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Effect of resveratrol in gestational diabetes mellitus and its complications

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Abstract

The incidence rate of diabetes in pregnancy is about 20%, and diabetes in pregnancy will have a long-term impact on the metabolic health of mothers and their offspring. Mothers may have elevated blood glucose, which may lead to blood pressure disease, kidney disease, decreased resistance and secondary infection during pregnancy. The offspring may suffer from abnormal embryonic development, intrauterine growth restriction, obesity, autism, and other adverse consequences. Resveratrol (RSV) is a natural polyphenol compound, which is found in more than 70 plant species and their products, such as *Polygonum cuspidatum*, seeds of grapes, peanuts, blueberries, bilberries, and cranberries. Previous studies have shown that RSV has a potential beneficial effect on complex pregnancy, including improving the indicators of diabetes and pregnancy diabetes syndrome. This article has reviewed the molecular targets and signaling pathways of RSV, including AMP-activated protein kinase, mitogen-activated protein kinases, silent information regulator sirtuin 1, miR-23a-3p, reactive oxygen species, potassium channels and CX3C chemokine ligand 1, and the effect of RSV on gestational diabetes mellitus (GDM) and its complications. RSV improves the indicators of GDM by improving glucose metabolism and insulin tolerance, regulating blood lipids and plasma adipokines, and modulating embryonic oxidative stress and apoptosis. Furthermore, RSV can ameliorate the GDM complications by reducing oxidative stress, reducing the effects on placentation, reducing the adverse effects on embryonic development, reducing

offspring's healthy risk, and so on. Thus, this review is of great significance for providing more options and possibilities for further research on medication of gestational diabetes.

Key Words: Gestational diabetes mellitus; Complication; Resveratrol; Polyphenol; Pathway

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Core Tip: Resveratrol (RSV) is a natural polyphenol compound. Previous studies have shown that RSV has a potential beneficial effect in complex pregnancy, including improving the indicators of diabetes and improving pregnancy diabetes syndrome. This article reviews the molecular targets and signaling pathways of RSV including AMP-activated protein kinase, mitogen-activated protein kinases, silent information regulator sirtuin 1, miR-23a-3p, reactive oxygen species, potassium channels and CX3C chemokine ligand 1, and the effect of RSV on gestational diabetes mellitus and its complications. It also provides more options and possibilities for further research on medication of gestational diabetes.

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INTRODUCTION

Diabetes is a metabolic disease caused by islet dysfunction, insulin resistance (IR), and other factors. Its clinical manifestation is hyperglycemia. Among them, type 1 diabetes refers to the inability of the body to produce enough insulin, and type 2 diabetes refers to the inability of cells to respond appropriately to insulin. Another type of diabetes is called gestational diabetes mellitus (GDM), which occurs when the blood glucose level of pregnant women is high.

Approximately 20% of all pregnancies are complicated by GDM, which includes hyperglycemia, IR, and fetal maldevelopment. Several factors contribute to the development of GDM, including low-grade inflammation in the mother and peripheral IR. Sterile inflammation and infection are key mediators of this inflammation and IR[1,2]. Due to the severe complications it causes to both mother and fetus, GDM is a serious problem worldwide[3]. At present, insulin and hypoglycemic western medicine are mainly used in clinical treatment. Pregnant B safe drugs and insulin treatment are mainly selected according to the blood glucose situation. However, long-term use of insulin will do harm to mothers and fetuses. Therefore, actively exploring natural non-toxic phytochemicals to prevent and treat diabetes during pregnancy is a future development trend.

Based on many *in vitro* and animal studies, dietary polyphenols have been shown to inhibit hyperglycemia, IR, inflammatory adipokines, and modify microRNA profile *via* the insulin signaling pathway[3]. Since the early 1990s, polyphenols have been extensively studied as adjuvant agents to attenuate obesity, cardiovascular disease, malignancies, neurodegenerative diseases, diabetes, and metabolic syndrome. Resveratrol (RSV) is one of the most studied natural polyphenols, with health benefits clearly demonstrated in various *in vitro* and *in vivo* models, as well as in clinical studies[4].

RSV belongs to the stilbene-type phytochemical, it is found in more than 70 plant species and their products such as *Polygonum cuspidatum*, seeds of grapes, peanuts, blueberries, bilberries, and cranberries [5]. The trans-RSV form, which is the most organic form, and the cis-RSV form are the two forms of RSV (Figure 1). Accumulating evidence suggests that RSV is a biological modulator and phytoalexin with multi-target and multi-action characteristics. In a variety of animal and human models, RSV has exhibited a diverse range of biological effects including cardioprotective[6], anti-hypertensive[7,8], antiobesogenic[9,10], antiatherosclerotic[11-13], potent anti-inflammatory[14], and antidiabetic[15,16] effects.

This article summarizes the mechanism and effect of RSV on GDM and its complications.

PATHWAY AND TARGETS OF RSV IN GDM

There have been many previous studies on the signaling mechanisms involved in diabetes, but there is less reported on RSV signaling pathways and targets in GDM. Studies have confirmed the link between molecular targets and signaling pathways of RSV including AMP-activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK), silent information regulator sirtuin 1 (SIRT1), miR-23a-3p,

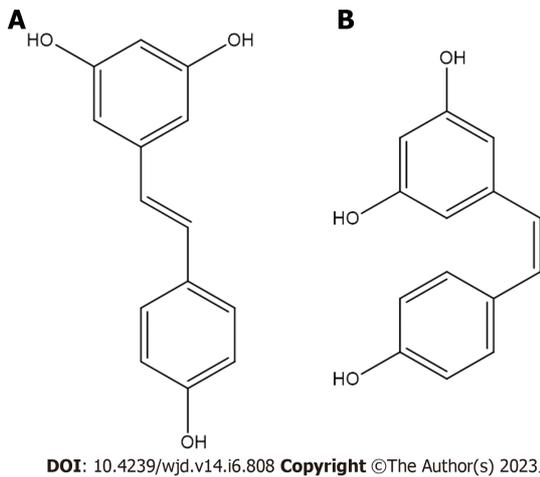


Figure 1 Chemical structures of trans-resveratrol (3,5,4'-trihydroxystilbene) and cis-resveratrol. A: Trans-resveratrol; B: Cis-resveratrol.

reactive oxygen species (ROS), potassium (K) channels, and CX3C chemokine ligand 1 (CX3CL1) (Figure 2).

AMPK

AMPK, a serine/threonine kinase, is conserved in eukaryotes. Under stressful circumstances, AMPK controls cellular and overall body energy homeostasis. It is well established that AMPK dysregulation is associated with a wide range of diseases including cancer[17], diabetes[18], inflammatory illness[19], hypertension, and kidney disease[20], and cardiovascular disease[21]. For optimal placental differentiation, nutrition transport, maternal and fetal energy homeostasis, and membrane protection during pregnancy, AMPK is required[22]. Metformin, RSV, and 5-aminoimidazole-4-carboxamide ribonucleotide are AMPK activators that have been shown to reverse pregnancy problems such as GDM, preeclampsia, intrauterine growth restriction (IUGR), and premature birth in preclinical studies[23].

A previous study investigated inflammation, oxidative stress, apoptosis, and AMPK in embryos on embryonic day 16 in a streptozotocin (STZ)-induced gestational diabetes mouse model. RSV inhibited AMPK activity and expression, which further decreased expression levels of p65, I κ B kinase beta, and I κ B alpha. RSV (8.0 mg/kg) administration significantly downregulated expression levels of ROS, superoxide dismutase (SOD), glutathione, and catalase in oxidative stress, and also inhibited inflammatory factors expression such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , C-reactive protein, and IL-6. Mechanism analyses indicated that RSV inhibited inflammation of embryonic cells by the AMPK-mediated nuclear factor kappa B signaling pathway[24].

MAPKs

In diabetes embryos exhibiting developmental abnormalities, a study identified downregulation of retinoid X receptors, retinoic acid receptor (RAR) expression, DNA-binding capabilities, and phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, but an increase of phosphorylation of p38 and c-Jun N-terminal kinase (JNK) 1/2. MAPKs and RARs were activated in rat embryos on embryonic day 12 after treatment with RSV (100 mg/kg body weight), then they displayed normalized patterns of p38, JNK, ERK, and RAR phosphorylation. This finding suggested that RSV might be able to prevent RAR and MAPK dysfunction in the embryos of a mouse model of diabetic embryopathy[25].

SIRT5

SIRT5 are involved in metabolic and circulatory processes. Adipocyte differentiation and insulin signaling, which are controlled by forkhead box protein O1 and phosphoinositide 3-kinase (PI3K) signaling, both depending on SIRT1. The path mechanisms of the nonalcoholic hepatitis, cardiovascular illnesses, diabetes mellitus type 2, and metabolic syndrome are partially explained by the decreased expression of SIRT5[26].

In fetal endothelial colony-forming cells (ECFCs) and human umbilical vein endothelial cells (HUVECs) from pregnancies complicated by GDM, the influence of GDM on SIRT expression and activity was researched in a study. RSV significantly increased SIRT expression and activity in HUVECs and ECFCs, which may provide new therapeutic targets in the future[27,28].

Another study's objective was to determine how oxidative stress affected the glucose transporters (GLUTs) and human placenta's glucose absorption. The reduction in GLUT1 expression and glucose uptake caused by hypoxanthine/xanthine oxidase was eliminated in the presence of the SIRT1 activator RSV. The information given here shows that oxidative stress decreases GLUT1 expression and placental glucose absorption through a SIRT1-dependent mechanism[29]. A study of RSV's effects on myocardial

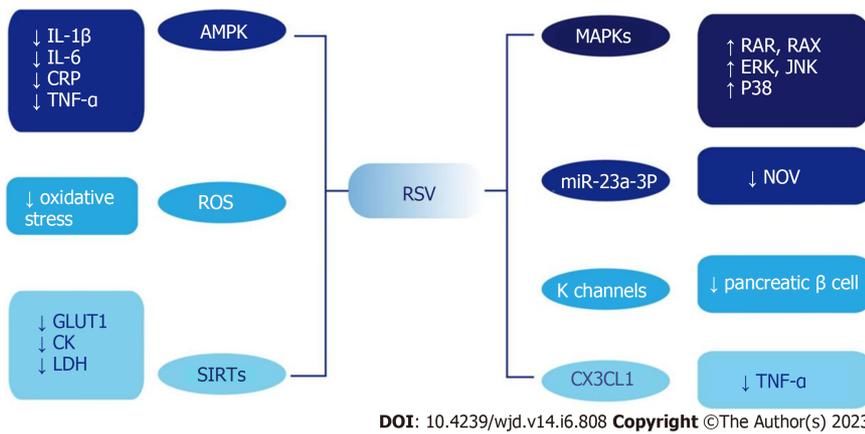


Figure 2 Pathway and targets of resveratrol in gestational diabetes mellitus. AMPK: AMP-activated protein kinase; CK: Creatine kinase; CRP: C-reactive protein; CX3CL1: CX3C chemokine ligand 1; ERK: Extracellular signal-regulated kinase; GLUT1: Glucose transporter type 1; IL: Interleukin; JNK: C-Jun N-terminal kinase; LDH: Lactate dehydrogenase; MAPK: Mitogen-activated protein kinase; NOV: Nephroblastoma overexpressed; RAR: Retinoic acid receptor; RAX: RNA-dependent protein kinase-associated protein X; ROS: Reactive oxygen species; SIRT: Sirtuin; TNF- α : Tumor necrosis factor- α .

cell injury also showed the role of the macrophage stimulating 1/SIRT3 signaling pathway in autophagy in type 2 diabetic mice by reducing the body weight of db/db mice, blood glucose level, serum creatine kinase, and lactate dehydrogenase levels[30].

MiR-23a-3p

The low miR-23a-3p expression in diabetic patients controls adipocytes' IR to insulin. Therefore, researchers hypothesized that the effect of RSV on mice with GDM was achieved by controlling miR-23a-3p. Increasing the expression of phosphorylated Akt (p-Akt), miR-23a-3p, p-PI3K, adiponectin, leptin, and glucose intake, as well as decreasing the expression of nephroblastoma overexpressed (NOV) in IR adipocytes were the end results of this study's additional treatment with RSV. This study shows that RSV can improve lipid metabolism and glucose uptake of mice with GDM and IR adipocytes by mediating the miR-23a-3p/NOV axis[31].

ROS

ROS are crucial components of cellular signal transduction and transcriptional regulation, but too much ROS production can damage proteins, cellular lipids, and nucleic acids by oxidative alteration. Indeed, higher levels of ROS are linked to complications induced by diabetes[32].

Transient hyperglycemia produces persistent ROS formation with decreased SOD2 expression, according to the findings of an *in vitro* study. Additionally, *in vivo* rat studies have demonstrated that maternal hyperglycemia causes amygdala SOD2 reduction, which results in autistic-like behavior in offspring. We came to the conclusion that hyperglycemia-mediated chronic oxidative stress and SOD2 reduction caused by maternal diabetes cause autism-like behavior[33].

RSV showed the unusual potential to lower oxidative stress by two separate pathways in both rats and non-human primates since it crosses the placenta in both species. First, improving fetal oxygen delivery and increasing uterine arterial blood flow by working through endothelial nitric oxide synthase. Consequently, reducing ROS generated by hypoxia prevents oxidative damage. Second, to control the genes involved in the redox system directly in fetal tissues. RSV stands out as a potential therapy to utilize as an intervention during a pregnancy complicated by GDM because of these special features[34].

K channels

K channels are essential for sustaining membrane potential. Pathologies include diabetes mellitus, preeclampsia, premature delivery, hypertension, cardiac arrhythmia, and different cancers can all be caused by abnormal K channel activity or expression. K channels may be possible targets in the mechanism of RSV action, according to an article that discusses the pharmacological effects of RSV on the various types of K channels that have been identified in smooth muscle cells[35].

A significant aspect of the pathophysiology of diabetes is the apoptosis of pancreatic beta cells. A study found that the expression of sulfonylurea receptor 1, the regulatory subunit of pancreatic ATP-sensitive K(+) channels, is necessary for RSV to cause beta-cell death[36].

CX3CL1

CX3CL1 contains three exons, is encoded on the long arm of human chromosome 16 at position13. The human placenta exhibits CX3CL1 hyperactivity that is induced by hyperglycemia. RSV has anti-inflam-

matory and antioxidant properties that are influenced by the signaling pathways of the chemokine CX3CL1 and its receptor, CX3CR1. RSV (50 μm and 100 μm) administration into the perfusion fluid decreased TNF- α and CX3CL1 production[37].

INDICATOR IMPROVEMENT OF GDM

We found that administration of RSV works *via* three different ways in GDM: (1) Improving glucose metabolism and insulin tolerance; (2) regulating blood lipids and plasma adipokines; and (3) modulating embryonic oxidative stress and apoptosis[38]. RSV, a potent antioxidant and free radical scavenger, can improve the activities of various antioxidative enzymes and reduce the increasing of ROS, and then reduce the probability of complications caused by diabetes.

Improving glucose metabolism

In a study, RSV significantly enhanced the pregnant db/+ GDM mouse model's insulin tolerance, glucose metabolism, and reproductive outcome (db/+ is a C57BL/KsJ-Lep mouse, which is genetic GDM model that closely resembled human GDM symptoms). Additionally, the researchers discovered that RSV reduced the symptoms of GDM by boosting AMPK activation, which in turn decreased glucose-6-phosphatase expression and activity in both pregnant db/+ females and their offspring[2]. This research provides more evidence in favor of the potential therapeutic benefits of RSV for GDM.

RSV enhanced insulin secretion and restored normoglycemia, glucose tolerance in pregnant dams. At 15 wk of age, the obesity of the male progeny of GDM + RSV-hemifacial spasm (HFS) was lower than that of the offspring of GDM-HFS. Therefore, supplementation of maternal RSV during the third trimester of pregnancy and lactation resulted in a number of positive metabolic health outcomes for mothers and offspring[39]. RSV may be a better option than the GDM therapies now available.

Furthermore, a pilot study found that supplementing with trans-RSV and Revifast in addition to plus D-chiro-inositol/Myo-inositol improves glucose levels, total cholesterol, low-density lipoprotein (LDL), and triglyceride (TG) in overweight pregnant women[40]. This data show that RSV is effective not only for pregnant diabetes mice but also for pregnant humans.

Regulating blood lipids and plasma adipokines

The level of insulin was substantially higher in the RSV treatment group than in the GDM group; however, both the body weight and blood glucose level were markedly decreased. The RSV (240 mg/kg) therapy group had lower levels of LDL cholesterol, TG, total cholesterol (TC) and leptin levels, and higher levels of high-density lipoprotein cholesterol, IL-6, TNF- α , and resistin than the control group. Adiponectin levels were markedly raised and significantly decreased in the 240 mg/kg RSV treatment group. RSV (240 mg/kg) was also more effective than metformin hydrochloride at regulating adipokine levels, controlling blood cholesterol levels, and increasing insulin secretion. RSV lowered blood glucose and body weight, increased insulin secretion, and controlled plasma adipokines and blood lipids in GDM rats in a dose-dependent manner[41].

A study found that maternal RSV therapy reduced the increase in leptin/soluble leptin receptor ratio caused by maternal high-fat (HF) exposure during pregnancy and changed the expression levels of genes for essential fatty acid manufacturing enzymes in the offspring. Thus, to lessen the harmful effects of GDM, maternal RSV administration may be employed[42].

In a study of human mature adipocytes, after the fat cells were incubated with 100 μM RSV (45 min to 4 h), RSV increased in triacylglycerol decomposition induced by isoproterenol stimulation, and showed an impairment of insulin antilipolytic action, after which the production of fat was significantly impaired[43].

Modulating embryonic oxidative stress and apoptosis

According to a study, RSV may be a useful treatment option for women who are pregnant with diabetes because it can improve glucose and insulin levels, improve glucose and lipid metabolism, prevent apoptosis, and reduce inflammation and embryonic oxidative stress in mice with GDM[24].

In ob/ob mice given RSV, plasma levels of insulin and testosterone levels, whereas the homeostatic index of resistance increased. After RSV therapy in obese mice, TNF- α and IL-6 levels returned to nearly normal levels. RSV administration led to considerably more oocytes being harvested in wild-type mice [44].

Coating chitosan with RSV bioactive compounds is an important way for the management of GDM. The treatment of RSV-zinc oxide complex coated chitosan (CS-ZnO-RS) maintained the lipid content and dramatically reduced the blood glucose concentrations of GDM induced rats. Additionally, the levels of inflammation-related components [monocyte chemoattractant protein-1 (MCP-1) and IL-6] as well as endoplasmic reticulum stress (p-PERK, p-eIF2 α , p-IRE1 α , and GRP78) were decreased by CS-ZnO-RS[45].

In a study, RSV treatment significantly improved defects in the glucose uptake and insulin signaling pathway caused by lipopolysaccharide, TNF- α , and poly (I:C) and significantly decreased the secretion and expression of pro-inflammatory cytokines IL-1 β , IL-6, IL-1 α , and pro-inflammatory chemokines MCP-1 and IL-8 in omental, human placenta, and subcutaneous adipose tissue. Taken together, these findings indicated that RSV lowered IR and inflammation generated by chemical and microbial agents, and RSV might be a helpful prophylactic treatment for pregnancies complicated by IR and inflammation [46].

AMELIORATION OF GDM COMPLICATIONS

Although pregnancy causes IR condition, it is natural and aids in the provision of glucose to the fetus's circulation and diffusion-mediated transfer of glucose into the placenta [47]. Multiple pregnancy complications can occur if blood glucose concentrations are not properly managed, and this suboptimal in utero environment is likely to affect fetal growth at critical developmental windows. Important organ systems undergo harmful structural changes in utero that last into adulthood and put offspring at a higher risk of developing non-communicable chronic metabolic disorders like obesity, diabetes and cardiovascular disease [34].

Many bioactive redox modulators are used during pregnancy; for example, vitamin C and vitamin E supplements can reduce the risk of pre-eclampsia [48], maternal treatment with a mitochondria-targeted antioxidant can provide protection during hypoxic pregnancy [49], and lazaroid (lipid peroxidation inhibitor) administered along with a low protein diet prevents blood pressure elevation [50]. Also, maternal supplementation with RSV has been used as a therapeutic agent for pregnancy complications in rodent models such as preeclampsia [51], GDM, and fetal growth restriction [52]. It has been reported that the safe dose of RSV for humans is 5 g per day [53]. Relevant studies about RSV intake and the effect are summarized in Table 1.

Reducing oxidative stress

RSV may act directly on diabetic pregnant embryos through normalizing oxidative stress induced by hyperglycemia [54]. Apoptosis induced by oxidative stress is related to diabetic embryopathies [55]. In embryos, RSV can modulate oxidative stress marker normalization, including increases in total thiol concentrations, lipid peroxidation and decreased amounts of glutathione associated with hyperglycemia. The weakening of oxidative stress further decreased and reduced the chance of apoptosis as well as embryonic malformations [38].

RSV was discovered to stop oxidative stress and apoptosis in developing embryos. In a rodent model of diabetic embryopathy, RSV (100 mg/kg body weight) administration improved lipid (triglyceride 60.64%, cholesterol 41.74%), and the glucose (33.32%) profile of the diabetic dams, demonstrating the protective effect of RSV on diabetic pregnancy [54]. Therefore, RSV's antioxidant capability is a desirable property for reducing oxidative stress during challenging pregnancies and thereby breaking the intergenerational cycle of chronic disease.

Using STZ at a dose of 50 mg/kg to cause diabetes in pregnant rats on day 4, followed by 100 mg/kg of RSV on days 8 to 12 to promote neurulation. Fetuses were taken on the 19th day of pregnancy and submitted to morphologic investigation. The activities of the glutathione peroxidase, superoxide dismutase, and scavenging enzymes catalase in the fetal liver were also assessed. RSV has been demonstrated with embryo protective effects that are mediated by reducing the oxidative stress brought on by maternal hyperglycemia [56].

By administering 100 μ M tert-butylhydroperoxide (tert-BOOH) for 24 h, oxidative stress was created in a human syncytiotrophoblast (STB) cell model, the BeWo cell line. The reduced STB glucose buildup was accompanied by an increase in transepithelial permeability. The inhibitory effect of tert-BOOH on 2-cleoxyglucose was fully reversed by RSV thanks to a particular effect on transport mediated by glucose transporters [57]. This result demonstrated that RSV may influence the results of pregnancy disorders linked to oxidative stress.

Reducing adverse effects on placentation

The key players in placentation, an early process essential for placental growth and function that involves an appropriate invasion and through remodeling of the maternal spiral arteries during early pregnancy, are extravillous trophoblasts (EVTs). The finding of a study indicated that oxidative stress interferes with EVT features necessary for the placentation process, which may help explain the link between pregnancy disorders and oxidative stress [58].

Using a first trimester extravillous human trophoblast cell line (HTR8/SVneo cells) as a cell model, our goal was to examine the impact of high levels of leptin, insulin, TNF- α , and glucose (indicators of diabetes in pregnancy), on the process of placentation. Therefore, insulin may have an impact on placentation [59]. Because placental formation was affected by leptin and insulin, so we can use RSV to regulate insulin release, thus protecting the placenta.

Table 1 Relevant studies about resveratrol intake and the effect

Model	Species	Resveratrol consumption	Duration of treatment	Maternal outcomes	Offspring outcomes	Ref.
C57BL/6	Mice	8.0 mg/kg	16 gestation days	Inhibit expression levels of inflammatory factors, IL-1 β , IL-6, CRP and TNF- α ↓		[24]
C57BL/KsJ-, Lepdb/+ (db/+)	Mice	10 mg/kg	During pregnancy	Glucose metabolism, insulin tolerance↑, glucose-6-phosphatase↓		[2]
C57BL/6	Mice	0.20%	18 gestation days	p-Akt, miR-23a-3p, p-PI3K, adiponectin, leptin↑		[31]
Female ob/ob mice, female C57BL/6J mice	Mice	3.75 mg/kg	20 d	Plasma insulin and T levels↓, IL-6, TNF- α levels reverted back to normalcy		[44]
Female Sprague-Dawley rats	Rats	100 mg/kg	10 gestation days		p38, JNK, ERK, and RAR phosphorylation return normal	[25]
Female Sprague-Dawley rats	Rats	240 mg/kg	12 gestation days	TC, TG, LDL-C, leptin, resistin, TNF- α , and IL-6↓, HDL-C, adiponectin↑		[41]
Female Sprague-Dawley rats	Rats	147 mg/kg	3-wk lactation period	Blood glucose levels↓, insulin secretion↑	Male offspring obese↓, hepatic steatosis, insulin resistance, glucose intolerance and dysregulated gluconeogenesis↓	[39]
Pregnant rats	Rats	100 mg/kg	10 gestation days	Glucose and lipid profile↑	Embryo weight↑, rump length, somite number↓	[54]
Pregnant rats	Rats	100 mg/kg	4 d (gestation days 8 th to 12 th)	-	Teratogenic effects↓, scavenging enzymes catalase, superoxide dismutase, glutathione peroxidase↓	[56]
Hypoxia-induced rat model of IUGR	Rats	4 g/kg	9 wk		Intra-abdominal fat deposition, accumulation of TG and ceramides↓, plasma lipid profile↑	[62]
Chicken embryo	Chicken	1 nM/egg	5 embryonic days		Death rate, developmental damage, vessel injury↓	[61]
Between the 24 th and 28 th weeks' gestation	Human	80 mg/day	60 d	Total cholesterol, HDL, LDL, triglycerides, and glucose blood levels↓		[40]
Mature adipocytes	Human	100 μ M	45 min to 4 h	Isoprenaline stimulation↑, impaired insulin antilipolytic action		[43]
Placenta, omental and subcutaneous adipose tissue and skeletal muscle	Human	200 μ M	20 h	IL-6, IL-1 α , IL-1 β , pro-inflammatory chemokines IL-8, MCP-1↓		[46]
Heparinized placentae	Human	50 and 100 μ M, 5 mL boluses at 30 min intervals	150 min		CX3CL1, TNF- α ↓	[37]

CRP: C-reactive protein; CX3CL1: CX3C chemokine ligand 1; ERK: Extracellular signal-regulated kinase; HDL: High-density lipoprotein; IL: Interleukin; IUGR: Intrauterine growth restriction; JNK: C-Jun N-terminal kinase; LDL: Low-density lipoprotein; MCP-1: Monocyte chemoattractant protein-1; RAR: Retinoic acid receptor; TC: Total cholesterol; TG: Triglyceride; TNF- α : Tumor necrosis factor-alpha.

Reducing adverse effects on embryonic development

Given that organogenesis and embryonal development are the most delicate stage of development, it is recognized that diabetes may impair these processes. Potential cause of the observed embryonal deformity in diabetic dams is oxidative stress induced by hyperglycemia, which results in apoptosis[4]. Numerous complications might arise during a diabetic pregnancy, particularly about embryo development. Inadequate or incomplete closure of the neural tube, impaired rate of neurogenesis, developmental delay, and failure to generate the right neural connections are a few examples of embryonic impairments[60]. Furthermore, several upcoming neurological, physical, and psychiatric illnesses may have their roots in these developmental problems. Diabetic malformations are more likely to happen in the first trimester.

In this work, the impact of RSV on the development of chicken embryos in conditions of high glucose and the RSV's underlying mechanism were examined. At the embryonic day 1, the high glucose concentration to chicken embryos caused growth retardation, stillbirth, and poor yolk sac blood vessel development. RSV supplementation had a substantial impact on reducing developmental harm, mortality, and vascular injury before glucose exposure. Aside from that, exposure to high glucose levels resulted in oxidative stress, which RSV might treat. Furthermore, excessive glucose dramatically reduced the neuronal developmental marker paired box 3, which was thereafter restored by RSV. RSV also interfered with gene expression that is controlled by the cell cycle. This study discovered a link between hyperglycemia-induced embryonic damage and RSV, which raised the possibility of RSV having a protective impact[61].

Reducing offspring's healthy risk

A study showed that RSV administration improved the plasma lipid profile, decreased intra-abdominal fat deposition, and reduced accumulation of TG and ceramides in the tissues of offspring with IUGR. Additionally, RSV reduced glucose intolerance and IR, decreased Akt signaling in the skeletal muscle and liver of offspring with IUGR, and activated AMP-activated protein kinase, all of which may have led to better metabolic parameters in IUGR rats treated with RSV. The findings implied that early postnatal RSV treatment could enhance the metabolic profile of HF-fed infants born from IUGR-complicated pregnancies[62].

DISCUSSION

Compared with synthetic drugs, RSV may become a safer and more effective natural drug to treat or prevent pregnancy diabetes and its complications. However, due to the low bioavailability and water solubility of RSV (< 0.05 mg/mL), we can start from two aspects: Modifying its structure to find derivatives with higher activity or developing new dosage forms through new carriers. At present, various RSV derivatives have been widely studied, including methoxylated, hydroxylated and halogenated derivatives[63,64]. In the preparation research, chitosan has been used to encapsulate CS-ZnO-RSV[45], a new RSV nano delivery system based on lipid nanoparticles[65], galactosylated poly lactic-co-glycolic acid nanoparticles for the oral delivery of RSV[66], and the microparticulate system for delivering liquid and solid microparticles of RSV[67]. These research bases provide the goal and direction for continue study of RSV absorption in depth.

In addition, RSV could reduce steroidogenesis in rat ovarian theca-interstitial cells by inhibiting of Akt/protein kinase B signaling pathway[68], and might enhance normal-weight females' responses to controlled ovarian hyperstimulation by RSV's anti-inflammatory, insulin-sensitizing, and antihyperandrogenism mechanisms[36]. Also there were evidences showed that RSV attenuated lipid peroxidation, sperm DNA damage[69] and alleviated testicular cell apoptosis in type 1 diabetes mice [70]. These observations demonstrated RSV's therapeutic potential for preserving ovarian reserve and male sperm quality, we can further increase the research on the beneficial effects of RSV on female and male reproduction, and believe that it is a good direction for the research of RSV.

CONCLUSION

As a natural polyphenol compound, RSV has the advantages of low side effects, wide sources, low price, and low safety risk. RSV could improve the indicators of GDM by improving glucose metabolism and insulin tolerance, regulating blood lipids and plasma adipokines, and modulating embryonic oxidative stress and apoptosis. Furthermore, RSV could ameliorate the GDM complications by reducing oxidative stress, reducing the effects on placentation, reducing the adverse effects on embryonic development, reducing offspring's healthy risk and so on. RSV has high application value in pregnancy diabetes and its complications, some of its targets are directly affected, while others are modulated indirectly, through changes in their expression levels. This may not only be the advantage of RSV in treating diabetes, but also may bring some unexpected side effects. Therefore, in order to meet the needs of users, it is still necessary to conduct in-depth research on RSV in the process of use.

FOOTNOTES

Author contributions: Ma HZ and Liu YF designed the review and wrote the manuscript; Chen Y and Guo HH conducted data collection and selection; Wang J designed the table and edited the manuscript; Xin XL and Li YC performed the data analyses; All authors read and approved the final manuscript.

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