



(REVIEW ARTICLE)



Gestational Diabetes Mellitus: An overview and its potential treatment with herbs

Devi Maya Arista ¹, Rizki Amelia ^{1,2,*}, Desiy Fitriani ¹, Husnul Khotimah ³, Safrina Dewi Ratnaningrum ⁴, Yahya Irwanto ⁵ and Tatit Nurseta ⁵

¹ Master Program of Midwifery, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

² State Health Polytechnic, Ministry of Health, Kalimantan Timur, Indonesia.

³ Department of Pharmacology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

⁴ Department of Anatomy Histology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

⁵ Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

GSC Biological and Pharmaceutical Sciences, 2023, 23(03), 261–273

Publication history: Received on 15 May 2023; revised on 24 June 2023; accepted on 27 June 2023

Article DOI: <https://doi.org/10.30574/gscbps.2023.23.3.0250>

Abstract

Gestational Diabetes Mellitus (GDM) is a hyperglycemia condition with onset in the second or third trimester of pregnancy. Currently, the first-line prevention and management of GDM are lifestyle modifications that must be implemented throughout pregnancy, even before pregnancy. When lifestyle management is unable to maintain normoglycemia in pregnancy, treatment therapy such as insulin and/or oral antidiabetic drugs is needed. Insulin as a first-choice therapy still has drawbacks, including its high price, potential weight gain, hypoglycemia, and uncomfortable route of administration. Herbal therapy using plant extracts and bioactive compounds with antidiabetic effects has become a concern as preventive, alternative, and complementary therapy. This article will provide information about GDM and the potential of herbal plants that can be used in the treatment of GDM.

This review will focus on recent herbal remedies derived from various types of medicinal plants that have been validated through scientific evaluation as promising treatments for GDM. Data was collected through Google Scholar using the keywords "herbs and gestational diabetes mellitus". The references were articles with publication years from 2019 to 2023, written in English, original research, and free full-text articles that were relevant. 6,970 works of literature met the keywords "herbs and gestational diabetes mellitus". Then we selected 15 articles that were most relevant.

The bioactive compounds found in plants may be used in the future to complement current treatment strategies for GDM. This review has demonstrated that herbal plants can reduce blood glucose levels in GDM. Additionally, unsaturated fatty acids have also shown the potential for lowering blood glucose levels in GDM. These findings have beneficial effects in regulating glucose metabolism, reducing inflammation, and protecting against oxidative damage associated with GDM.

Keywords: Herbs; Gestational Diabetes Mellitus; GDM; Treatment; Hyperglycemia

1. Introduction

In pregnancy, there are a series of physiological changes to support the growth of the fetus in the womb. One of the physiologically metabolic adaptations in pregnancy is a change in insulin sensitivity. In early pregnancy, insulin sensitivity increases with respect to increased glucose uptake into adipose stores in preparation for energy for later pregnancy (1). However, as pregnancy progresses, surges in estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone physiologically result in a decrease in insulin sensitivity of approximately 50-60% by

* Corresponding author: Rizki Amelia

the end of pregnancy (1,2). Individuals who fail to adapt to this decrease in insulin sensitivity will increase the risk of damage or dysfunction of pancreatic β cells and insulin resistance that will result in hyperglycemia in pregnancy, called Gestational Diabetes Mellitus (3–5). Gestational Diabetes Mellitus (GDM) is a hyperglycemia condition with onset in the second or third trimester of pregnancy and can become normal after delivery or develop into Type 2 Diabetes Mellitus (T2DM) (2,3,6). The prevalence of GDM worldwide ranges from 5% to 25.5%, depending on race, ethnicity, age, and screening criteria (7). According to the International Diabetes Federation (IDF) Diabetes Atlas for 2021, hyperglycemia in pregnancy affected 16.7% of all pregnancies worldwide, with 80.3% attributable to GDM (8).

Gestational Diabetes Mellitus (GDM) can lead to adverse complications, both maternal and neonatal. Currently, the first-line prevention and management of GDM are lifestyle modifications that include regulation of nutrition and physical activity that must be implemented throughout pregnancy, even before pregnancy. When lifestyle management is unable to maintain normoglycemia in pregnancy, treatment therapy such as insulin and/or oral antidiabetic drugs is needed (9). Insulin as a first-choice therapy still has drawbacks, including its high price, potential weight gain, hypoglycemia, and uncomfortable route of administration (10,11). According to the FDA, Metformin is included in category B drugs and Glibenclamide category C. Although metformin tends to be safe, it has been proven to cross the placental barrier, so exposure to high doses can affect the intrauterine fetus (12). On the other hand, as pregnancy progresses, the placenta becomes thinner and more permeable to certain drugs, while the fetal liver still has a limited capacity to metabolize drugs (13). This results in the fact that the safety of oral antidiabetic drugs in the long term is still questionable, so safer treatment and prevention of GDM with minimal, effective, and affordable side effects are still expected (14).

Herbal therapy using plant extracts and bioactive compounds that have antidiabetic effects has become a concern as preventive, alternative, and complementary therapies (14,15). Several scientific studies prove that phytochemicals have antidiabetic potential based on research results (16,17). This article will provide information about GDM and the potential of herbal plants that can be used in the treatment of GDM.

2. Methods

In this review, data were collected through Google Scholar regarding the use of herbs in GDM. We use the keywords "herbs and gestational diabetes mellitus". The references we use are articles that meet the inclusion criteria, namely articles with publication years from 2019 to 2023 written in English, original research or research articles, open access or free full-text articles, and are relevant to the purpose of the review.

3. Results

The results obtained were 6,970 works of literature that examined the keywords "herbs and gestational diabetes mellitus". Then we selected some of the literature that was most relevant to the purpose of the topic of discussion and obtained 15 research articles. Based on these research articles, it is known that some herbs have positive results as an alternative to GDM therapy. The research article characteristics obtained are shown in Table 1.

Table 1 Characteristics of a research article on herbs for the treatment of gestational diabetes mellitus studies

No	Herbs	Bioactive Compounds	Research Sample	Induction of Hyperglycemia (GDM Model)	Treatment	Outcome	References
1.	Jackfruit Seeds (<i>Artocarpus heterophyllus</i> Lam.)	Alkaloid, flavonoid, tannin, steroid, saponin, and terpenoid	Sprague Dawley strain pregnant female rats	Streptozotocin (STZ)	The samples were divided into 6 groups: The normal control group The negative control group induced STZ The positive control group was given Glibenclamide The group was given ethanol jackfruit seeds 100 mg/kg BW The group was given ethanol jackfruit seeds 200 mg/kg BW The group was given ethanol jackfruit seeds 400 mg/kg BW	The ethanol extract of 70% jackfruit seeds at a dose of 3 (400 mg/kg BW) for 14 days was able to reduce blood glucose levels in gestational diabetic rats, comparable to positive control glibenclamide.	(18)
2.	Basil Extract (<i>Ocimum basilicum</i>)	Flavonoids, phenolics (tannins), saponins, terpenoids, and steroids.	Pregnant white rats (<i>Rattus norvegicus</i> L)	Streptozotocin 40 mg/kg BW	The samples were divided into 4 groups: The negative control group The positive control group The other 2 groups were gestational diabetes mellitus treated with basil extract 100 mg/kg and 200 mg/kg BW for 14 days.	The average blood glucose level decreased in the basil extract group by 100 mg/kg and 200 mg/kg body weight compared with the positive control group.	(19)

3.	<i>Paeonia lactiflora</i> Pall	Paeoniflorin (phenolics)	Pregnant female albino rats (<i>Rattus norvegicus</i>)	Streptozotocin (STZ) 25 mg/kg and fatty-sucrosed diet	The samples were divided into five groups (seven rats in each group) as indicated: The control group: normal diet The GDM group: fatty-sucrose diet was given to rats for the entire study until five weeks The other 3 groups were GDM+paeoniflorin 3 different doses (5 mg/kg, 15 mg/kg, and 30 mg/kg) daily.	Administration of paeoniflorin reduces dysregulation of blood glucose levels, leptin, insulin, and suppresses the overactivation of Akt / mTOR signals in placental tissue. Paeoniflorin normalized fetal size and body weight in GDM rats.	(20)
4.	<i>Salvia miltiorrhiza bunge</i>	Cryptotanshinone (CTS) (diterpenoid)	Pregnant female mice	GDM C57BL/KsJdb+	The samples were divided into three groups (18 rats in each group): wild-type (normal pregnancy, C57BL/KsJ+/+) GDM (C57BL/KsJdb+, db/ + mice treated with vehicle) GDM + CTS group (C57BL/KsJ db+, db/ + mice treated with different doses of CTS (5,15 and 45 mg/kg BW) daily for 18 days since pregnancy. Metformin (10 mg/kg) daily for 18 days and collect blood from the heart on GD 18 to compare with CTS-treated mice.	CTS could reduce oxidative stress, inflammation, and NF-κB signaling pathway in the placenta and blood of GDM mice.	(21)
5.	<i>Puerarin lobata</i>	Puerarin (isoflavonoid)	Pregnant Wistar rats	Streptozotocin (25 mg/kg) combined with high-fat feeding	The samples were divided into three groups (6 rats in each group): Control group: healthy pregnant rats GDM group GDM group and treated with puerarin (resuspended in 0.9% saline, 0.25 g (kg/day).	Puerarin effectively ameliorated disorders of glucose and lipid metabolism and IR in GDM rats and has a potentially anti-inflammatory effect related to the downregulation of TLR4/MyD88/NF-κB.	(22)

6.	<i>Dendrobium nobile</i> Lindl	Dendrobine (alkaloid, sesquiterpenoid)	Pregnant C57BL/KsJ db/+ mice	C57BL/KsJdb/+ (db/+) mice were utilized as genetic GDM mouse model	The samples were divided into 2 groups: The control group was orally administered phosphate-buffered saline (PBS) The treatment group was orally given dendrobine (20 mg/kg) daily for 20 days.	Dendrobine reduced maternal BW, blood glucose levels, decreased birth weight and birth size, and increased insulin levels in GDM mice. Dendrobine reduced Th17 cells and reduced the secretion of IL-1 β , IL-6, TNF- α , and IL-17.	(23)
7.	<i>Aloe vera</i> L	Barbaloin (phenolics)	C57BL/KsJ-Lepdb/+ (db/+) and pregnant wild-type (+/+) mice	C57BL/KsJ-Lepdb/+ (db/+) as GDM mice model	The samples were divided into 5 groups (8 rats in each group): normal control group GDM group GDM + barbaloin (20 mg/kg) group GDM + barbaloin (50 mg/kg) group GDM + metformin (10 mg/kg) group	Barbaloin reduced blood glucose levels, increased insulin levels, and reduced inflammatory response and ROS levels in the liver of GDM mice.	(24)
8.	<i>Juglans regia</i> L.	Polyunsaturated fatty acids (PUFA), phenolic acids, and flavonoids	Pregnant Wistar rats	Streptozotocin (40 mg/kg)	The samples were divided into 5 groups (8 rats in each group): Pregnant control group (PC): rats that received the 1% carboxy methyl cellulose sodium (CMC) solution by oral gavage. GDM group: GDM rats that received the 1% CMC solution by oral gavage. LPUFA group: GDM rats that received a low PUFA dose (225 mg/kg BW, LPUFA). MPUFA group: GDM rats that received a middle dose of PUFA (450 mg/kg BW, MPUFA). HPUFA group: GDM rats that received a high dose of PUFA (900 mg/kg BW, HPUFA). PUFA was dissolved in 1% CMC solution and administered by oral per day from GD 0 to GD 17.	Walnut oil-derived PUFA can lower fasting blood glucose, increase insulin, and liver glycogen levels. PUFA suppresses oxidative stress and reduces abnormal changes in lipid profiles in plasma and liver tissue.	(25)

9.	<i>Oldenlandia diffusa</i> (OD)	Flavonoid	Pregnant Wistar rats	Streptozotocin (25 mg/kg)	The pregnant rats were divided into five groups: sham, GDM, GDM + 75-mg/kg OD, GDM + 150-mg/kg OD, and GDM + 300-mg/kg OD twice a day for a week.	OD decreased blood glucose level, insulin secretion OD, reduced TNF- α , IL-6, and IL-1 β , inhibited NF- κ B pathway, and activated AMPK pathway in the pancreatic tissue of GDM rats.	(26)
10.	<i>Virgin Coconut Oil</i> (VCO)	Medium chain fatty acids (MCFA)	Pregnant mother with GDM	Pregnant mother with GDM	The sample used 46 respondents. The treatment given was VCO at a dose of 5 ml, six times a day, and a low-carb diet. The instrument used to measure the fasting blood glucose was a glucose stick before and after treatment on day 21st.	Giving VCO with a low-carb diet can reduce blood glucose in GDM.	(27)
11.	Moringa leaf powder (<i>Moringa oleifera</i>)	Flavonoids	Pregnant white rats	Alloxan (150 mg/day/kg BW)	The samples were divided into six groups: Negative control Positive control Positive control + Moringa leaf powder at a dose of 100, 200, 400, 800 mg/day/kg BB	Moringa leaf powder reduces the average number of liver cells undergoing apoptosis and blood glucose levels.	(28)
12.	<i>Lentinus edodes</i>	Tocopherols and phenolic compounds (p-hydroxybenzoic, p-coumaric, and vanillic acid)	Pregnant female wistar rats (<i>Rattus norvegicus</i> var. <i>albinus</i>)	Streptozotocin (40 mg/kg)	The samples were divided into 4 groups (6 rats in each group): Negative control group Positive control group: GDM group GDM + Leb group: GDM rats which are given 100 mg/kg/day <i>Lentinus edodes</i> from gestation day 1 to 19 (before fetus implantation) GDM + Lea group: GDM rats which are given 100 mg/kg/day <i>Lentinus edodes</i> from gestation day 9 to 19 (after fetus implantation)	<i>Lentinus edodes</i> did not reduce the severe hyperglycemia of the mother, but increased maternal insulin levels, reduced the levels of alanine aminotransferase, aspartate aminotransferase, triglyceride, and total cholesterol, protected the animals from post-implantation losses.	(29)

13.	<i>Zingiber officinale</i>	Phenolic	Pregnant female Wistar rats	Streptozotocin (45 mg/kg)	The samples were divided into 4 groups (10 rats in each group): Group 1: pregnant rats Group 2: pregnant rats with diabetes Group 3: pregnant rats consuming ginger (100 mg/kg, by gavage) Group 4: pregnant rats with diabetes consuming ginger (100 mg/kg, by gavage).	<i>Zingiber officinale</i> modulated genes involved in glucose and lipid metabolism, inflammation, oxidative damage, and the WNT pathway in GDM.	(30)
14.	<i>Pimpinella anisum</i> (anis) and <i>Laurus nobilis</i> (laurel) essential oils (AEO and LEO)	Phenolic acids, flavonoids, monoterpenes, and sesquiterpenes, trans-anethole, and 1,8-cineole.	Endothelial cells isolated from the umbilical cord vein of females with gestational diabetes mellitus (GDM-HUVEC)	GDM-HUVEC	The samples were divided into 5 groups: Negative control (C-HUVEC): umbilical cords were collected at full-term delivery from healthy Caucasian mothers. GDM-HUVEC The C- and GDM-HUVEC groups were stimulated for 24 h and 48 h with different concentrations of oils (0.025%, 0.05%, and 0.1% v/v) dissolved in DMSO.	The treatment with both EOs significantly reduced: (i) the adhesion of the U937 monocyte to HUVEC; (ii) vascular adhesion molecule-1 (VCAM-1) protein and gene expression; (iii) Nuclear Factor-kappa B (NF-κB) p65 nuclear translocation.	(31)
15.	<i>Sesamum indicum</i> L. (sesame) and <i>Thymus vulgaris</i> (thymus) seeds	Thyme: alkaloid, indole alkaloid, flavonoids, tannins, terpenoids Sesame: sesamin, sesamol, and sesaminol glucosides	Pregnant women aged 20 to 45 years with GDM	Gestational diabetic women (GDM)	The control group (CG): non-diabetic group were 20 to 45-year-old pregnant women without GDM The GDM group: had GDM (fasting glucose of more than 126 mg/dL) This cross-sectional retrospective study used a semi-quantitative food frequency questionnaire (FFQ) to assess the consumption of thyme and sesame and portion sizes (5-10 and >10- 15 grams), and diets over the previous week or month.	Consuming thyme and sesame seeds can decrease blood glucose levels and weight gain in pregnant women with GDM.	(32)

4. Discussion

4.1. Gestational Diabetes Mellitus

Gestational diabetes mellitus is a type of diabetes whose manifestations first appear during the 2nd and 3rd trimesters of pregnancy (7). The pancreatic β cell dysfunction and insulin resistance that occur in GDM are influenced by increased secretion of placental hormones during pregnancy (33). On the other hand, GDM is a hyperglycemia condition that occurs in pregnancy due to a series of metabolic complications resulting from adaptive failure in the gestation period (5). Gestational diabetes mellitus occurs when the insulin which regulates blood glucose levels, is not produced adequately.

Pharmacological intervention is carried out if management through lifestyle adjustments for at least 1 to 2 weeks fails in achieving normal blood glucose levels (34). However, the high price of insulin and invasive procedures that require daily injections cause patient compliance to be less than optimal. Glyburide (Glibenclamide) should not be used to treat women with GDM if metformin or insulin are available (12). The main concern with using oral antihyperglycemics in pregnancy is the occurrence of congenital anomalies and fetal hypoglycemia (35). The Food and Drug Administration (FDA) categorizes metformin in Category B and glibenclamide in Category C (36). Although metformin tends to be safe and has not been proven to cause teratogenicity, it has been shown to be able to cross the placental barrier during pregnancy, so exposure to high doses can affect the intrauterine fetus with long-term implications for cardiometabolic health (12).

4.2. Risk Factors

GDM risk factors are categorized into modifiable and non-modifiable factors as well as socioeconomic and geographical factors (37). Modifiable GDM risk factors include overweight, obesity, and body mass index (BMI) before pregnancy, metabolic syndrome, and diet, PCOS, pre-eclampsia, and other factors such as prolonged psychological stress during pregnancy, use of antidepressants and psychotropic drugs, smoking, and poor sleep quality. Non-modifiable GDM risk factors include maternal age, parity, ethnicity, genetics, and family history of DM. In addition, there are socioeconomic and geographical risk factors, which include climate and geographic location as well as education and socioeconomic status.

4.3. Pathophysiology

Gestational diabetes mellitus is characterized by hyperglycemia, or increased blood glucose levels, that occur during pregnancy (1). During pregnancy, pancreatic β cells undergo hypertrophy or hyperplasia to compensate for the metabolic needs of the pregnancy. A decrease in insulin sensitivity leads to an increase in glucose concentration. After pregnancy, insulin sensitivity and blood glucose concentrations return to normal. In GDM, β cells do not adequately compensate for the metabolic needs of pregnancy. Decreased insulin sensitivity leads to hyperglycemia. This is exacerbated by decreases in insulin-receptor-substrate (IRS)-1, phosphoinositide 3-kinase (PI3K), and glucose transporter type 4 (GLUT4) expression. After pregnancy, β cells, blood glucose concentrations, and insulin sensitivity may return to normal or remain impaired, resulting in an increased risk of sustained insulin resistance (38).

The physiological change in insulin sensitivity is mediated by several factors, including increased levels of hPL, estrogen, progesterone, cortisol, and prolactin. In addition to altering the components of the insulin signaling cascade, it also activates various mechanisms that improve β cell function. Gestational diabetes mellitus develops when insulin secretion fails to overcome physiological insulin resistance during pregnancy (39). Changes in expression and/or phosphorylation of insulin signaling regulators, including insulin receptor substrate (IRS)-1, phosphatidylinositol 3-kinase (PI3K), glucose transporter (GLUT)-4, and decreased PPAR γ also occur during and after pregnancy.

Gestational diabetes mellitus is associated with increased oxidative stress due to the overproduction of free radicals, abnormal mitochondrial function, and impaired mechanisms of lowering free radicals. Reactive oxygen species inhibit the uptake of insulin-stimulated glucose by interfering with the actions of IRS-1 and GLUT4. Activation of NADPH oxidase by lipid accumulation in adipocytes is also a potential mechanism shown to increase TNF- α , IL-6, MCP-1, and decrease adiponectin production (39).

4.4. Screening and Diagnosis

GDM screening can be carried out using two approaches, namely universal screening or based on risk factors (40). In developed countries such as the United States with an increased percentage of GDM risk, the ADA and ACOG recommend

that routine GDM screening be carried out in all second-trimester pregnant women (24-28 weeks of gestation) and at the first antenatal visit in at-risk groups (41). In several other countries, screening is carried out only in groups that have gone through a risk assessment (4).

GDM screening generally uses the Oral Glucose Tolerance Test (OGTT) with two methods: the 1-step method and the 2-step screening test method. In the 1-step screening method, a single OGTT uses 75 grams of glucose, while in the 2-step method, it is preceded by a glucose challenge test using 50 grams of glucose and followed by an OGTT using 100 grams of glucose (4). The single-step GDM screening procedure is to use OGTT 75 grams in 250-300 ml of water, which is drunk in the morning (fasting condition overnight ≥ 8 hours). Blood glucose levels were measured three times, namely during fasting, 1 hour, and 2 hours after OGTT. The diagnosis of GDM is established if there is ≥ 1 value that meets the following criteria: fasting blood glucose level ≥ 92 mg/dl, 1-hour blood glucose level ≥ 180 mg/dl, and 2-hour blood glucose level ≥ 153 mg/dl. In the 2-step procedure, starting with a 50-gram glucose challenge test, if the blood glucose level 1 hour later is ≥ 140 mg/dl, then the 100-gram OGTT is continued a few days later in a fasting state. The threshold for fasting blood glucose is 95-105 mg/dl, 1-hour blood glucose level is 180-190 mg/dl, 2-hour blood glucose level is 155-165 mg/dl, and 3-hour blood glucose level after 140-145 mg/dl. The diagnosis of GDM is enforced if there are ≥ 2 values exceeding this threshold value (42,43).

4.5. Complications of Gestational Diabetes Mellitus

The complications of GDM include maternal and neonatal complications. GDM increases the risk of complications in pregnancy, such as recurrent urinary tract infections, pre-eclampsia, prolonged labor, perineal ruptures, sectio caesarean (SC) delivery, uterine atony, and uterine rupture (especially in mothers with a previous history of SC). About 60% of maternal conditions with a history of GDM will progress to T2DM afterward and are also at risk for cardiovascular disease, obesity, and other metabolic syndromes (1,5).

In infants, GDM conditions in the mother will increase the risk of premature birth (birth <37 weeks), macrosomia, shoulder dystocia, hypoglycemia, and hyperinsulinemia. Long-term risks in infants of mothers with GDM include obesity, T2DM, cardiovascular disease, and other metabolic diseases (1,5). Babies born to women with uncontrolled diabetes during pregnancy are at risk of congenital abnormalities due to hyperglycemia (44). GDM may increase the risk of congenital heart defects and other congenital malformations (45,46).

4.6. Mechanism of Action of The Bioactive Compounds of Medicinal Herbs as Anti-diabetic Agents

Based on the results of literature studies, it is known that the most common chemical compounds in medicinal plants used to treat GDM are flavonoids, followed by saponins, tannins, polyphenols, terpenoids, and alkaloids (47). Chemical compounds in herbs can be obtained from various parts of plants, such as seeds, leaves, or those that have been processed into essential oils (48). Medicinal plants containing flavonoids can activate GLUT4 synthesis and translocation, increase hexokinase activity in the liver, reduce apoptosis, activate PPAR- γ expression to improve glucose uptake, activate AMPK pathways, inhibit tyrosine kinase activity, and activate NF- κ B (49). Flavonoids in basil extract lowered blood sugar, inhibiting carbohydrate metabolism by inhibiting α -glucosidase and α -amylase enzymes (50)

Flavonoids also play a role in antioxidant activity by increasing SOD, CAT, GSH, and decreasing AGE. In addition, flavonoids also have anti-inflammatory effects by reducing IL-1 β , IL-6, and TNF- α (51). The flavonoid component may suppress oxidative stress by regulating redox imbalance, regulating antioxidant enzyme gene expression through the Nrf2/ARE (nuclear erythroid 2-related factor 2/antioxidant response element) signaling pathway, and the activity of various cellular signaling pathways. extracellular signal-regulated protein kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (P13K/Akt/mTOR), and the mitogen-activated protein kinase pathway (p38 MAPK) (52).

The alkaloid can act as an antidiabetic agent, promoting glucose absorption and glycogen synthesis (53). This caused a significant change in the activity of liver hexokinase, or glucokinase, and glucose-6-phosphatase. This effect was consistent with altered expression levels of hepatic hexokinase type IV, glucose-6-phosphatase, and phosphoenolpyruvate carboxykinase, enzymes involved in glucose storage and glycogen production. This change in enzyme activity and expression patterns may occur because of alkaloids, which play an important role in improving carbohydrate metabolism. These alkaloids can stimulate glucose transport by increasing glucose transporter 1 (GLUT1) activity. In addition, they also increase the phosphorylation of adenosine monophosphate-activated protein kinase and acetyl coenzyme A carboxylase (54). The alkaloid can also play an important role as an antioxidant by increasing SOD, CAT, and GSH enzymes (51).

Terpenoids improve hyperglycemia by regulating insulin receptor expression, GLUT4 and AMP-activated protein kinase transcription levels; and inhibition of α -amylase and α -glucosidase activity and mitochondrial oxidative stress through activation of Nrf2-GCLc signaling (51). The mechanism of action of the antidiabetic effect of triterpenoids, i.e., increases glucose uptake and synthesis, insulin sensitivity, and antioxidant activity; activates PPAR- γ and incretins, AMPK pathway, and iNOS; promotes the expression of GLUT4, GLP-1, HSP, and adiponectin; and inhibits glycation end products and enzymes responsible for protein glycation, inflammatory pathways, and insulin resistance (55).

In addition, the antihyperglycemic effect of the diterpene may be due to an increase in glycolysis and inhibition of gluconeogenesis by inducing genes involved in glycolysis or by inhibiting ATP phosphorylation and NADH oxidase activity in liver mitochondria (56). The terpene can also affect antioxidant enzyme activity by reducing ROS and MDA levels; reducing oxidative stress by increasing SOD and MDA levels; reducing the inflammatory factor; increasing IRS1 and Akt phosphorylation; and stimulating GLUT4 translocation with increased activity of AMP-activated protein. It improves the condition by regulating inflammatory regulators such as MCP-1, TNF- α , and adiponectin, which reduce the accumulation of macrophages in adipose tissue (57)

Tocopherols are known as vitamin E, a very powerful antioxidant that easily donates hydrogen atoms to reactions capable of converting peroxy radicals to tocopherol radicals, which are less powerful and therefore unable to damage fatty acid chains, thus protecting β -cells from damage, an important part of the antioxidant defense system of the cell, which also includes other enzymes such as SODs. Tocopherol can protect the fatty peroxide chain of cell membranes from oxidation caused by free radicals (58). Hyperglycemia-induced production of reactive oxygen species (ROS) in diabetes can cause direct and indirect damage through oxidative stress and the inflammatory response (59).

5. Conclusion

Currently, the review presents an overview and the potential use of herbal therapy in managing gestational diabetes mellitus (GDM), which is a condition of hyperglycemia occurring in the second and third trimesters of pregnancy. Data from animal and human studies show heterogeneity. GDM is a growing health concern, and current evidence suggests that proper screening, early detection, and management can significantly improve outcomes for both the baby and the mother. The original research has shown that some herbs have antidiabetic agents and could potentially be used for the treatment of GDM. Bioactive compounds contained in herbs have various mechanisms of action, including modulating glucose metabolism, increasing antioxidant activity, and reducing inflammatory factors. However, most of these studies have been conducted on animal models, so further research is needed to confirm these effects in humans, especially in pregnant women, and to determine appropriate dosage levels.

Compliance with ethical standards

Acknowledgments

We are highly grateful to our lecturers for their advice and guidance. And, also, to the Master Program of Midwifery, Faculty of Medicine, Universitas Brawijaya, Malang, for the support.

Disclosure of conflict of interest

The authors declare no conflict of interest.

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