Placental hormones like progesterone, growth hormone, corticotropin-releasing hormone and placental lactogen lower insulin sensitivity of target tissues, increase insulin resistance hence the induction of diabetes during pregnancy [15]. Hence, a sound and healthy pregnancy requires a normal interplay between the pituitary, thyroid, adrenal and parathyroid glands to meet the metabolic activities during pregnancy [16]. Although GDM often resolves after child delivery, there is an over sevenfold risk of developing type 2 diabetes mellitus later in life compared with those with normal glycemic levels [17]. Hypoglycemic agents (metformin, sulfonylureas, glyburide) and insulin are used to improve the conditions of GDM mothers when exercise and diet fail to reduce blood glucose [18]. There have been concerns about the safety and efficiency of hypoglycemic drugs in pregnant women. The oral hypoglycemic agents have been reported to have gastrointestinal (nausea, flatulence, diarrhea, vomiting) side effects. Medicinal plants are safe therapeutic agents that have been successfully utilized in managing and treating different diseases. This review elucidates some of the alternative ways of managing gestational diabetes mellitus.

METHODOLOGY

Different databases such as PubMed, Scopus, Web of Science, ScienceDirect, ResearchGate, Google Scholar were used in this review article with the following keywords: “alternative treatment”, “gestational diabetes”, “bioactive compounds”, “medicinal plants”, “herbal treatment” and “functional foods”. The references for this review were selected based on these criteria: articles published between 2010-2023, full-text original articles, animal and human studies and relevance to the review topic.

Table 1: Summary of studies on the various alternative treatments of gestational diabetes mellitus

S/N	Medicinal Plant/Bioactive compounds	Research Sample	Description	Outcome	References
1.	*Abelmoschus esculentus (L.) Moench.*	Pregnant rats	27 pregnant female rats were induced with GDM using streptozotocin (STZ). 200 mg/kg okra extract was administered orally for 19 days	Okra extract significantly reduced triglycerides, fasting blood glucose and insulin, total cholesterol, low-density lipoprotein; increased high-density lipoproteins; pancreatic and hepatic glutathione peroxidase, superoxide dismutase and catalase	[12]
2.	*Lotus leaf selenium (Se)-polysaccharide (LLP)*	Pregnant wistar rats	Pregnant wistar rats were induced with GDM using 2% streptozotocin at 40 mg/kg. The GDM groups were treated with 50 mg/kg and 100 g/kg of LLP for 14 days	Hepatic SOD, CAT, glutathione, glutathione peroxidase, HDL and glycogen were significantly increased. FBG, FINS, total cholesterol, LDL and triglycerides were reduced	[76]
3	Soybean oligosaccharides (SBOS)	Pregnant women	46 pregnant women with GDM were treated with 10 g SBOS orally	SBOS significantly increased SOD, GPx, CAT and adiponectin while TBARS, insulin, HOMA-IR and fasting insulin were decreased	[79]

after 4 weeks of intervention [28]. Nine weeks of administration with garlic reduced serum C-reactive protein high-sensitivity (hs-CRP) and increased plasma GSH with no significant difference in plasma total antioxidant capacity (TAC), serum lipid profiles, HOMA-IR levels and homeostatic model assessment of β-cell function (HOMA-β) index in the pregnant women. Insulin and FBG levels were significantly decreased (P>0.05) [26].

***Hibiscus rosa sinensis* L.**: *H.rosa sinesis* is an ornamental plant and the flower has been discovered to have wound healing, antidepressant [29], antioxidant and antibacterial [30] effects. Afiune *et al.* [31] administered aqueous extract of *H.rosa sinesis* at doses of 100, 200 and 400 mg/kg to diabetic pregnant rats, a significant increase in body weight was observed but with no change in the blood glucose level compared to the untreated group (P<0.05). A significant reduction in very low-density lipoproteins (VLDL-c) and triglycerides levels and a significant increase in HDL-c level were reported. The SOD activity was significantly increased with no change in MDA, CAT and GSH levels after treatment with the extract (P<0.05). Administration with the extract however increased embryo loss and maternal diabetes-induced fetal abnormalities. Doses of *H.rosa sinesis* up to 2000 mg/kg have no toxic effects [32].

Ginger (*Zingiber officinale Roscoe*): Ginger, a plant used as spice or seasoning while cooking has been discovered to have antioxidant, anti-inflammatory, hypolipidemic, insulinotropic and hypoglycemic effects [33]. Animals administered up to the dose of 3000 mg/kg showed no sign of toxicity [34]. Raouia *et al.* [35] conducted a study whereby pregnant diabetic rats were orally treated with ginger extract (80 mg/kg) for 6 days. Ginger was discovered to significantly reduce maternal elevated blood glucose, increase body weight (P<0.001), recognition and memory in offspring.

Olive leaf extract: Olive leaves (*olea europaea L. folium*) are considered to possess antioxidant, anti-hypertensive, hypoglycemic, antimicrobial, and anti-atherosclerotic properties [36]. The role of olive extract in the renal tissues of diabetes-induced pregnant mice and their offspring was investigated by Mohammed *et al.* [37]. It was discovered that 100 mg/kg olive leaf extract (OLE) inhibited maternal body weight loss, increased placental weight leading to an elevated placenta/fetal ratio, reduced serum creatinine and urea levels (P< 0.05), ameliorated histopathological changes in the renal tissues of both mother and fetus and reduced Angiotensin II content in the renal tissue. Doses around 100, 200, 400 and 1000 mg/kg are considered safe [38].

BIOACTIVE COMPOUNDS

Cinnamaldehyde: Cinnamaldehyde is derived from cinnamon bark that possesses antihyperglycemic, anti-inflammatory and antioxidant potentials [39]. According to Hosni *et al.* [8], treatment of GDM rats with cinnamaldehyde (20mg/kg) for a duration of 4 weeks resulted in a significant increase in the weight of the pregnant diabetic rats after the reduced body weight observed due to feeding with fatty-sucrose diet. Cinnamaldehyde lowered the FINS and FBG levels compared with the untreated group. In the gestational diabetic rats administered cinnamaldehyde, liver glycogen and HDL-cholesterol significantly increased while fructosamine, triglycerides and total cholesterol levels were significantly lowered compared to the untreated gestational diabetic rats (P<0.05). Adiponectin levels significantly increased while leptin and TNF-α significantly reduced post-cinnamaldehyde administration (P<0.05). Furthermore, MDA and nitrite levels were significantly decreased while GSH and CAT levels were significantly elevated after cinnamaldehyde treatment. Expression of peroxisome proliferator-activated receptor gamma (PPARγ) mRNA was significantly increased in the treated group. Finally, the number of live fetuses significantly increased in the treated group with a significant decrease in implantation loss, fetal insulin, and fetal glucose (P<0.05) [8]. The lethal dose of cinnamaldehyde is 0.6-3.4 g/kg.bw [40].

Naringenin: Naringenin, a polyphenol abundant in grapes and citrus fruits, was discovered to possess antidiabetic [41-42], anti-inflammatory [43] and antioxidant activities [44]. Administration of naringenin up to 1250 mg/kg for 6 months had no observed adverse effects [45]. In in vitro human model, Nguyen-Ngo *et al.* [46] investigated the effect of naringenin (400 µm) on insulin resistance, antioxidant and inflammation expression in placenta, skeletal muscle and adipose tissue obtained from normal glucose-tolerant women at elective caesarean section. These tissues were stimulated with tumor necrosis factor to simulate a GDM-like environment. Pregnant heterozygous leptin receptor-deficient *db/+* mice were used for the in vivo GDM model. The mice were administered 50 mg/kg naringenin from gestation day 10-18. The administration of naringenin significantly enhanced insulin-stimulated glucose uptake in the skeletal muscle, decreased TNF-α expression and increased antioxidant mRNA expression with no effect on the chemokines and pro-inflammatory cytokines but reduced interleukin-1A mRNA expression. Treatment with naringenin enhanced glucose tolerance and fasting glucose level in the GDM mice. Activation of NF-κB was inhibited while catalase and SOD mRNA expressions were upregulated ($P<0.05$).

Resveratrol: Resveratrol (RESV), a natural polyphenol present in vegetables and fruits like berries, grapes [47] has been discovered to possess anti-hyperglycemic, anti-inflammatory and antioxidant potentials in diabetes-induced rats [48-50]. Resveratrol supplements when consumed throughout the gestation period decreased obesity, liver triglycerides and enhanced insulin sensitivity in the mature offspring [51]. Brawerman *et al.* [52] discovered that RESV supplementation in the mother reduced blood glucose, improved glucose tolerance, insulin sensitivity and inhibited glucose-stimulated insulin production during gestation with no effect on body weight. RESV can cross the placenta, therefore this same study investigated the effect on fetal development and normal litter sizes and sex distributions were reported. In newborn males treated with RESV, macrosomia and obesity were prevented but not in female newborns compared with the untreated group. Although a study by Ros *et al.* [53] reported otherwise whereby RESV prevented obesity in the female newborns but not the males of mothers fed high-fat diet. During GDM, prenatal administration of RESV inhibited the development of liver steatosis in the dams by improving PPAR-α expression in the hepatic tissues. GDM has adverse effects on the pancreatic islet thereby impairing insulin and glucagon production. However, RESV supplementation in pregnant diabetic mice resulted in offspring with similar islet size and structure as the lean offspring [52]. Pregnant diabetic mice administered with 10 mg/kg/day resveratrol had improved glycemic index and were responsive to insulin. Increased survival rates and reduced body weight were observed in their offspring. There was also reduced hepatic glucose production as a result of an upregulation in hepatic AMPK which led to reduced expression of glucose-6-phosphatase [54]. In pregnant mice that consumed 0.2% RESV supplement mixed with high-fat diet (HFD), their male offspring exhibited enhanced insulin sensitivity and decreased body weight compared with those who consumed HFD without RESV supplementation [55].

Berberine: Berberine, an isoquinoline protoalkaloid derived from rhizome coptidis, turmeric, Oregon grape, barberry is discovered to have antidiabetic and anticancer potentials [56]. According to Li *et al.* [57], berberine (100 mg/kg/day) administered to GDM rats from 7^{th} to 20^{th} gestation day reduced insulin resistance, fetal loss, maternal body weight, placental and fetal weight in comparison to the untreated group. It also reduced CRP and TNF-α levels, expression of IKKβ, nuclear translocation of NF-κB /P65 and modified the phosphorylation of AKT, JNK and IRS-1 in the hepatic tissues of the pregnant diabetic rats.

Curcumin: Curcumin, a polyphenol derived from the rhizomes of *curcuma longa L*. has been reported to possess anti-diabetic, antioxidant, neuroprotective, antimicrobial, antidepressant, and anti-inflammatory properties [58-61]. In human clinical trials, up to 2 g/day curcumin was considered safe with no toxicity [62]. Low dose (50 mg/kg) and high dose (100 mg/kg) of curcumin were orally administered to gestational diabetic mice. The high dose significantly reduced fasting blood glucose and insulin levels (P< 0.05). The levels of hepatic TBARS were reduced while GSH, SOD and CAT and glycogen were significantly increased following curcumin (100 mg/kg) administration (P< 0.05). The same study also reported that a high dose of curcumin could improve litter size and offspring body weight. Curcumin also enhanced the activation of AMPK-related proteins and reduced G6Pase activity in the offspring [63].

Specnuezhenide (SPZ): Specnuezhenide (SPZ), a bioactive compound isolated from the *Ligustrum lucidum* fruit has been reported to have anti-inflammatory, antioxidant, neuroprotective and immune-regulatory properties [64-65]. SPZ significantly reduced blood glucose, insulin, and resistin in GDM rats. Also, treatment with STZ significantly reduced the expression of NF-κB mRNA and increased IκB expression in pancreatic β-cells. Expression of Caspase-3 and Bax were significantly reduced while Bcl-2 expression was significantly elevated in the β-cells of the pancreas [66].

Ganoderma lucidum Karst: *Ganoderma lucidum* (GL) which is comprised of different bioactive compounds (polysaccharides, polyphenols, sterols and terpenoids) is a medicinal mushroom and has been discovered to be effective in regulating blood glucose [67-69]. Viroel *et al.* [70], reported that GL (100 mg/kg) administered for 19 days had no effect on insulin and total cholesterol levels in streptozotocin-induced diabetic pregnant rats but significantly reduced ALT, AST and triglycerides levels (P< 0.05). The levels of CAT was significantly increased while TBARS level was significantly reduced following GL administration (P< 0.05). GL shows no signs of toxicity at doses up to 5000mg/kg [71].

Puerarin: Puerarin, an isoflavonoid isolated from the root of *Puerarin lobata* has been discovered to possess hypoglycemic and anti-inflammatory potentials. It is also suggested to be effective in treating myocardial infarction, arteriosclerosis, and diabetes mellitus [72-73]. Puerarin (0.25 g/kg) was administered to high-fat diet fed rats with STZ-induced GDM for 2 weeks, it was discovered that insulin receptor substrate 1 (IRS-1) expression was significantly upregulated (P< 0.01) while the expression levels of TLR4 and MyD88 were downregulated. The levels of TNF-α and phosphorylated NF-κB were also reduced (P < 0.05) [74].

FUNCTIONAL FOODS

Lotus leaf selenium (Se)-polysaccharide: Lotus leaf selenium (Se)-polysaccharide (LLP) has been discovered to have hypolipidemic, antidiabetic, ant obesity and anti-inflammatory potentials [75]. Pregnant diabetic rats administered 50 and 100 mg/kg of LLP for 14 days had higher levels of HDL (P< 0.05) and liver glycogen and lower FBG and FINS, total cholesterol (TC), LDL and triglycerides levels (P<0.05). This suggested that LLP improves insulin sensitivity [76].

The administration of LLP significantly increased SOD, catalase, GSH and GPx (P< 0.05) in the hepatic tissues. The result was almost the same as those of the normal-pregnancy control [76]. No toxic effects or death were observed during this study.

Soybean oligosaccharides: Soybean oligosaccharides (SBOS) are potential prebiotics isolated in soybean seeds composed of sucrose, raffinose and stachyose [77]. The SBOS reduced oxidative stress and aberrant lipid profile stimulated by high-fat diet [78]. Fei *et al.* [79], investigated the effects of 10 g SBOS in 200-300 mL of warm water on insulin resistance and antioxidant

enzymes in pregnant women with GDM and it was reported that SBOS significantly (P<0.01) increased SOD, CAT, GPx levels while the thiobarbituric acid reactive substances (TBARS) level was significantly (P<0.01) reduced. There was a significant reduction in the insulin levels of SBOS-treated group in comparison with the GDM group. Homeostatic model assessment for insulin resistance (HOMA-IR) and FINS were significantly lower, adiponectin level was significantly higher (P<0.01) while fasting plasma glucose (FPG) and islet β-cells function index (HBCI) were reduced although with no significant difference [79].

Soy protein: Consumption of soy diet containing 0.8-g/kg protein (35% animal protein, 35% soy protein, 30% other plant proteins) in pregnant diabetic women for 6 weeks resulted in a significantly reduced level of serum insulin, HOMA-IR, fasting plasma glucose, VLDL-C and triglycerides (P<0.001) with a significant increase in plasma GSH and total antioxidant capacity (P>0.05) with no significant difference in hs-CRP, LDL-C, HDL-C, nitric oxide (NO) and MDA levels compared with the pregnant diabetic group that did not consume soy protein [80].

Vitamin D and Evening primrose oil (EPO): Vitamin D is vital in the regulation of calcium, and it plays a significant role in GDM because calcium signaling is essential in insulin production from the β-cell. It improves immune functions and possesses anti-inflammatory activity [81]. Omega-6 essential fatty acids like linoleic acid and gamma-linolenic acid are abundant in EPO which has been reported to reduce labor, increase HDL, total cholesterol levels. Individually, vitamin D supplements reduced insulin resistance while EPO improved lipid profile, hence Jamilian *et al.* [82] co-administered EPO (1000 mg) and vitamin D3 (1000 IU) in gestational diabetic women for 6 weeks. This resulted in HOMA-IR, serum insulin levels, HOMA and fasting plasma glucose being significantly reduced in comparison to the placebo (P<0.05). Serum triacylglycerol (TAG), VLDL, total cholesterol, LDL levels were significantly reduced (P<0.001) with no significant difference in HDL were observed after joint administration with EPO and vitamin D.

N-3 fatty acids from flaxseed oil: α-linolenic acid (ALA), the precursor of polyunsaturated fatty acids (PUFAs), eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) is abundant in flaxseed oil. Flaxseed oil has been suggested to improve immunity, reduce lipogenesis, and possess antioxidant potential [83]. Jamilian *et al.* [84] investigated the effect of n-3 fatty acids from flaxseed oil in gestational diabetic women. The gestational diabetic women received 2 capsules with 1000 mg/d n-3 fatty acid from flaxseed oil containing 400 mg α-linolenic acid in each capsule and it was discovered to significantly reduce fasting plasma glucose, HOMA-IR, TAG, VLDL-C, total cholesterol levels, hs-CRP, malondialdehyde (MDA) and increase GSH and total NO levels (P< 0.001). Expression of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) were down-regulated after administration with flaxseed oil. It had no effect on TAC and gene expression of transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF).

CONCLUSION

Gestational diabetes mellitus is a common metabolic disease that can affect the mother and child. This review, therefore, highlights some alternative treatments reported to be effective in the management of gestational diabetes mellitus. Some of the modes of action include the reduction of fasting blood glucose and insulin, improving lipid and pro-inflammatory cytokine profiles, increasing placenta/fetal ratio. However, more basic, and clinical studies should be done to further validate the safety, efficacy and discover more mechanisms of action of these medicinal plants and compounds.

Abbreviations: GDM: Gestational Diabetes Mellitus, TNF-α: Tumor necrosis factor-α, IL-6: Interleukin-6, LDL: Low-

density lipoprotein, FINS: Fasting insulin, FBG: Fasting blood glucose, HDL: High-density lipoprotein, GPx: Glutathione peroxidase, SOD: Superoxide dismutase, CAT: Catalase, TC- Total cholesterol, TBARS: thiobarbituric acid reactive substances, FPG:Fasting plasma glucose, TAC: total antioxidant capacity, MDA: malondialdehyde, NO: Nitric oxide, TAG:triacylglycerol.

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