Electronic Supplementary Material (ESI) for Food & Function.

Supplementary Table 1. Experimental data of polyphenols in improving maternal and fetal outcomes of diabetes during pregnancy.

Experimental model	Polyphenol consumption	Intervention period	Maternal function and outcomes	Embryonic, fetal function and outcomes	Potential mechanisms	Reference
Human placenta, omental and subcutaneous adipose tissue (GDM-like model)	Resveratrol (200 μM)	20 hours	↓inflammation; ↓insulin resistance	NA	NA	[1]
STZ-induced rat GDM model	Resveratrol (60, 120, and 240 mg/kg)	2 weeks (1 time/day) from 8 days of pregnancy	↑insulin secretion; ↓blood glucose; ↓body weight; ↓blood lipids; adipocytokines (↓leptin, ↑adiponectin, ↓resistin, ↓TNF-α, ↓IL-6)	NA	NA	[2]
db/+ mouse GDM model	Resveratrol (10 mg/kg/day) by orally gavage	4 weeks before pregnancy and during pregnancy	↓hyperglycemia; ↓insulin resistance	↑litter size; ↓birth weight	↑AMPK signaling pathway (↑p-AMPK, ↓p-HDAC4,	[3]

					↓G6Pase)	
HFD diet-induced mosue GDM model	Resveratrol (mixed with the powdered HFD diet to a concentration of 0.2 %) by dietary intervention	From GD0 to GD18	↓bodyweight; ↓blood glucose; ↓insulin intolerance	NA	↑miR-23a-3p/NOV axis	[4]
STZ-induced rat GDM model	Resveratrol-zinc oxide complex encapsulated with chitosan (CS-ZnO-RS) (50, 100, and 200 mg/kg body weight) by orally gavage	30, 60, 90 and 120 hours	↓blood glucose; ↑antioxidant activities; ↓inflammatory activity; ↓endoplasmic reticulum stress; ↓hepatic fibrosis	NA	NA	[5]

STZ-induced rat model of diabetic embryopathy	Resveratrol (100 mg/kg b. wt.) via gavage feeding	For 10 days (from day E3 to E12)	↑blood glucose; ↑serum lipid profile; ↑outcome of diabetic pregnancy	↓embryonic maldevelopment; ↓apoptosis; ↓caspases activation; ↓oxidative stress; ↑antioxidant status; ↓embryonic development delay	NA	[6]
STZ-induced rat model of diabetic embryopathy	Resveratrol (100 mg/kg) via gavage feeding	For 10 days (from day E3 to E12)	NA	↑neuronal marker proteins (GAP-43, total tau, and neurofilament B)	↑RAR and RXR; ↑RAR and RXR DNA-binding activity; ↑ERK1/2, JNK1/2 and p38 phosphorylation	[7]
STZ-induced rat model of diabetic embryopathy	Resveratrol (100 mg/kg/day) by oral administration	From day E8 to E12	↓serum glucose	↓teratogenic effect; ↓oxidative stress	NA	[8]

Fertilized eggs cultured in high glucose (HG; 0.4 mmol/egg)	Resveratrol (0.1, 1, and 10 nmol/egg)	From incubation to embryo development day (EDD) 3.5 or EDD5	NA	↓developmental damage; ↓vascular injury; ↓oxidative stress; cell cycle (↓p21, ↑cyclin D1)	↑Pax3	[9]
db/+ mouse GDM model	Curcumin (50 and 100 mg/kg/day) by orally gavage	From GD0 to GD20	↓glucose and insulin intolerance; ↓oxidative stress	↑litter size; ↓birth weight	↑AMPK signaling pathway (↑p-AMPK, ↓p-HDAC4, ↓G6Pase)	[10]
Whole-embryo culture of mouse embryo in high glucose (HG; 300 mg/dL)	Curcumin (0, 10 and 20 μM)	24 or 36 hours	NA	↓NTD rate; ↓oxidative stress, nitrosative stress and ER stress; ↓caspase activation	NA	[11]

Whole-embryo culture of mouse embryo in high glucose (HG; 300 mg/dL)	Punicalagin (0, 10 and 20 μmol/L)	24 or 36 hours	NA	↓NTD rate; ↓oxidative stress, nitrosative stress and ER stress; ↓caspase activation	NA	[12]
db/+ mouse GDM model	Oleuropein (5 or 10 mg/kg/day) by i.p.	From GD0 to GD20	↓blood glucose; ↓insulin and hepatic glycogen levels; ↓oxidative stress; ↓inflammation	↓birth weight; ↑litter size	↑AMPK signaling pathway (↑p-AMPK, ↓p-HDAC4, ↓G6Pase)	[13]
db/+ mouse GDM model	Naringenin (50 mg/kg)	From GD0 to GD20	↑insulin response; ↑glucose metabolism	↑litter size; ↓litter weight	NA	[14]
db/+ mouse GDM model	Naringenin (100 mg/kg/day) by orally gavage	4 weeks before pregnancy and during pregnancy	↓bodyweight; ↓blood glucose; ↑glucose and insulin tolerance; ↓inflammation	↓birth weight; ↑litter size		
C2Cl2 mouse myoblasts (insulin	Naringenin (50 μg/mL)	36 hours	↓ROS; ↑GLUT4 membrane translocation; ↑glucose uptake	NA	↑AMPK activation	[15]

resistance model)						
Human placenta trophoblast HTR-8/SVneo cell and HUVEC culured in medium with insulin (1 ng/mL)	Naringenin (50 μg/mL)	48 hours	NA	NA	↓miR-140-3p, ↑insulin resistance signaling	[16]
Human placenta, VAT, and skeletal muscle (GDM-like environment)	Naringenin (400 μM)	20 hours	↑glucose uptake; ↓inflammation; ↑antioxidant activity			
db/+ mouse GDM model	Naringenin (50 mg/kg/day) by i.p.	From GD10 to GD17	↑glucose tolerance; ↑antioxidant expression; ↑anti-Inflammatory	NA	↑IκB-α, ↓NF-κB pathway	[17]
STZ-induced rat GDM model	Quercetin (75 mg/kg) by orally	On days 0, 7, 14, and 20 of the	↓number of glycogen cells; ↓histological abnormalities of	NA	NA	[18]

	gavage	gestation	placenta; ↑adiponectin; ↓adiponectin receptors (AdipoR1 and AdipoR2)			
HFD diet-induced mouse GDM model	Quercetin (700 mg/d) by dietary intervention	1 month before pregnancy	↓placental necrosis, inflammation, or hemorrhage; ↓labyrinthine placental vasculopathy; ↓lipid peroxidation	NA	NA	[19]
STZ-induced mouse GDM model	Quercetin (30 mg/kg/day) by orally gavage	4 weeks before conception	↓blood glucose; ↑17β-estradiol; ↑Igf1r, integrin αvβ3, Cox2 genes; ↓Caspase-3 gene; ↓inactive β-catenin	↑development of preimplantation embryo	↑nuclear Wnt-β-catenin signaling pathway	[20]
STZ-induced mouse model of diabetic embryopathy	Quercetin (100 mg/kg/day) via gavage feeding	From E7.5 to E10.5	NA	↓NTD rate; ↓apoptosis; ↓nitrosative stress and oxidative stress	NA	[21]

Mouse embryonic neural stem cells cultured in high glucose (HG; 33 mM)	Q3M (2, 5, 10 and 20 μM)	24 hours	NA	↓ROS		
STZ-induced mouse model of diabetic embryopathy	Q3G (100 mg/kg) via gavage feeding	From E6.5 to E9.5	NA	↓NTD rate; ↓apoptosis; ↓intracellular stress conditions	↓NF-κB transcription regulation system	[22]
Human placenta, VAT and skeletal muscle (GDM-like model)	Nobiletin (100 or 200 μM)	Overnight or 3 h	↑glucose uptake; ↓inflammation			
db/+ mouse GDM model	Nobiletin (daily doses of 50 mg/kg) by oral gavage or	From GD1 to GD17 or GD10 to GD17	↑fasting glucose levels; ↓inflammation	NA	↓NF-κB, Akt or MAPK ERK1/2 activation	[23]

	i.p.					
Human placentae, primary amnion cell and primary myometrium cells (inflammation model)	Apigenin (20 μM); Curcumin (60 μM); Naringenin (400 μM)	24 hours	↓pro-labour mediators	NA	↓NF-κB p65 binding activity	[24]
Human amnion, choriodecidua and myometrium (inflammation model)	Honokiol (100 μM)	21 hours	↓pro-inflammatory and pro-labour mediators	NA	↓NF-κB RelA transcriptional activity	[25]
Human villous trophoblast cell lines HTR8	Baicalein (0, 5, 10, 20, 50, and 100 μM)	48 hours	↓inflammatory responses; ↓apoptosis; mitochondrial fission (↓p-Drp1, ↑Mfn1/2)	NA	↓NF-κB signaling though miR-17-5p-Mfn1/2 pathway	[26]

cultured in high glucose (HG; 25 mmol/L)						
STZ-induced mouse diabetic model	Baicalin (40 mg/kg) by intragastric gavage	For 10 days	↓hyperglycemia	NA		
Chick embryos cultured in high glucose (HG; 50 mM)	Baicalin (3, 6, 12 and 24 μM)	26, 39 and 48 hours	NA	↑embryo development; ↓malformation of cardiovascular system; ↑cell proliferative; ↓apoptosis increase; ↓oxidative stresses	NA	[27]
HFHS diet-induced mouse GDM model	Procyanidins (27.8 mg/kg) by orally gavage	4 weeks before pregnancy and during pregnancy	↓insulin resistance; ↓inflammation; ↑glycometabolism	NA	↓NF-κB p65 nuclear translocation and NLRP3 inflammasome	[28]

					activation	
Fertilized eggs cultured in high glucose (HG; 0.2 mmol/egg)	Proanthocyanidins (1 and 10 nmol/egg)	From EDD0 to EDD3.5	NA	↓eye malformation; ↓oxidative stress	↑Pax6	[29]
Human visceral (omental) adipose tissue from pregnant women with GDM	Protocatechuic acid (100 μM)	1 or 18 hours	↑glucose uptake; ↑adiponectin release	NA	↑p38 MAPK activation	[30]
Oocytes from diabetic mice	Tea polyphenols (0, 25, 50 or 150 μM)	16 hours	↑oocyte maturation; ↑spindle morphology and chromosome alignment; ↑mitochondrial function; ↓ROS; ↓DNA damage	NA	NA	[31]

Oocytes from diabetic mice	EGCG (0, 20, 30 or 50 μM)	16 hours	↑oocyte maturation; ↑spindle morphology and chromosome alignment; ↑mitochondrial function; ↓ROS; ↓DNA damage	NA	NA	[32]
STZ-induced mouse model of diabetic embryopathy	EGCG (1 or 10 μM) in drinking water	From E3.5 to E8.75 or E10.5	NA	↓NTD rate; ↓DNA methylation	↓methylation in CpG islands of Grhl3, Pax3, and Tulp3	[33]
Whole-conceptus culture of rat embryo in high glucose (HG; 500 mg/dl)	EGCG (1, 10 mM)	48 hours	NA	↓embryonic vasculopathy; ↓embryonic malformations	↑Foxo3a and Akt activation	[34]
STZ combined with HFD diet-	Puerarin (0.25g/kg/day) by	Pregnancy until offspring were	↓pathological changes of pancreatic and liver tissues;	NA	↓TLR4/MyD88/NF-κB signaling	[35]

induced rat GDM model	intragastrically administration	born	↓glucose and lipid metabolism disorders; ↓insulin resistance; ↓inflammatory mediators		pathway	
db/+ mouse GDM model	Calycosin (15 mg/kg or 30 mg/kg) by intragastric administration	From the day of pregnancy to GD18	↓glucose intolerance; ↓insulin resistance; ↓inflammation; ↑pancreatic β cells function	NA	↓RNF38/SHP-1/STAT3 signaling pathway	[36]
STZ-induced rat GDM model	Pomegranate ellagic polyphenols (50, 150, 300 mg/kg/day) by orally gavage	14 days from GD0 to GD14	↑body weight; ↓insulin resistance; ↓blood glucose; ↓FINS; biochemical criterion (↓RBP4, Hcy, GA, FFA and ↑11β-HSD2); ↓pathological damage of placenta and pancreatic tissues; ↓apoptosis; ↓APN and Chemerin;	↑weight of the fetal rats	↑PPAR signal pathway	[37]

			↓inflammation-associated proteins			
STZ-induced rat GDM model	*Ganoderma lucidum* (100 mg/kg/day) by oral administration	From gestational day GD1 to GD19 or GD9 to GD19	↓glycemia; ↓lipid peroxidation	↑fetal head, thorax, craniocaudal and tail in fetuses	NA	[38]

GDM, gestational diabetes mellitus; STZ, streptozotocin; db/+, C57BL/KsJ-Lep$^{db/+}$; db/+, B6.BKS(D)-Lepr$^{db/+}$/J; HFD, high-fat diet; GD, gestational day; E, embryonic day; EDD, embryo development day; i.p., intraperitoneal injection; HUVEC, human umbilical vein endothelial cell; VAT, visceral adipose tissue; Q3M, 3-O-methylquercetin; Q3G, quercetin-3-glucoside; HFHS, high-fat-high-sucrose diet; EGCG, epigallocatechin gallate; EGCG, epigallocatechin-3-gallate

References

[1] Tran, H.T., Liong, S., Lim, R., Barker, G., and 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.

[2] Zhang, G., Wang, X., Ren, B., Zhao, Q., and 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: 2956795.

[3] Yao, L., Wan, J., Li, H., Ding, J., Wang, Y., Wang, X., and Li, M., Resveratrol relieves gestational diabetes mellitus in mice through activating AMPK. Reprod Biol Endocrinol, (2015). 13: 118.

[4] Zheng, T. and 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.
[5] Du, S., Lv, Y., Li, N., Huang, X., Liu, X., Li, H., Wang, C., and Jia, Y.F., Biological investigations on therapeutic effect of chitosan encapsulated nano resveratrol against gestational diabetes mellitus rats induced by streptozotocin. Drug Deliv, (2020). 27(1): 953-963.
[6] Singh, C.K., Kumar, A., Hitchcock, D.B., Fan, D., Goodwin, R., LaVoie, H.A., Nagarkatti, P., DiPette, D.J., and Singh, U.S., 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): 1186-96.
[7] Singh, C.K., Kumar, A., LaVoie, H.A., DiPette, D.J., and Singh, U.S., Resveratrol prevents impairment in activation of retinoic acid receptors and MAP kinases in the embryos of a rodent model of diabetic embryopathy. Reprod Sci, (2012). 19(9): 949-61.
[8] Trejo-González, N.L., Chirino-Galindo, G., and Palomar-Morales, M., [Antiteratogenic capacity of resveratrol in streptozotocin-induced diabetes in rats]. Rev Peru Med Exp Salud Publica, (2015). 32(3): 457-63.
[9] Tan, R.R., Zhang, S.J., Tsoi, B., Huang, W.S., Zhuang, X.J., Chen, X.Y., Yao, N., Mao, Z.F., Tang, L.P., Wang, Q., Kurihara, H., Li, Y.F., and He, R.R., A natural product, resveratrol, protects against high-glucose-induced developmental damage in chicken embryo. J Asian Nat Prod Res, (2015). 17(5): 586-94.
[10] Lu, X., Wu, F., Jiang, M., Sun, X., and Tian, G., Curcumin ameliorates gestational diabetes in mice partly through activating AMPK. Pharm Biol, (2019). 57(1): 250-254.
[11] Wu, Y., Wang, F., Reece, E.A., and Yang, P., Curcumin ameliorates high glucose-induced neural tube defects by suppressing cellular stress and apoptosis. Am J Obstet Gynecol, (2015). 212(6): 802.e1-8.
[12] Zhong, J., Reece, E.A., and Yang, P., Punicalagin exerts protective effect against high glucose-induced cellular stress and neural tube defects. Biochem Biophys Res Commun, (2015). 467(2): 179-84.
[13] Zhang, Z., Zhao, H., and Wang, A., Oleuropein alleviates gestational diabetes mellitus by activating AMPK signaling. Endocr Connect, (2021). 10(1): 45-53.
[14] Xing, B.H., Yang, F.Z., and Wu, X.H., Naringenin enhances the efficacy of human embryonic stem cell-derived pancreatic endoderm in treating gestational diabetes mellitus mice. J Pharmacol Sci, (2016). 131(2): 93-100.
[15] Li, S., Zhang, Y., Sun, Y., Zhang, G., Bai, J., Guo, J., Su, X., Du, H., Cao, X., Yang, J., and Wang, T., Naringenin improves insulin sensitivity in gestational diabetes mellitus mice through AMPK. Nutr Diabetes, (2019). 9(1): 28.
[16] Zhao, C., Zhao, C., and Zhao, H., Defective insulin receptor signaling in patients with gestational diabetes is related to dysregulated miR-140 which can be improved by naringenin. Int J Biochem Cell Biol, (2020). 128: 105824.
[17] Nguyen-Ngo, C., Willcox, J.C., and Lappas, M., Anti-Diabetic, Anti-Inflammatory, and Anti-Oxidant Effects of Naringenin in an In Vitro Human Model and an In Vivo Murine Model of Gestational Diabetes Mellitus. Mol Nutr Food Res, (2019). 63(19): e1900224.
[18] Mahabady, M.K., Shamsi, M.M., Ranjbar, R., Tabandeh, M.R., and Khazaeel, K., Quercetin improved histological structure and upregulated adiponectin and adiponectin receptors in the placenta of rats with gestational diabetes mellitus. Placenta, (2021). 106: 49-57.

[19] Liang, C., DeCourcy, K., and Prater, M.R., High-saturated-fat diet induces gestational diabetes and placental vasculopathy in C57BL/6 mice. Metabolism, (2010). 59(7): 943-50.
[20] Bolouki, A., Zal, F., and Alaee, S., Ameliorative effects of quercetin on the preimplantation embryos development in diabetic pregnant mice. J Obstet Gynaecol Res, (2020). 46(5): 736-744.
[21] Cao, L., Tan, C., Meng, F., Liu, P., Reece, E.A., and Zhao, Z., Amelioration of intracellular stress and reduction of neural tube defects in embryos of diabetic mice by phytochemical quercetin. Sci Rep, (2016). 6: 21491.
[22] Tan, C., Meng, F., Reece, E.A., and Zhao, Z., Modulation of nuclear factor-κB signaling and reduction of neural tube defects by quercetin-3-glucoside in embryos of diabetic mice. Am J Obstet Gynecol, (2018). 219(2): 197.e1-197.e8.
[23] Nguyen-Ngo, C., Salomon, C., Quak, S., Lai, A., Willcox, J.C., and Lappas, M., Nobiletin exerts anti-diabetic and anti-inflammatory effects in an in vitro human model and in vivo murine model of gestational diabetes. Clin Sci (Lond), (2020). 134(6): 571-592.
[24] Lim, R., Barker, G., Wall, C.A., and Lappas, M., Dietary phytophenols curcumin, naringenin and apigenin reduce infection-induced inflammatory and contractile pathways in human placenta, foetal membranes and myometrium. Mol Hum Reprod, (2013). 19(7): 451-62.
[25] Wijesuriya, Y.K. and Lappas, M., Potent anti-inflammatory effects of honokiol in human fetal membranes and myometrium. Phytomedicine, (2018). 49: 11-22.
[26] Li, J., Wang, Y., Wu, T., Li, S., Sun, Y.N., and Liu, Z.H., Baicalein suppresses high glucose-induced inflammation and apoptosis in trophoblasts by targeting the miRNA-17-5p-Mfn1/2-NF-κB pathway. Placenta, (2022). 121: 126-136.
[27] Wang, G., Liang, J., Gao, L.R., Si, Z.P., Zhang, X.T., Liang, G., Yan, Y., Li, K., Cheng, X., Bao, Y., Chuai, M., Chen, L.G., Lu, D.X., and Yang, X., Baicalin administration attenuates hyperglycemia-induced malformation of cardiovascular system. Cell Death Dis, (2018). 9(2): 234.
[28] Liu, Y., Sun, R., Lin, X., Wu, L., Chen, H., Shen, S., Li, Y., Wei, Y., and Deng, G., Procyanidins and its metabolites by gut microbiome improves insulin resistance in gestational diabetes mellitus mice model via regulating NF-κB and NLRP3 inflammasome pathway. Biomed Pharmacother, (2022). 151: 113078.
[29] Tan, R.R., Zhang, S.J., Li, Y.F., Tsoi, B., Huang, W.S., Yao, N., Hong, M., Zhai, Y.J., Mao, Z.F., Tang, L.P., Kurihara, H., Wang, Q., and He, R.R., Proanthocyanidins Prevent High Glucose-Induced Eye Malformation by Restoring Pax6 Expression in Chick Embryo. Nutrients, (2015). 7(8): 6567-81.
[30] Scazzocchio, B., Filardi, T., Varì, R., Brunelli, R., Galoppi, P., Morano, S., Masella, R., and Santangelo, C., Protocatechuic acid influences immune-metabolic changes in the adipose tissue of pregnant women with gestational diabetes mellitus. Food Funct, (2021). 12(16): 7490-7500.
[31] Lu, J., Zhao, S.X., Zhang, M.Y., Ji, P.Y., Chao, S., Li, L.J., Yin, S., Zhao, L., Zhao, H., Sun, Q.Y., and Ge, Z.J., Tea polyphenols alleviate the adverse effects of diabetes on oocyte quality. Food Funct, (2022). 13(9): 5396-5405.
[32] Chao, S., Li, L.J., Lu, J., Zhao, S.X., Zhao, M.H., Huang, G.A., Yin, S., Shen, W., Sun, Q.Y., Zhao, Y., Ge, Z.J., and Zhao, L., Epigallocatechin gallate improves the quality of diabetic oocytes. Biomed Pharmacother, (2023). 159: 114267.
[33] Zhong, J., Xu, C., Reece, E.A., and Yang, P., The green tea polyphenol EGCG alleviates maternal diabetes-induced neural tube defects by inhibiting DNA hypermethylation. Am J Obstet Gynecol, (2016). 215(3): 368.e1-368.e10.

[34] Yang, P. and Li, H., Epigallocatechin-3-gallate ameliorates hyperglycemia-induced embryonic vasculopathy and malformation by inhibition of Foxo3a activation. Am J Obstet Gynecol, (2010). 203(1): 75.e1-6.
[35] Xu, W., Tang, M., Wang, J., and Wang, L., Anti-inflammatory activities of puerarin in high-fat diet-fed rats with streptozotocin-induced gestational diabetes mellitus. Mol Biol Rep, (2020). 47(10): 7537-7546.
[36] Li, Y., Duan, B., Li, Y., Yu, S., and Wang, Y., The isoflavonoid calycosin inhibits inflammation and enhances beta cell function in gestational diabetes mellitus by suppressing RNF38 expression. Immunopharmacol Immunotoxicol, (2020). 42(4): 366-372.
[37] Sun, Y.L., Zhou, F.M., and Wang, H.R., Mechanism of pomegranate ellagic polyphenols reducing insulin resistance on gestational diabetes mellitus rats. Am J Transl Res, (2019). 11(9): 5487-5500.
[38] Viroel, F.J.M., Laurino, L.F., Caetano É, L.A., Jozala, A.F., Spim, S.R.V., Pickler, T.B., Sercundes, M.K., Gomes, M.C., Hataka, A., Grotto, D., and Gerenutti, M., Ganoderma lucidum Modulates Glucose, Lipid Peroxidation and Hepatic Metabolism in Streptozotocin-Induced Diabetic Pregnant Rats. Antioxidants (Basel), (2022). 11(6).