nascimento LCP, *et al.* Influence of maternal protein malnutrition on oxidative stress and regulators of mitochondrial biogenesis in female rat hearts over succeeding generations. *Life Sci.* 2019; 232, 116579.
56. Vega CC, Reyes-Castro LA, Rodriguez-Gonzalez GL, *et al.* Resveratrol partially prevents oxidative stress and metabolic dysfunction in pregnant rats fed a low protein diet and their offspring. *J Physiol.* 2016; 594(5), 1483–1499.
57. Tanaka M, Kita T, Yamasaki S, *et al.* Maternal resveratrol intake during lactation attenuates hepatic triglyceride and fatty acid synthesis in adult male rat offspring. *Biochem Biophys Rep.* 2017; 9, 173–179.
58. Franco JG, de Moura EG, Koury JC, *et al.* Resveratrol reduces lipid peroxidation and increases sirtuin 1 expression in adult animals programmed by neonatal protein restriction. *J Endocrinol.* 2010; 207(3), 319–328.
59. Menichini D, Longo M, Facchinetti F. Maternal interventions to improve offspring outcomes in rodent models of diet-induced obesity: a review. *J Matern-Fetal Neonat Med.* 2019; 32(17), 2943–2949.
60. Hsu MH, Chen YC, Sheen JM, Huang LT. Maternal obesity programs offspring development and resveratrol potentially reprograms the effects of maternal obesity. *Int J Environ Res Pub Health.* 2020; 17(5), 1610.
61. Tain YL, Lee WC, Wu KLH, Leu S, Chan JYH. Resveratrol prevents the development of hypertension programmed by maternal plus post-weaning high-fructose consumption through modulation of oxidative stress, nutrient-sensing signals, and gut microbiota. *Mol Nutr Food Res.* 2018; 62(15), e1800066.
62. Franco JG, Dias-Rocha CP, Fernandes TP, *et al.* Resveratrol treatment rescues hyperleptinemia and improves hypothalamic leptin signaling programmed by maternal high-fat diet in rats. *Eur J Nutr.* 2016; 55(2), 601–610.
63. Zou T, Chen D, Yang Q, *et al.* Resveratrol supplementation of high-fat diet-fed pregnant mice promotes brown and beige adipocyte development and prevents obesity in male offspring. *J Physiol.* 2017; 595(5), 1547–1562.
64. Tsai TA, Tsai CK, Huang LT, *et al.* Maternal resveratrol treatment re-programs and maternal high-fat diet-induced retroperitoneal adiposity in male offspring. *Int J Environ Res Pub Health.* 2020; 17(8), 2780.
65. Sheen JM, Yu HR, Tain YL, *et al.* Combined maternal and postnatal high-fat diet leads to metabolic syndrome and is effectively reversed by resveratrol: a multiple-organ study. *Sci Rep UK.* 2018; 8(1), 5607.
66. Ros P, Diaz F, Freire-Regatillo A, *et al.* Resveratrol intake during pregnancy and lactation modulates the early metabolic effects of maternal nutrition differently in male and female offspring. *Endocrinology.* 2018; 159(2), 810–825.
67. Ros P, Diaz F, Freire-Regatillo A, *et al.* Sex differences in long-term metabolic effects of maternal resveratrol intake in adult rat offspring. *Endocrinology.* 2020; 161(8), 101.
68. Roberts VHJ, Pound LD, Thorn SR, *et al.* Beneficial and cautionary outcomes of resveratrol supplementation in pregnant nonhuman primates. *FASEB J.* 2014; 28(6), 2466–2477.
69. Pound LD, Comstock SMC, Grove KL. Consumption of a Western-style diet during pregnancy impairs offspring islet vascularization in a Japanese macaque model. *Am J Physiol Endocrinol Metab.* 2014; 307(1), E115–E23.
70. O'Tierney-Ginn P, Roberts V, Gillingham M, *et al.* Influence of high fat diet and resveratrol supplementation on placental fatty acid uptake in the Japanese macaque. *Placenta.* 2015; 36(8), 903–910.
71. Li S-W, Yu H-R, Sheen J-M, *et al.* A maternal high-fat diet during pregnancy and lactation, in addition to a postnatal high-fat diet, leads to metabolic syndrome with spatial learning and memory deficits: beneficial effects of resveratrol. *Oncotarget.* 2017; 8(67), 111998–112013.
72. Hsu MH, Sheen JM, Lin IC, *et al.* Effects of maternal resveratrol on maternal high-fat diet/obesity with or without postnatal high-fat diet. *Int J Mol Sci.* 2020; 21(10), 3428.
73. Huang Y-C, Huang L-T, Sheen J-M, *et al.* Resveratrol treatment improves the altered metabolism and related dysbiosis of gut programed by prenatal high-fat diet and postnatal high-fat diet exposure. *J Nutr Biochem.* 2020; 75, 108260.
74. Dolinsky VW, Rueda-Clausen CF, Morton JS, Davidge ST, Dyck JRB. Continued postnatal administration of resveratrol prevents diet-induced metabolic syndrome in rat offspring born growth restricted. *Diabetes.* 2011; 60(9), 2274–2284.
75. Castro-Rodriguez DC, Reyes-Castro LA, Vargas-Hernandez L, *et al.* Maternal obesity (MO) programs morphological changes in aged rat offspring small intestine in a sex dependent manner: effects of maternal resveratrol supplementation. *Exp Gerontol.* 2021; 154, 111511.
76. Serrano A, Ribot J, Palou A, Bonet ML. Long-term programming of skeletal muscle and liver lipid and energy metabolism by resveratrol supplementation to suckling mice. *J Nutr Biochem.* 2021; 95, 108770.
77. Izquierdo V, Palomera-Avalos V, Pallas M, Grinan-Ferre C. Resveratrol supplementation attenuates cognitive and molecular alterations under maternal high-fat diet intake: epigenetic inheritance over generations. *Int J Mol Sci.* 2021; 22(3), 1453.
78. Hsu MH, Sheen JM, Lin IC, *et al.* Effects of maternal resveratrol on maternal high-fat diet/obesity with or without postnatal high-fat diet. *Int J Mol Sci.* 2020; 21(10), 3428.
79. Cerdeira AS, O'Sullivan J, Ohuma EO, *et al.* Randomized interventional study on prediction of preeclampsia/eclampsia in women with suspected preeclampsia: INSPIRE. *Hypertension.* 2019; 74(4), 983–990.
80. Care AS, Sung MM, Panahi S, *et al.* Perinatal resveratrol supplementation to spontaneously hypertensive rat dams mitigates the development of hypertension in adult offspring. *Hypertension.* 2016; 67(5), 1038–1044.
81. Chen HE, Lin YJ, Lin IC, *et al.* Resveratrol prevents combined prenatal N(G)-nitro-L-arginine-methyl ester (L-NAME) treatment plus postnatal high-fat diet induced programmed hypertension in adult rat offspring: interplay between nutrient-sensing signals, oxidative stress and gut microbiota. *J Nutr Biochem.* 2019; 70, 28–37.
82. Jia X, Zhang R, Guo J, *et al.* Resveratrol supplementation prevents hypertension in hypertensive pregnant rats by increasing sodium excretion and serum nitric oxide level. *Int J Hypertens.* 2020; 4154010(2020), 1–7.
83. Shah A, Reyes LM, Morton JS, Fung D, Schneider J, Davidge ST. Effect of resveratrol on metabolic and cardiovascular function in male and female adult offspring exposed to prenatal hypoxia and a high-fat diet. *J Physiol.* 2016; 594(5), 1465–1482.
84. Rueda-Clausen CF, Morton JS, Dolinsky VW, Dyck JRB, Davidge ST. Synergistic effects of prenatal hypoxia and postnatal high-fat diet in the development of cardiovascular pathology in young rats. *Am J Physiol Regul Integr Comp Physiol.* 2012; 303(4), R418–26.
85. Tain YL, Lin YJ, Sheen JM, *et al.* Resveratrol prevents the combined maternal plus postweaning high-fat-diets-induced hypertension in male offspring. *J Nutr Biochem.* 2017; 48, 120–127.
86. Tain YL, Lee WC, Wu KLH, Leu S, Chan JYH. Resveratrol prevents the development of hypertension programmed by maternal plus post-weaning high-fructose consumption through modulation of oxidative stress, nutrient-sensing signals, and gut microbiota. *Mol Nutr Food Res.* 2018; 62(15), e1800066.
87. Zou Y, Zuo Q, Huang S, *et al.* Resveratrol inhibits trophoblast apoptosis through oxidative stress in preeclampsia-model rats. *Molecules.* 2014; 19(12), 20570–20579.
88. Zou Y, Li S, Wu D, *et al.* Resveratrol promotes trophoblast invasion in preeclampsia by inducing epithelial-mesenchymal transition. *J Cell Mol Med.* 2019; 23(4), 2702–2710.
89. Poudel R, Stanley JL, Rueda-Clausen CF, *et al.* Effects of resveratrol in pregnancy using murine models with reduced blood supply to the uterus. *PloS One.* 2013; 8(5), e64401.


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90. Huang H, Chen G, Liao D, Zhu Y, Pu R, Xue X. The effects of resveratrol intervention on risk markers of cardiovascular health in overweight and obese subjects: a pooled analysis of randomized controlled trials. *Obes Rev.* 2016; 17(12), 1329–1340.
91. Tran HT, Liong S, Lim R, Barker G, Lappas M. Resveratrol ameliorates the chemical and microbial induction of inflammation and insulin resistance in human placenta, adipose tissue and skeletal muscle. *PLoS One.* 2017; 12(3), e0173373.
92. Caldeira-Dias M, Montenegro MF, Bettiol H, *et al.* Resveratrol improves endothelial cell markers impaired by plasma incubation from women who subsequently develop preeclampsia. *Hypertens Res.* 2019; 42(8), 1166–1174.

https://doi.org/10.1017/S2040174422000332 Published online by Cambridge University Press