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Functional food ingredients for control of gestational diabetes mellitus: a review

Huiting LIN[1], Shiyang LI[1], Jiawen ZHANG[1], Shaoling LIN[1], Bee K. TAN[2,3]*, Jiamiao HU[1,4]*

Abstract

Gestational diabetes mellitus (GDM) is highly prevalent worldwide, with an estimated 10-15% percent of pregnancies affected. Increasing evidence indicates that functional food ingredients (FFIs) may help relieve GDM *via* multiple mechanisms, such as eliminating free radicals, downregulating inflammation, promoting insulin secretion and signaling, targeting hepatic gluconeogenesis and glycogen storage metabolism, and regulating the intestinal microflora. In this article, the effects of functional food ingredients on GDM and the possible underlying mechanisms of action are reviewed. This review provides reference information that can be useful for the development of novel functional supplements for the control of GDM.

Keywords: gestational diabetes mellitus; food ingredients; insulin signaling; oxidative stress; intestinal microflora.

Practical Application: Used as natural substances for GDM management.

1 Introduction

Gestational diabetes mellitus (GDM) refers to carbohydrate intolerance resulting in hyperglycemia that is first diagnosed during pregnancy. It is characterized by high blood glucose levels in pregnant women who have not been previously diagnosed with diabetes (Patti et al., 2018). The cause of GDM is multifactorial (Dean et al., 2014); age, pre-gestational obesity and a family history of diabetes have been identified as risk factors for GDM (Cho et al., 2016). GDM was thought to be a transient state and that glucose homeostasis would recover shortly after delivery (Ponzo et al., 2019). However, increasing evidence demonstrates that GDM has profound and long-lasting adverse effects on both the mother and child. Without proper treatment, GDM may increase perinatal morbidity and mortality (Farrar et al., 2017). Moreover, long-term metabolic risks are also being recognized in women who had GDM as well as in their offspring (Stewart, 2020). GDM pregnancies may increase the risk of type 2 diabetes in the mother by 30-50% within 10-20 years, while the offspring show an increased risk of childhood obesity and diabetes mellitus (Johns et al., 2018). Currently, diet intervention is recommended for women with GDM, especially those with mild GDM, in addition to drug interventions i.e. metformin, insulin, with its potential side effects. In addition to general guidelines, such as switching to low glycemic index foods and/or reducing carbohydrate intake, a variety of functional food may help control this condition or make GDM less likely to occur. Functional foods have been defined as industrially processed or natural foods that, besides providing basic nutrition, beneficially promote optimal health and help reduce the risk of disease when consumed on a regular basis (Granato et al., 2020). Increasing number of non-conventional food plants show great potential to be novel functional foods (Folharini et al., 2019). Particularly, functional foods are often rich in bioactive compounds associated with prevention of metabolic disease (Konstantinidi & Koutelidakis, 2019). Indeed, the beneficial effects of various functional food ingredients (FFIs) on GDM have been demonstrated using experimental animal models as well as human trials. However, the mechanisms of action underlying the beneficial effects of FFIs on GDM are not fully understood. We will focus on these mechanisms in this review.

2 Experimental animal models to evaluate the effects of FFIs on GDM

Although food ingredients are usually safe, safety concerns cannot be overlooked. Therefore, despite invaluable clinical data on the beneficial effects of FFIs on GDM in humans, animal models are also widely used in GDM studies. In general, rodent models of GDM can be divided into the following three types: 1) genetically engineered rodent models of GDM. For instance, C57BL/KsJ$^{db/+}$ (db/+) mice, a typical diabetes model, harbor a heterozygous mutation in the leptin receptor gene *Lepr* and can mimic gestational diabetes. In general, six- to eight-week-old mice are used; 2) Alloxan/Streptozotocin (STZ)-induced GDM models. Chemical agents alloxan and STZ selectively damage pancreatic β-cells, resulting in hyperglycemia and diabetes with its attending complications (Pasek & Gannon, 2013). Therefore, alloxan/STZ administration during/before pregnancy can be used to mimic both severe and mild GDM, depending on the dose (Kiss et al., 2009). This treatment is generally supplemented with high-fat high-fructose (HFHF) fodder. 3) Obesogenic diet-induced GDM models. Pre-pregnancy overweight and excess gestational weight gain have been identified as important causes of GDM. Therefore, obesogenic diets, such as high-fat high-fructose diets, or cafeteria-style foods are also widely used

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[1] *College of Food Science, Fujian Agriculture and Forestry University, Fuzhou, China*
[2] *Department of Cardiovascular Sciences, Leicester Diabetes Centre, College of Life Sciences, University of Leicester, Leicester, United Kingdom*
[3] *University Hospitals Leicester NHS Trust, Leicester, United Kingdom*
[4] *Leicester Institute for Advanced Studies, University of Leicester, Leicester, United Kingdom*
*Corresponding author: bee.k.tan@leicester.ac.uk, jiamiao.hu@fafu.edu.cn

to mimic GDM. ICR mice, Wistar rats, and Sprague Dawley rats are usually used for this purpose. Admittedly, the causes of GDM are complex; therefore, the previous rodent models are unlikely to fully mirror the pathogenesis of GDM in humans. Choosing a suitable rodent model is crucial for evaluating FFIs before human trials. Continued development of animal models is essential to investigate FFIs as potential treatments or preventive therapies for GDM.

3 Molecular mechanisms

3.1 FFIs increase insulin secretion and potentiate insulin signaling

Insulin signaling is believed to play a central role in the regulation of glucose homeostasis. Lack of insulin secretion and insulin sensitivity results in hyperglycemia in GDM patients. Not surprisingly, various FFIs with anti-GDM properties have shown positive effects on insulin secretion and the insulin signaling pathway. For example, Li et al. (2019) found that naringenin showed great potential for treatment of GDM due to its insulin sensitivity-enhancing effect in skeletal muscle; this is dependent on AMPK activation. Zou et al. (2018) reported that mogroside IIIE greatly improved insulin sensitivity by activating the AMPK/HDAC4/G6Pase signaling pathway, alleviating GDM in mice. Plows et al. (2020) reported that intracellular insulin signaling in adipose tissue could be improved by adding myoinositol and probiotics, although neither myoinositol nor probiotics improved glucose tolerance. PPARs are well-characterized transcriptional regulators with key functions in insulin metabolism (Wahli & Michalik, 2012). Indeed, PPAR agonists have a long history as effective treatments for type 2 diabetes (T2D). Therefore, FFIs exhibiting PPAR-activating properties (often weak PPAR agonists) could be explored as anti-GDM agents. For instance, Sun et al. (2019) showed that pomegranate ellagic polyphenols activated PPARα-TRB3-AKT2-p-FOXO1-GLUT2 signaling (associated with insulin sensitivity) in a dose-dependent manner. Fornes et al. (2020) reported that a diet supplemented with 6% olive oil prevented the increase in PPARγ and PPARδ levels in the male fetuses of pregnant rats. On the other hand, Capobianco reported that a maternal diet supplemented with polyunsaturated fatty acids attenuated mTOR signaling, preventing fetal overgrowth (Capobianco et al., 2018b). These observations indicate a possible relationship between improved insulin sensitivity and the anti-GDM effects of FFIs.

3.2 FFIs target hepatic gluconeogenesis and glycogen storage

GDM is associated with inhibition of glycogen synthesis, affecting the citric acid cycle and gluconeogenesis (Gao et al., 2019b). One study reported that the prevalence of non-alcoholic fatty liver disease among women with a history of GDM was 14–38% higher than in women without such history (Sattari et al., 2020). Moreover, hepatic insulin resistance can result in increased release of glucose (from gluconeogenesis) and free fatty acids (due to enhanced lipolysis), leading to fetal overgrowth (Lee et al., 2019). Several studies have revealed that normalization of glycogen synthesis in the liver is one mechanism by which FFIs relieve GDM. For instance, Zhang et al. (2020) reported that astragaloside IV treatment reduced hepatic gluconeogenesis by downregulating cAMP accumulation in the liver of GDM mice. Yao et al. (2015) reported that resveratrol influenced glucose production in the fetus by reducing the enzymatic activity of G6P, and that the AMPK signaling pathway was the potential target of resveratrol in GDM. Furthermore, Brawerman et al. (2019) showed that hepatic glucose metabolism in the offspring of GDM rats could be restored by maternal resveratrol administration and that the utilization of glucose was enhanced by glycolytic flux. These studies support the notion that FFIs can modulate cellular and whole-body energy homeostasis under stress conditions during pregnancy by activating the energy sensor system: AMPK (Kumagai et al., 2018). Besides, SREBP-1 is also considered a target to improve hepatic glycogen content and relieve GDM. Hua et al. (2016) found that diosgenin supplementation normalized gluconeogenesis by increasing expression of Srebp-1 and its target genes, attenuating FAS, SDC-1, ACC. In conclusion, hepatic gluconeogenesis and glycogen storage are promising FFI targets for the treatment of GDM.

3.3 FFIs ameliorate GDM-induced oxidative stress

GDM is a pathological condition often associated with oxidative stress (Zygula et al., 2019). Reduced activity of endogenous antioxidant enzymes such as CAT, SOD, TBARS, GPX, and GSH is a common finding in GDM pregnancies. As shown in Table 1, administering FFIs to GDM mice significantly enhances the activity of antioxidant enzymes and attenuates GDM outcomes. For example, Sha et al. (2019) reported that mangiferin attenuated GDM outcomes by increasing GPX, GSH, SOD, and CAT levels in the placenta of GDM mice. Likewise, Hua et al. (2016) determined that diosgenin could ameliorate oxidative stress in pregnant db/+ mice, as evidenced by decreased TBARS, and upregulation of GSH levels and SOD and CAT activity. Similar conclusions were reported in a study by Hosni et al. which showed that the defective antioxidant defense system in GDM could be improved by daily supplementation with 20 mg/kg cinnamaldehyde (Hosni et al., 2017). Therefore, one of the mechanisms by which FFIs exert beneficial effects in pregnancies complicated by GDM appears to be by inhibiting oxidative stress.

3.4 FFIs attenuate GDM-induced inflammation

GDM is often strongly associated with an inflammatory state, as evidenced by increased levels of proinflammatory cytokines like IL-β, IL-6, and TNF-α, and elevated CRP (Pantham et al., 2015). Suppression of inflammatory responses is also believed to be a mechanism by which FFIs relieve the deleterious outcome of GDM. For example, treatment of GDM mice one week before mating with cinnamaldehyde had glucose lowering effects and reduced the levels of proinflammatory cytokines like TNF-α, as well as MDA and NO (Hosni et al., 2017). Another study suggested that apocynin (4-hydroxy-3-methoxyacetophenone) reduced the serum levels of glucose by downregulating IL-1β, IL-6, and TNF-α, while activating the TLR4/NF-κB signaling pathway (Liu et al., 2020). Zou et al. (2018) reported that a maternal diet supplemented with mogroside IIIE reduced pancreatic and serum levels of IL-1β, IL-6, and TNF-α, while enhancing AMPK activity and reducing G6Pase production. Nguyen-Ngo et al. (2020) also

Table 1. Effects of FFIs on molecular mechanisms associated with GDM.

Model	Intervention	Mechanism	Reference
C57BL/KsJ$^{db/+}$mice	Resveratrol at 10 mg/kg *d	body weight↓; glucose↓; insulin sensitivity↑; G6P↓; AMPK signaling↑; p-AMPK/AMPK↑; p-HDAC4/HDAC4↓;	Yao et al. (2015)
C57BL/KsJ$^{db/+}$ mice	Naringenin at 100 mg/kg *d	body weight↓; GTT↑;ITT↑; FPG↓; HOMA-IR↓; APN↑; 2-Deoxyglucose↓; GLUT4↑; insulin sensitivity↑; IL-1β↓; IL-6↓; TNF-α↓; MCP-1↓; TLR2↓; TLR4↓; phorspho-JNK↓; phorspho-NF-κB p65↓; fetal birth weight↓; litter size↑; p-AMPK /AMPK↑; AMPK signaling↑	Li et al. (2019)
C57BL/KsJ-Lep$^{db/+}$mice	Naringenin at 50 mg/kg*d	SOD↑; GSH↑; MDA↓; body weight↑; glucose↓; insulin↑; offspring(litter size↑;litter weight↓)	Xing et al. (2016)
C57BL/KsJ$^{db/+}$mice	Mangiferin at 50 mg/kg*d	body weight↓; glucose↓; insulin↑; HOMA-IR↓; HOMA-β↑; TC↓; TG↓; HDL-C↑; LDL-C↓; atherogenic index↓; fetal survival rate↑; fetal weight↑; fetal crown-rump length↑; placenta(weight↑;SOD↓; GPX↓; GSH↓; CAT↓; IL-6↓;MCP-1↓; GRP78↓; p-IRE1α↓; p-eIF2α↓)	Sha et al. (2019)
C57BL/KsJ$^{db/+}$mice	Diosgenin at 10 and 20 mg/kg*d	GTT↑; ITT↑; glucose↓; FPG↓; insulin↓; hepatic glycogen↑; liver (TBARS↑; GSH ↑; SOD↑; CAT↑; TC↓; TG↓;) plasma(TC↓; TG↓; LDL-C↓; HDL-C↑); Srebp-1↓; FAS↓; SCD-1↓; Acc↓	Hua et al. (2016)
C57BL/KsJ$^{db/+}$mice	Mogroside IIIE at 20 mg/kg*d	body weight↓; glucose↓; insulin↑; ITT↑; GTT↑; birth weight↓; litter size↑; IL-1β↓; IL-6 ↓; TNF-α↓;AMPK signaling↑; p-AMPK/AMPK↑; p-HDAC4/HDAC4↓; G6P↓	Zou et al. (2018)
C57BL/KsJ $^{db/+}$mice	Astaxanthin at 30 mg/kg *d	glucose↓; insulin↑; GTT↑; ITT↑; TC↓; TG↓; HDL↑;LDL↓; MDA↑; atherogenic index↓; liver(GSH↑; SOD↑; CAT↑; MDA↑; GPX↑)	Chen et al. (2020)
C57BL/KsJ$^{db/+}$mice	Apocynin at 5,20 and 50 mg/kg*d	body weight↑; glucose↓; insulin↑; HOMA-IR↑; HOMA-β↑; TG↓; TC↓; HDL↑; LDL↓;atherogenic index↓; fetal survival rate↑; fetal weight↑; crown-rump length↑; placenta weight↑; placental(MDA↑ ; SOD↑; GPx↑; GSH↑); IL-1β↓; IL-6↓; TNF-α↓; TLR4/NF-κB signaling↑	Liu et al. (2020)
Lepr^{db}/+ (db/+)mice	Nobiletin at 50 mg/kg*d	FPG↓; placenta(Cxcl1↓; Il1a↓); VAT(Ccl2 ↓; Il1a↓; d Il1b↓); subcutaneous adipose(Ccl2↓, Cxcl1↓, Il1a↓,Il1b↓; TNF-α↓); NF-κB↓; Akt↓; MAPK signaling↓	Nguyen-Ngo et al. (2020)
C57BL/KsJ$^{db/+}$mice	Curcumin at 50 and 100 mg/kg*d	insulin↓;FPG↓; GTT↑; ITT↓; liver(TBARS↓; GSH↑; SOD↑; CAT↑); AMPK signaling↑; p-AMPK/AMPK↑; p-HDAC4/HDAC4↓; G6P↓; hepatic glycogen↑; fetuse(birthweight↓; litter size↑)	Lu et al. (2019)
Wistar rats by STZ	lotus leaf polysaccharides at 50 and 100 mg/kg*d	FPG↓; FINS↓; TG↓; TC↓; HDL↑; LDL↓; hepatic glycogen↑; SOD↑CAT↑; GPX↑; GSH↑	Wang (2013)
Wistar rats by STZ	lotus leaf selenium polysaccharide at 50 and 100 mg/kg*d	FPG↓; FINS↓; TG↓; TC↓; HDL↑; LDL↓; hepatic glycogen↑; liver(SOD↑; GSH↑; GPX↑; CAT↑); fetal body weight↑; placental weight↑; prenatal body weight ↑	Zeng et al. (2017)
Wistar rats by STZ	pomegranate ellagic polyphenols at 50, 150 and 300 mg/kg*d	serum(RBP4↓; Hcy↓; GA↓ ; FFA↓); prenatal body weight↑; fetal rats body weight↑; FPG↓; FINS↓; HOMA-IR↓;TG↓; TC↓; HDL↑; placenta(p-PI3K↓; p-AKT↓); PPARα↑; TRB3↑; AKT2↑; p-FOXO1↑; GLUT2↑; pancreas(TNF-α↓; IL-6↓; CRP↓; APN↓; Chemerin↓); 11β-hydroxy steroid dehydrogenase type 2 level↓; PPARα-TRB3-AKT2-p-FOXO1-GLUT2 signaling↓	Sun et al. (2019)
Sprague Dawley rats by STZ	daily 0.5% vitamin E plus 1% vitamin C; daily 2% vitamin E and 4% vitamin C	maternal bodyweight↑; maternal liverweight↑; glucose↓; plasma(vitaminE↑; vitaminC↑; TBARS↓); Liver(vitaminE↑; vitaminC↑;TBARS↓); fetal livers(ascorbic acid↑; a-tocopherol↑; carbonylated proteins to total protein amounts↓; dintrophenylated proteins.↓); malformations rate↓; fetal weight↑; fetal liver weight↑	Cederberg et al. (2001)

Table 1. Continued...

Model	Intervention	Mechanism	Reference
Wistar rats (Rattus norvegicus var. albinus) by STZ	Lentinus edodes at 100 mg/kg*d	GTT↑; insulin↓; lipase; glucose↓; red blood cells↑;hematocrit↓; leukocyte↓; hemoglobin; platelet↑;HDL↑; LDL↓;TG↓; TC↓; ALT↓; AST↓; CAT↑; GPX↑; GSH↓; TBARS↓; placenta(CAT↑; GPX↓; GSH↓; TBARS↓); uterus weight↑; ovary weight↓; placenta weight↓; fetal survival rate↑	Laurino et al. (2019)
Albino rats by STZ	Cinnamal dehyde at 20 mg/kg*d	body weight↓; glucose↓; insulin↑; leptin↓; hepatic glycogen↑; fructosamine↓; TC↓; TG↓; HDL-C↑; GTT↑; ITT↑; birth weight↓; litter size↑; IL-1β↓; IL-6↓; TNF-α↓	Hosni et al. (2017)
Albino Wistar rats by STZ	A daily 6% olive oil supplemented diet	maternal rat(TG↓;TC↓); male offspring(TG↓;TC↓;free fatty acids↓; phospholipids↑; PLIN2↓ ; PPARγ1↓; PPARγ2↓; PPARδ↓; PPARα↑; Srebp-1c↓; Acc1↓; Fasn↓; Aoo↓; Cpt1-L↓; Scd-1↓; Cpt1-L↓; PGC-1α↓; SRC-1↓); female offspring(TG↓; TC↑; free fatty acids↓; cholesterylesters↓; phospholipids↓; PLIN2↑; PPARγ1↑; PPARγ2↓; PPARδ↓; PPARα↑;Srebp-1c↑; Acc1↓; Fasn↓;Aoo↓; Cpt1-L↓; Scd-1↓; Cpt1-L↓; PGC-1α↑; SRC-1↓)	Fornes et al. (2020)
Albino Wistar rats by STZ	A daily 6% olive oil supplemented diet	maternal rat(glucose↓; weight↓; CTGF↓); offspring(glucose↑; weight↓); placenta(mTORC1 signaling↑; mTORC2signaling↑; PPARγ↓; 4EBP-1↑; lipoperoxidation↓; TBARS↓; CTGF↓; MMP2↓)	Capobianco, et al. (2018b)
Albino Wistar rats by STZ	6% safflflower oil Supplemented diet from day 1 to 14 of pregnancy,then 6% chia oil supplemented diet from day 14 to term	maternal rat(glucose↓; TG↓; TC↓); offspring(glucose↓; TG↓; TC↓; body weight↓; lipoperoxidation↓); placenta(weight↓; mTORC2 signaling↓; mTORC1 signaling↓; PPARγ↑)	Capobianco et al. (2018a)
SD rats by STZ	okra extract at 200 mg/kg*d	prenatal body weight↑; fetal rats weight↑; placenta weight↑; HbA1c↓; TG↓; TC↓; FFA↓; FPG↓; HDL↑; LDL↓; FINS↓; Serum CP↓; hepatic glycogen↑; liver (SOD↑; CAT↑; GPX↑; GSH↑); pancreas(SOD↑; CAT↑; GPX↑; GSH↑)	Tian et al. (2015)
Wistar rats by STZ	A daily supplemented highly-pure-Cellulose-enriched-diet (10%cellulose)	glucose↓; urea↓; creatinine↓; uric acid↓; albumine↓; TC↓; TG↓; HDL↑; LDL↓; VLDL-C↓; VLDL-TG↓; HDL-TG↓; LDL-TG↓; carbonyl proteins↓; MDA↓; CAT↑; SOD↑	Bensalah et al. (2018)
Wistar rats by STZ	A daily 60% Omega-3 polyunsaturated fatty acids supplemented diet	pancreas of offspring (TC↓; TG↓; CAT↑; GSH↑; MDA↓; SOD↑; TNF-α↓; IL-1β↓; IL-6↓; IL-10↑; pancreatic telomere length↑)	Gao et al. (2019a)
Wistar rats by STZ	A daily n−3 PUFAs (EPA and DHA) supplemented diet	offspring(body weight↓; glucose↓; insulin↓; TG↓ ; TC↓; adipose tissue weight↓; adipose tissue lipid↓; liver lipid↓); liver fatty acid of offspring($C_{20:5n-3}$↑; $C_{22:6n-3}$↑; $C_{20:4n-6}$↓; SFA↓)	Soulimane-Mokhtari et al. (2005)
Wistar rats by STZ	Zuogui Wan(rhizome of adhesive Rehmannia, Rhizoma Dioscoreae, Barbary Wolfberry fruit, Cornus officinalis, China dodder, Colla Cornus Cervi, tortoise shell glue, and medicinal Cyathula root)	body weight↓; FPG↓; 2hPG↓; fat weight↓;abdominal fat weight↓; TG↓; TC↓; HDL↓; LDL↓; insulin↓; leptin↓;APN↑;HOMA-IR↓	Wang et al. (2016)
Wistar rats by STZ	100 mg/kg*daqueous extract of Hibiscus rosa-sinensis from day 0 to 7 of pregnancy; 200 mg/kg*d from day 8 to 14 of pregnancy; 400 mg/kg*d from day 15 to term	glucose↓; body weight gain↑; food intake↓; water intake↓; TG↓; TC↓; HDL↑; VLDL↓; CRI↓; liver(MDA↓; GSH↑; SOD↑; CAT↓); malformations rate↓	Afiune et al. (2017)
Rats by Alloxan	grape seed and skin extract at 4 g/kg*d	body weight↑; glycemia↓; insulinemia↓; prolactinemia↓; kidney index↓; kidney(TG↓; G6PDH↓; MDA↓; protein carbonylation↑; non protein thiols depletion↓; SOD↑; CAT↑);1/ creatinine↓; proteinuria↓; uricemia↓; Kidney magnesium↑; plasma magnesium↑; urine magnesium↑;H_2O_2↓; AChE↑; calpain↑; Cu↓; Se↑; tyrosinase↑; GPx↑	Oueslati et al. (2016)

Table 1. Continued...

Model	Intervention	Mechanism	Reference
Sprague Dawley rats	resveratrol at 147 mg/kg*d	energy intake↓; food consumption↓; FPG↓;GTT↓;ITT↓; PTT↓; FINS↑; glucagon↑; TG↓; hepatic TG↓; Srebp1c↓; PPARα↑; lpl↑; g6p↑; pck1↓; offspring(food consumption↓; litter size↑; body weight ↓; body length ↑; TG↓; Srebp1c↓; PPARα↑; lpl↑; G6P↑; pck1↓)	Brawerman et al. (2019)
Sprague Dawley rats	A daily 10% oligofructose supplemented diet	energy intake↓; offspring(GTT↑;ITT↓; AST↓; ALT↑; IL-1β↓;IL-6↓; MCP-1↓; body weight↓; body fat↓; insulin↓; glucose↓; body fat↓; leptin↓; PPAR-β↓; FABP4↓; PGC-1α↓); Bifidobacterium spp↑	Paul et al. (2019)
ICR mice	A daily 15% lactulose supplemented diet	LDL↓; HDL↑; TG↓; TC↓; AST↓; ALT↓; estradiol↑; prolactin↑; luteinizing hormone↑; progesterone↑; trimethyl-amine N-oxide↓; immunoglobulin A↑; intestinal permeability↓; DAO activity↓; D-LA activity↓; ZO-1↑; Occludin↑; small intestines(villus height/crypt depth↑); colon($CD4^+$↑; $CD8^+$↑; IgA↑; content pH↓); Bifififidobacterium↑; Bacteroides↑	Zhang et al. (2019)
human	Lycium barbarum L. polysaccharides at 10 mg*d	miR-33↓; ABCA1↑; Srebp1↓; TG↓; TC↓; HDL↑; LDL↓; MDA↓	Yang et al. (2018)
human	250 mg*d magnesium oxide plus 400 IU*d vitamin E	body weight↓; BMI↓; FPG↓; insulin↓; QUICKI↑; HOMA-IR↓; TG↓; TC↓; LDL↓; VLDL↓	Maktabi et al. (2018)
human	soybean oligosaccharides at 10 g*d	HOMA-IR↓; SOD↑; GPx↑; CAT↑; TBARS↓; FPG↓; FINS↓; APN↑; HBCI ↓	Fei et al. (2014)
human	5 g*d black garlic treated Lactobacillus bulgaricus	1hPG↓; 2hPG↓; FPG↓; GTT↑; T-AOC↑; SOD↑; GSH-PX↑; MDA↓	Si et al. (2019)
human	1000 mg*d omega-3 fatty acids plus 400IU*d vitamin E	VLDL↓; LDL↓; HDL↑; TG↓; TC↓; HOMA-IR↓; HOMA-β↓; insulin sentivity↓	Taghizadeh et al. (2016)
human	supplemented 40 mL extra virgin olive oil plus a handful of pistachios per day	FPG↓; body weight gain↓; HOMA-IR↓; insulin↓; offspring(birth weight↑; body length↑; hypoglycemia↓)	Assaf-Balut et al. (2017)
human	A daily high-fibres diet	VLDL↓; LDL↓; HDL↑; GlycA↓; LPS↓; Lachnospira↑	Röytiö et al. (2018)
human	oligosaccharide-sialic acid at 60g*d	IL-1β↓; IL-6↓; IL-8↓; IL-10↓; TNF-α↓; CRP↓; VLDL↓; LDL↓; HDL↑; TG↓; TC↓; GTT↑; FPG↓	Wang et al. (2019)
human	A daily 2% myo-inositol supplemented diet	TG↓; TC↓; LDL↓; HDL↑; FPG↓; birth weight↑; ponderal index↓	Plows et al. (2020)
human	Supplemented 2g myo-inositol *d	Insulin↓; leptin↑; APN↑; fasting c-peptide↓; HOMA-IR↓; GTT↑; fasting glucose↓; 2hPG↓; birth weight↓; macrosomia rate↓	Amaefule et al. (2018)
human	A daily Ca-rich low-fat diet (200 mg Ca)	22% reduction in GDM risk	Osorio-Yáñez et al. (2017)
human	A daily capsule (Lactobacillus acidophilus LA-5,BifidobacteriumBB-12,Streptococcus thermophilus STY-31 and Lactobacillus delbrueckii bulgaricus LBY-27)	body weight gain↓; FPG↓; FINS↓; HOMA-IR↓	Dolatkhah et al. (2015)
human	A daily capsule (Lactobacillus acidophilus, Lactobacillus casei and Bifififidobacterium bifididum) plus 800 mg inulin	insulin↓; HOMA-IR↓; HOMA-B↓; TAG↓; VLDL↓; TC↓; LDL↓; HDL↓	Ahmadi et al. (2016)
in vitro human placenta, adipose and skeletal muscle model of GDM	Placental explants were incubated in 100 μM nobiletin;skeletal muscle explants and VAT explants were incubated in 200 μm nobiletin	VAT(IκB-α↑); placenta(Akt ↓; MAPK ERK1/2↓)	Nguyen-Ngo et al. (2020)
in vitro human placenta, omental and subcutaneous adipose tissue and skeletal muscle model of GDM	incubated in 200 um resveratrol	placenta/omental adipose/skeletal muscle (IL-1α↓; IL-1β↓; IL-6↓; IL-8↓; MCP-1↓); tyrosine phosphorylated PIRS-1/IRS-1↑; GLUT4↑; 2DG uptake↑	Tran et al. (2017)
in vitro human placental, amnion, and choriodecidua model of GDM	incubated in 50, 100, and 200 uM resveratrol	placenta(SIRT1↑; TNF↓; IL6↓; IL8↓; PTGS2↓; RELA↑; PGE_2↓; $PGF_{2\alpha}$↓); amnion(SIRT1↑); choriodecidua(SIRT1↑)	Lappas et al. (2011)

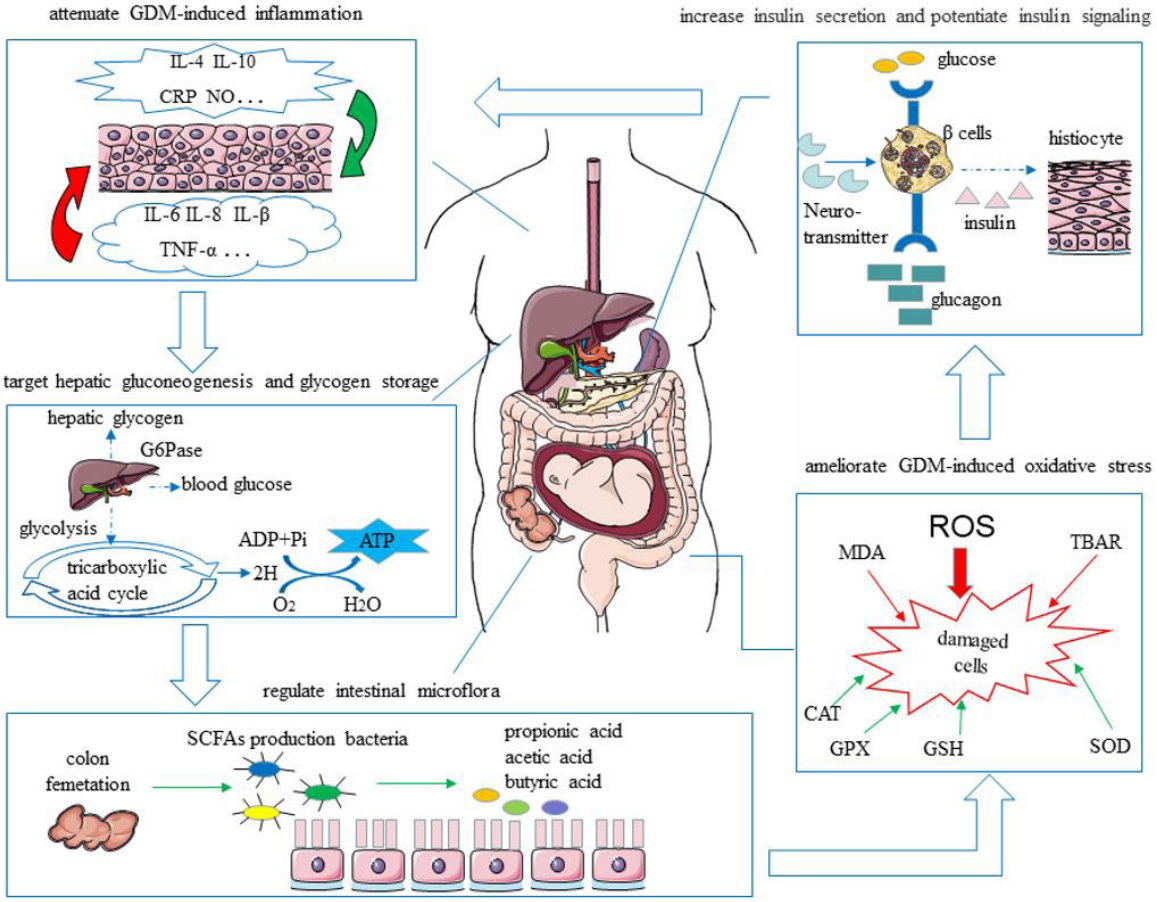

Figure 1. A schematic representation of molecular metabolism with FFIs supplementation. The metabolic pathway of insulin secretion and potentiate insulin signaling, hepatic gluconeogenesis and glycogen storage, oxidative stress, inflammation and intestinal microflora cycle overthrough the body was revealed. The red arrows indicated the negative effects, the green arrows indicated the positive effects, and the blue arrows indicated the neutral effects.

reported that a maternal diet supplemented with nobiletin inhibited mRNA expression and secretion of proinflammatory cytokines and chemokines while activating the NF-κB/Akt/MAPK signaling pathway in the placenta. Therefore, the anti-GDM effects of FFIs appear to be also mediated through inhibition of inflammatory signaling pathways.

3.5 Correlation between the intestinal microflora and GDM

The interplay between the intestinal microflora and energy metabolism has been studied extensively in recent years. Evidence from studies investigating changes in the intestinal microflora before and after labour revealed that women with GDM may possess unique intestinal microflora patterns significantly different to that of normal pregnancies. For instance, 1) Whole-metagenome shotgun sequencing of fecal samples revealed *Parabacteroides distasonis*, *Klebsiella variicola*, etc., were enriched in women with GDM, whereas *Methanobrevibacter smithii*, *Alistipes spp.*, *Bifidobacterium spp.*, and *Eubacterium spp.* were enriched in healthy controls (Kuang et al., 2017); 2) OTUs assigned to *Akkermansia* were associated with lower insulin sensitivity, while *Christensenella* OTUs were associated with higher fasting plasma glucose concentrations in women with GDM (Crusell et al., 2018); 3) Ccorrelations between gut microbiome composition and circulating metabolic hormones have also been reported. For example, Gomez-Arango et al. (2016) determined that adipokine levels were strongly correlated with *Ruminococcaceae* and *Lachnospiraceae*, while insulin was positively correlated with the genus *Collinsella*; 4) Moreover, evidence from both rodent models and human trials support the notion that prebiotics exert significant therapeutic effects in GDM by upregulating *Bifidobacterium* and *Bacteroides* (Dolatkhah et al., 2015; Paul et al., 2019). Therefore, a range of FFIs may exert anti-GDM effects by acting similarly to prebiotics. For example, a maternal diet supplemented with lactulose increased the abundance of *Bifidobacterium* and *Bacteroides*, with significant increases in the levels of 15 metabolites (including 1-monoolein, glucose-6-phosphate, and short-chain fatty acids) and decreases in serum glucose and total cholesterol concentrations in pregnant mice (Zhang et al., 2019). Wang et al. (2019) reported that oligosaccharide-sialic acid relieved GDM by regulating the intestinal microflora, resulting in the generation of short-chain fatty acids (SCFAs). In summary, prebiotics as well as certain FFIs can exert potential therapeutic benefits for women with GDM by providing nutrient resources to specific beneficial bacteria and thus promoting a diverse and healthy intestinal microflora. In addition, prebiotics such as oligosaccharides can also be utilized as carbon sources to stimulate the production of SCFAs by gut microflora, which are

key factors in optimising glucose homeostasis (Müller et al., 2020) and suppressing low-grade inflammation in women with GDM (Hideo et al., 2013).

4 Conclusions

Multiple studies support the notion that FFIs can help regulate a variety of mechanisms to ameliorate the negative outcomes associated with GDM (Figure 1 and Table 1). However, the pathogenesis of GDM remains complex, and there can be further mechanisms that are involved in the pathophysiology of GDM. Future studies are needed to further elucidate the beneficial effects and the underlying mechanisms of FFIs in the context of GDM. This may provide the basis to design the personalized dietary recommendations for women with GDM. Meanwhile, innovation in functional foods presents great opportunities to provide high-quality and affordable dietary supplements to GDM pregnancies to improve their health outcomes. For example, microencapsulation of phytochemicals can be used to protect FFIs against degradation and enhance their solubility, bioavailability (Costa et al., 2020); while development of high-fiber cookies with low glycemic index using pomace is considered as a an environment-friendly way to revalorize by-product of the juice industry (Tagliani et al., 2019; Lin et al., 2017). Notably, regarding to the GDM management with functional foods, there are many questions still to be answered. For instance, whether combining multiple FFIs can potentiate the beneficial effects of FFIs remains unknown. Relevant trials are urgently needed and should be carefully designed to account for individual differences.

In summary, considering the potential negative side effects of antidiabetic drugs (e.g., glyburide, metformin, baitangping) in women with GDM and their offspring, food supplements, in particular, FFIs could have beneficial benefits of FFIs on maternal and fetal health, without the associated side effects of drugs. We believe that in the near future, food supplements in pregnancy to combat metabolic disorders of pregnancy as GDM could become a reality.

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