Review Article

Efficacy of Flavonoids in Increasing Insulin Sensitivity among Pregnant Women with Gestational Diabetes Mellitus: A Systematic Review

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ABSTRACT

Introduction: Pregnant women can experience a lot of risks and complications during the entirety of the pregnancy with gestational diabetes mellitus (GDM) as one of the most prevalent. Researchers have conducted studies that monitored the conditions of insulin sensitivity among pregnant women as well as determining factors that lead to evaluating the probability of developing gestational diabetes mellitus. Studies on flavonoids have also been conducted to test their efficacy as a source of intervention in preventing the risk of gestational diabetes mellitus. **Aim:** This paper aims to discuss the various physiological changes and adjustments throughout gestation, and the insulin activity and sensitivity of a pregnant woman with gestational diabetes mellitus. This also aims to give an overview of the interactions and biochemical effects of flavonoids on pregnant women with gestational diabetes mellitus. **Methods:** There were 277,790 research articles garnered from credible sites, such as Google Scholar, MDPI, NCBI, and ScienceDirect that were all published from 2011 up to the present, and only nine (9) were used in this review paper. **Results:** Flavonoid derivatives (i.e., Flavanones, naringenin, etc.) show normal BMI in varying amounts of flavonoids 718 mg per day and 105 mg per day and are proven to have a lesser risk in developing diabetes among women: type 2 Diabetes and Gestational Diabetes Mellitus. Also, a 24- dietary recall on pregnant women has shown a great contribution in maintaining normal BMI and glucose level [OR 0.62 (95 percent CI 0.38; 0.96)]. In addition, a significant increase in insulin sensitivity is shown in Pregnant women who have taken flavonoids with their derivatives and is associated with NF-κB, Akt, and MAPK Erk1/2 pathways. **Conclusion:** Upon careful review of the research articles, it was observed that there is a significant relationship between the intake of flavonoids and their derivatives in pregnant women with GDM that entails higher insulin sensitivity, consequently lowering the risk of GDM by helping the metabolic pathway metabolism and regulation.

Keywords: Gestational Diabetes Mellitus, Flavonoids, Pregnant Women, Insulin Sensitivity, Placenta.

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INTRODUCTION

Improving maternal health has become an increasingly important priority of the global development agenda over the last 20 years. The maternal mortality rate decreased by 43% between 1990 and 2015, from 532 000 in the year 1990 and 303 000 in the year 2015

fatalities.[1] However, regardless of these improvements, in 2017 about 810 women died each day from complications related to pregnancy and childbirth that may have been prevented.[2] One of which is Gestational Diabetes Mellitus (GDM), a diabetes that develops during pregnancy, which is often referred to as the most common metabolic condition in pregnant women, with prevalence rising to epidemic proportions.[3] Although gestational diabetes is reversible, if it is not managed properly, it may increase the risk of further complications such as high blood pressure, preeclampsia, future diabetes, which could be fatal and lead to permanent damage.[4]

This condition may affect insulin sensitivity in their body depending on the mother's demands. Insulin sensitivity is an important metabolic trait where it may increase glucose absorption during early pregnancy into adipose storage in preparation of later pregnancy's energy demand.[5] These decreases to 50% of the typical values as pregnancy progresses to the third trimester. Medications such as metformin and insulin shots are typical in women with gestational diabetes.[6] but alternative medication with specific chemical compounds could potentially add to the solution. Flavonoids, found in a wide range of foods such as fruits, vegetables, and tea, have antioxidant, anti-inflammatory, and anti-carcinogenic, and ability to influence important cellular enzyme processes, have been linked to a wide range of health-promoting benefits.[7] This can also influence glucose metabolism or insulin sensitivity, enhancing glucose absorption and insulin production while blocking glucose synthesis.[8]

The purpose of this review is to provide a peer-reviewed study regarding the insulin-sensitizing capability of flavonoids. Mainly, it will target the discussion of the clinical significance of its phenolic properties in lowering the risk of gestational diabetes mellitus and its impact on the number of physiological changes and adaptations during pregnancy. The researchers point out the third trimester of the pregnancy in determining the insulin-sensitizing nature of flavonoids as insulin sensitivity may gradually decline to 50% of the normal expected value regulated by several mechanisms including increased estrogen, progesterone, and human placental lactogen (hPL) levels which may lead to the development of gestational diabetes mellitus during this stage of the pregnancy.[9]

MATERIALS AND METHODS

This chapter presents the methods used to collect data from different resources that may be relevant to the review. The methods used for this paper are the literature search strategy and the inclusion and exclusion criteria which will determine the eligibility of each article used in the study.

Literature Search Strategy

The strategy used to search related literature was retrieving data from credible online search engines which include Google Scholar, MDPI Open Access Journals, ScienceDirect, and NBCI. The articles were retrieved using a combination of focal keywords such as "Flavonoids", "Gestational Diabetes Mellitus", "Pregnancy", "Insulin Sensitivity", "Diabetes", and "Pregnant Women" without the use of any limitation that may be set in every online database. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses or PRISMA approach was also utilized for better organization during the search for articles and each article was collected and reviewed through ZOTERO, an open-source reference management software to sort and filter the references that will be used in the study. The general scheme for evaluating the significance of the paper in the study was shown in Figure 1.

Eligibility Criteria

The systematic review includes the insulin-sensitizing ability of flavonoids, gestational diabetes mellitus among pregnant women, causes of gestational diabetes mellitus, the effect of flavonoids on gestational diabetes mellitus, and experimental studies related to flavonoids on gestational diabetes mellitus that are published not more than 10 years ago. The data that are excluded are articles whose language is not in English, published before 2011, inaccessible and inadequate, serve as a secondary source, respondents are not pregnant, and pregnant women without gestational diabetes mellitus.

Inclusion Criteria

Studies are included in this review if they identify with the following criteria: (a) the article is an experimental study that is related to flavonoids on gestational diabetes mellitus, (b) the publication date is not more than 10 years ago, (c) the Flavonoid tested insulin-sensitizing agent in Gestational Diabetes Mellitus is/are found in Asia, (d) the language of the article is in English, and (e) the data of the study are sufficient and accessible.

Exclusion Criteria

Studies are excluded from this review if any of the following criteria are identified: (a) the article is a secondary source (b) the publication date is before 2011, (c) the Flavonoid tested insulin-sensitizing agent in Gestational Diabetes Mellitus is not found in Asia.,

Prisma Flowchart

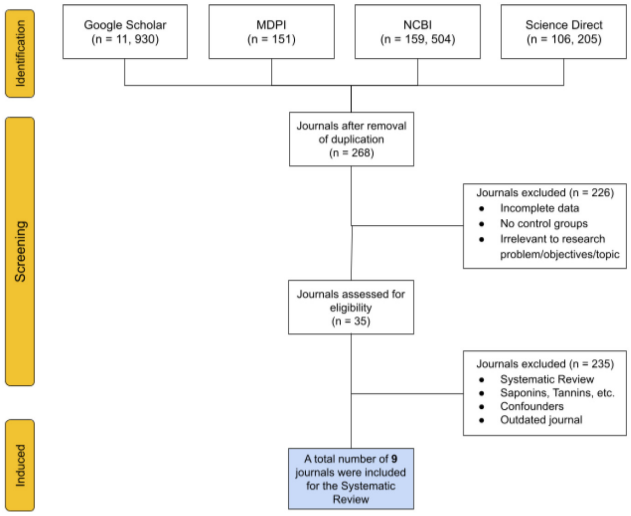

Figure 1: Prisma Flowchart.

(d) the article is written in languages other than English, and (e) the data are inaccessible and inadequate.

RESULTS

Effects of Consumption of Flavonoids on pregnant women with Gestational Diabetes

As seen in Table 1, the study by Balbi Mde A *et al.*[10] The study by Balbi Mde A *et al.*[10] conducted a test to see if there are any effects in the consumption of flavonoids during the gestational period leading to obesity and gestational diabetes mellitus. The study was conducted with a total of 785 respondents. The dietary consumption was measured using the "multiple-pass" approach in three phases across two non-consecutive 24-hr dietary recalls. The Multiple Source Method (MSM) was used to assess the total consumption of flavonoids and the type of flavonoid consumed. It was observed that pregnant women who consume a high amount of anthocyanidin, flavan-3-o, and flavanones have normal weight as compared to the ones who intake less. It was also noted that those who consumed a total of 718 mg of flavonoids per day had a decreased risk of diabetes than women who consumed 105 mg per day.

Physiological and hormonal changes such as weight gain, raised blood sugar levels, increased oxygen levels, etc. are typically experienced by women during the period of their pregnancy, thus, this increases their risk of obtaining gestational diabetes. Since gestational diabetes is reversible, regular care and management during pregnancy must be done such as with diet and exercise, to effectively control the changes occurring in a pregnant woman. Data shows that a diet high in flavonoids may protect against type 2 diabetes mellitus and obesity that could lead to gestational diabetes.[10] Flavonoid, a dietary polyphenol, which is mostly found in fruits, vegetables, leaves, and plants has anti-diabetic properties that could help in the management of gestational diabetes and prevent the risk of developing severe complications.

Two studies investigated the effects of consumption of flavonoids during pregnancy on gestational diabetes and obesity.[10] showed a beneficial role in a diet rich in flavonoids and anthocyanidins in obese pregnant women. In their study, 785 pregnant women were evaluated for food intake, three periods were evaluated using "multipath" techniques, and two 24-hr meal recalls were performed on non-consecutive days. The first 24hr of diet reminders were collected during the interview, and the second reminders were contacted by phone during a repeat of at least 7 days. The results showed that pregnant women with high flavonoid consumption [OR 0.62 (95% CI 0.38; 0.96)] were 39% and 38% obesity is unlikely to be diagnosed. However, due to low intake of flavonoids the researchers interpreted the results that there is no correlation between flavonoids and GDM.

Another study conducted by Li S *et al.*[11] assessed the supplementation of naringenin, a prominent citrus flavonoid that is found mostly in oranges and grapes, in mice with gestational diabetes. It was found that the administration of naringenin has a prominent role in the management of Gestational diabetes since GDM symptoms were decreased, glucose and insulin tolerance were improved, inflammation was reduced, and outcomes were improved. Figure 2 shows that naringenin treatment led to significantly lower blood sugar levels in mice with gestational diabetes on GD9 and GD18. Furthermore, on GD18, GDM mice treated with naringenin had noticeably lower weight

Table 1: Association of dietary flavonoid intake during pregnancy with excess weight and obesity.

	1st tertile	2nd tertile		3rd tertile	
		Odds Ratio[b]	95%CI	Odds Ratio[b]	95%CI
Total Flavonoids					
Median (mg/day)	26.29		50.44		89.29
Overweight	1.00 (Ref.)	1.21	0.80; 1.85	0.75	0.49; 1.13
Obesity	Ref.	1.27	0.81; 1.99	0.61	0.38; 0.96
Anthocyanidins					
Median (mg/day)	0.58		1.93		7.06
Overweight	Ref.	0.85	0.56; 1.30	0.75	0.50; 1.31
Obesity	Ref.	1.01	0.65; 1.58	0.62	0.40; 0.99
Flavan-3-ols	1.00				
Median (mg/day)	2.41		7.82		17.99
Overweight	Ref.	1.23	0.81; 1.88	1.05	0.69; 1.60
Obesity	Ref.	0.89	0.57; 1.40	0.72	0.46; 1.14
Flavanones	Ref.				
Median (mg/day)	1.39		2.25		24.36
Overweight	Ref.	1.19	0.79; 1.79	0.67	0.44; 1.02
Obesity	Ref.	2.17	1.36; 3.47	1.24	0.77; 1.98
Flavones	1.00				
Median (mg/day)	0.15		0.32		0.75
Overweight	1.00	1.19	0.79; 1.79	0.88	0.58; 1.32
Obesity	1.00	1.10	0.71; 1.73	0.84	0.54; 1.33
Flavonols	1.00				
Median (mg/day)	15.82		24.82		35.25
Overweight	1.00	1.21	0.80; 1.83	0.85	0.56; 1.31
Obesity	1.00	0.65	0.41; 1.03	0.75	0.49; 1.17

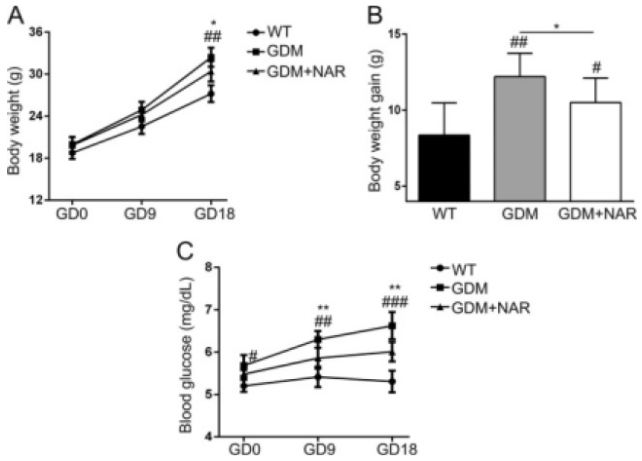

Figure 2: Naringenin minimizes the symptoms of gestational diabetes mellitus (GDM).

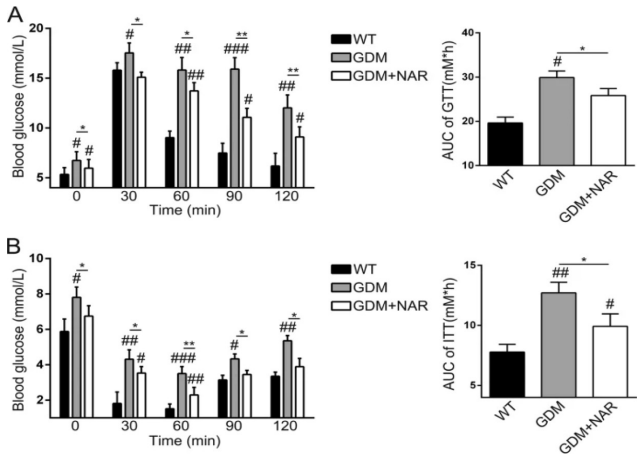

Figure 3: Supplementing mice with naringenin enhances their glucose and insulin tolerance.

than untreated GDM mice, indicating that naringenin treatment hindered GDM mice from gaining weight. In Figure 3, it was displayed that naringenin significantly attenuated and standardized fasting blood sugar levels in mice with gestational diabetes compared to controls. Figure 4 shows that GDM mice had relatively high levels of IL-1, IL-6, TNF-, and MCP-1 in their blood. In relation, serum levels within these cytokines were considerably lower in GDM mice treated with naringenin compared with the non-GDM mice.[11] mentioned in their study that naringenin treatment reduced birth weight and increased litter size in GDM mice. Furthermore, it was reported that NTNF-induced insulin resistance was mitigated by Naringenin via AMPK. Naringenin drastically reduced ROS levels in TNF-treated C_2C1_2 cells, implying that Naringenin suppressed TNF-induced ROS upregulation.

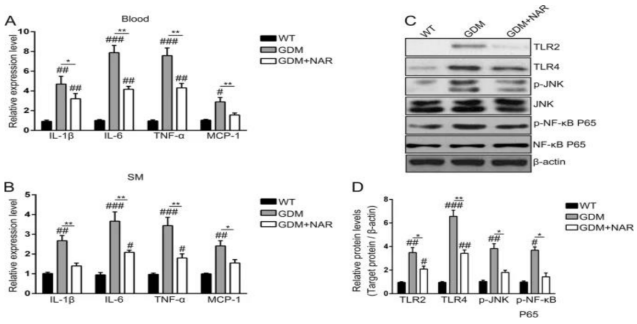

Figure 4: Naringenin is an anti-inflammatory agent.

Effect of Flavonoids on Insulin Sensitivity

Pregnancy leads to the increase of insulin that is secreted into the body as early as life is conceived within the womb while the body's sensitivity to insulin remains unaffected or shows a slight increase or decrease. Through the course of the pregnancy, however, insulin sensitivity may begin to dwindle until the body becomes overwhelmed with the continuous increase of insulin which would put the pregnant woman at risk of gestational diabetes mellitus or GDM.[5] The cause of this condition is said to be associated with pancreatic ß-cell dysfunction together with hormonal imbalances that directly affect insulin sensitivity.[12] A definitive cause is yet to be determined in the meantime.

As shown in Figure 5, a study by Nguyen-Ngo C *et al*.[13] A study by Nguyen-Ngo C *et al*.[13] used human tissues (skeletal muscle, placenta, and VAT) from 26 non-obese NGT mothers who gave birth to healthy children by caesarean section were used. Researchers investigated the effect of nobiletin, a flavonoid contained in tangerine skin, on glucose uptake that is stimulated with insulin in the skeletal tissue, human placenta, and VAT submitted by an inflammatory mediator (inflammatory cytokine TNF). It functioned as an *in vitro* model of diabetes. TNF is used to study the effects of TNF as a pro-inflammatory agent on mRNA expression and protein production in placenta and VAT. TNF is used to affect glucose uptake by skeletal tissue and cause inflammation of the placenta and VAT. Researchers have also investigated how it affects the NFB, Akt, and MAPK signaling pathways. All of these are affected by TNF.

Despite the fact that the tissues were damaged by the presence of TNF, the effect of nobiletin on these tissues was significant. While placental inflammation was reduced, glucose uptake into skeletal tissue was increased. Nobiletin also prevented decreased IB expression in placental tissue and VAT, as well as suppression of placental Akt and activation of MAPK ERK1 / 2. In the placenta, nobiletin-added combination

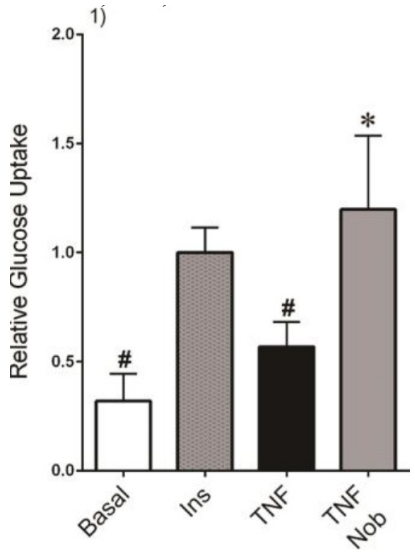

Figure 5: Effect of nobiletin on glucose uptake in human skeletal muscle tissue.

treatment inhibited Ccl2 mRNA expression and protein secretion, l1b, Il6, Ccl2, and Ccl3 mRNA expression, IL6, CCL2, CCL3, and CXCL8 secretion. These results indicate that nobiletin has the capability to improve sensitivity of insulin in tissues damaged by inflammation and pro-inflammatory cytokines via the NFB, Akt, and MAPK Erk1 / 2 pathways as seen in Figure 6.

Insulin Sensitivity in association with Gestational Diabetes

During pregnancy, pregnant women have a high physiologic activity which means pregnant women undergo an imbalance in the homeostasis of glucose due to metabolic adaptation. This will result in hyperglycemia, which will be referred to as Gestational Diabetes Mellitus (GDM) affecting 14% of pregnancies worldwide annually for every 18 million births.[14] The majority of these cases involve a failure in pancreatic β-cells being unable to compensate for the glucose uptake, insulin resistance increases while insulin sensitivity decreases. Among 809 women at 24 to 30 weeks of pregnancy, insulin secretion and sensitivity is tested using Oral Glucose Test (OGTT) 67 [8.3%] women have (GDM). 30% of them have problems with insulin secretion, 51% have problems with insulin sensitivity, and the remaining 18% have both problems. All of the metabolic problems have been found to have a similar physiologic process.

Insulin sensitivity after childbirth starts to improve and becomes normal. In Figure 7, the lowest level can be seen in late postpartum and early postpartum a huge increase in insulin sensitivity can be seen and a slight decrease during late postpartum.

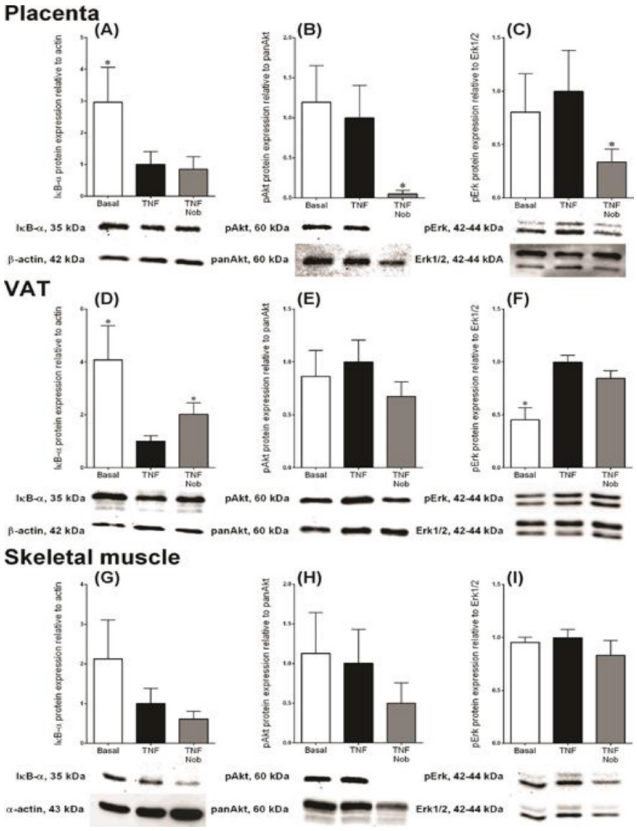

Figure 6: Effect of nobiletin on activation of NF-κB, Akt, and MAPK in the placenta, VAT, and skeletal muscle.

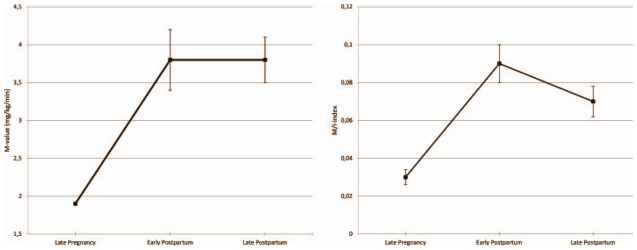

Figure 7: Insulin Sensitivity of Pregnant Women with GDM.

There are many reasons why insulin sensitivity changes during pregnancy, one of which is Placental DNA methylation. Pregnant women's body mass index (BMI) and gestational weight gain (GWG) increase due to placental DNA methylation. These five Single-Nucleotide Polymorphisms (SNPs) are associated with Genetic Risk Score (GRS) indicating methylation activity at cg01618245 (CHRNA4), cg03699074 (BDP1P), cg08099672 (ENTPD2), cg12673377 (MICALL2/UNCX), and cg24475484 (DLGAP2). Elevated DNA methylation levels (as measured by GRS) are in conjunction with a lower Matsuda index in all five (SNPs).[18]

The Matsuda index is a measurement of insulin sensitivity obtained via oral glucose tolerance test (OGTT) that simultaneously measures both insulin and glucose

levels. Another study backs up the idea that women with GDM have a genetic susceptibility to insulin secretion and sensitivity, and thus diabetes development. In 374 women from Southern Sweden who had previously had GDM, 72 SNPs were genotyped. Age, BMI, and ethnicity were all considered in all analyses.[19]

DISCUSSION

Benefits of Flavonoids on Pregnant women with Gestational Diabetes Mellitus

As shown in Table 2, there are effects of flavonoids in increasing insulin sensitivity of pregnant women with gestational diabetes mellitus performed by number of researchers. Pregnancy is usually accompanied by minor complications. However, in some cases, these issues can result in major health problems for both mother and child, including death. Flavonoids-rich foods, for example, have been shown to protect against type 2 diabetes and obesity. pregnant women of a healthy weight consumed more anthocyanidin and flavan-3-ol than pregnant women of an obese weight. Flavonoids have been shown to lower pancreatic lipase activity and intestinal lipid absorption, resulting in less visceral fat formation and hyperglycemia. It may also have anti-inflammatory and antioxidant qualities, as well as a modifying influence on gut flora, which may aid in the regulation of obesity. However, there were no significant differences in glycemic homeostasis. To further understand the relationship between flavonoids and GDM, a higher average flavonoid consumption is necessary.[10]

Women often endure physiological and hormonal changes during pregnancy, such as weight growth, increased blood sugar levels, and increased oxygen levels, among others. According to a research by, Li S *et al*.[11] diets rich in bioactive compounds such as flavonoids, which are present in plant-based foods, may help to prevent type 2 diabetes and obesity. The health of the fetus benefits from foods that are high in flavonoids and anthocyanidins. Flavonoid intake during pregnancy and gestational diabetes and obesity were evaluated in two studies. Obesity was shown to be less likely in 39 and 38 percent of the participants. Moreover, there is a study that shows that the flavonoid naringenin, found in citrus fruits, has an important role in the treatment of gestational diabetes. When compared to controls, it reduced dramatically and controlled fasting blood sugar levels in mice with gestational diabetes. In GDM mice, it also lessened birth weight and increased litter size.[11]

Effect of Flavonoids on Insulin Sensitivity *B.2*

Pregnancy causes an increase in the amount of insulin secreted into the body as soon as life is conceived within the womb, although the body's sensitivity to insulin remains unchanged or increases slightly. Insulin sensitivity may decrease during pregnancy, until the body is overwhelmed by the constant increase in insulin, putting the pregnant woman at risk of gestational diabetes mellitus, or GDM. According to, Nguyen-Ngo C *et al*.[13] nobiletin, a flavonoid found in tangerine skin, was studied for its effect on insulin-stimulated glucose absorption in skeletal tissue, the human placenta, and VAT produced by an inflammatory mediator (inflammatory cytokine TNF) thus, it was seen that it has served as a diabetes *in vitro* model. After all the findings, nobiletin appears to increase insulin sensitivity in tissues affected by inflammation and pro-inflammatory cytokine and results show that it associates increasing the insulin sensitivity among pregnant women with GDM.

Insulin Sensitivity in Gestational Diabetes Mellitus (GDM)

Insulin Sensitivity and Insulin Secretion D.1

Due to the physiological changes in the mother's body, a pregnant woman is at risk for impaired glucose tolerance or hyperglycemia during her pregnancy. Insulin sensitivity may decline as the pregnancy progresses into the third trimester. Insulin sensitivity pertains to how responsive a person's body cells are to insulin, whilst insulin secretion is a mechanism driven by an increased plasma glucose membrane. In previous studies, the oral glucose test (OGTT) has been used to test insulin sensitivity and secretion in pregnant women, and it was reported that 30% of pregnant women have difficulty with their insulin secretions, 51% experience insulin sensitivity issues, and 18% have both.[15] With a concern regarding the decline of insulin sensitivity being the most prevalent problem among pregnant women, it is likely that they will develop insulin resistance, putting them at risk for Gestational Diabetes Mellitus (GDM).

Changes in Insulin Sensitivity D.2

Insulin sensitivity has a significant role in reducing blood sugar in the body. Due to metabolic changes, the insulin sensitivity of a pregnant woman decreases during pregnancy. According to Skajaa *et al*. (2020), the insulin sensitivity of women after childbirth gradually becomes normal, with the most significant improvement in the early postpartum up until late postpartum; hence, gestational diabetes mellitus (GDM)

Table 2: Research in Effects of Flavonoids in Increasing insulin sensitivity of Pregnant Women with Gestational Diabetes Mellitus.

No.	Reference	Study Area	Sample size (N)	Respondents	Flavonoids, Insulin Sensitivity, Pregnant Women, and Gestational Diabetes	Study Duration	Findings
1.	Balbi *et al*., 2019	Brazil,	785	Adult Women	Efficacy of flavonoid intake for women with GDM and excess weight	2 non-consecutive days with at least 7 days in between	Foods rich in flavonoids have been shown to reduce risk of obesity in pregnant women. No data was found regarding the relationship of dietary flavonoids with GDM. pregnant women who consume a high amount of anthocyanidin, flavan-3-o and flavanones have normal weight as compared to the ones who intake less. Those who consumed 718 mg of total flavonoids per day had a decreased risk of diabetes than women who consumed 105 mg per day.
2.	Li *et al*., 2019	China	7–12 for each group	Mice induced with GDM	Effectiveness of Naringenin in enhancing insulin sensitivity in mice induced with GDM	4 weeks	Naringenin reduced GDM symptoms, improved glucose and insulin tolerance, reduced inflammation, and increased productivity.
3.	Wu, *et al*., 2021	China	16,819 cases in the training data set; 15,371 cases in testing data set	Recruited patients International Peace Maternal and Child Health Hospital, Shanghai Jiao Tong University School of Medicine	Gestational Diabetes Mellitus	2017-2018	Machine Learning models were used to accurately predict gestational diabetes mellitus.
4.	Nguyen, *et al*., 2020	Australia	26	NGT non-obese women who had delivered healthy newborns at term (37-41 weeks) through elective Caesarian.	Insulin Sensitivity	2019-2020	Nobiletin increased insulin sensitivity of *in vitro* models by increasing the glucose uptake of skeletal muscles, prevented the degradation of IκB-α expression on the placental tissue and VAT, suppressed placental Akt, and activated MAPK ERK1/2.
5.	Plows *et al*., 2018	USA	23,000 HAPO study	Pregnant women	Development of Gestational Diabetes Mellitus	2013 to 2017	Hyperglycemia in pregnant women advanced in the genetic, epigenetic, and environmental factors that are associated with the progression of GDM.
6.	Powe *et al*., 2016	Québec	809	Pregnant Women with (GDM)	Insulin Secretion and Insulin sensitivity	14 Days	GDM among pregnant women share heterogenic physiology in association of insulin secretion and insulin sensitivity.
7.	Skajaa *et al*., 2020	Denmark	13	Women with GDM	Development of GDM and Physiologic recovery	6 months and 2 weeks	Insulin sensitivity after delivery of the baby improves drastically and leptin levels decrease. Insulin secretion is highest in late pregnancy.
8.	Hivert *et al*., 2020	Orlando	12	Pregnant women in their 1st trimester	DNA methylation in insulin sensitivity of pregnant women	12 to 14 weeks	The Placental DNA methylation is influencing the insulin sensitivity of pregnant women.
9.	Prasad *et al*., 2021	Sweden	374	Women with GDM	insulin secretion and sensitivity in relation to genetics	5 years	Indicates the chances of Women with past diagnosis of GDM having insulin secretory and insulin sensitivity problems.

inevitably happens due to pregnancy. DNA methylation, an essential mechanism of gene regulation in the placenta, has a significant effect on gestational diabetes mellitus (GDM) and insulin sensitivity through which the placental DNA methylation affects the pregnant women's body mass index and gestational weight gain (GWG).[16] Gestational diabetes mellitus (GDM) is highly associated with a mother's genes in which insulin sensitivity and insulin secretion were tested and proven to have genetic susceptibility and, thus, diabetes development. Therefore, a mother's gene contributes to the development of gestational diabetes mellitus (GDM).

CONCLUSION AND RECOMMENDATION

Our review paper suggests that a diet rich in flavonoids would help reduce the risk of obtaining gestational diabetes and alleviate the condition's symptoms for those who have already acquired it. Upon careful review of the research articles, it was observed that there is a significant relationship between flavonoids and GDM. Naringenin and Nobiletin, a few of the flavonoids discussed in the study, showed promising results in lowering GDM symptoms by increasing insulin sensitivity that may have deteriorated during the pregnancy. The effects of flavonoids to obtain such results were lowering the risk of obesity, improving glucose and insulin resistance by enhancing glucose uptake, reducing inflammation of the placenta and other tissues, and suppressing the degradation of pathways that affects the increase or decrease in insulin sensitivity. However, the data gathered did not entirely suffice the findings because the subjects of the studies took in low consumption of flavonoid-rich foods, and human tissue models were only used in some studies. The authors suggest that the best way to reveal the relationship between flavonoids and GDM is by imposing higher consumption of pure single flavonoids for a more extensive find of their effects including their anti-oxidant and anti-inflammatory effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Akt: Protein kinase B; **AMPK:** AMP-activated protein kinase; **BMI:** Body Mass index; **CCL2:** Chemokine Ligand 2; **CCL3:** Chemokine Ligand 3; **Ccl2 mRNA e:** monocyte chemoattractant protein-1; **CXCL8:** chemokine receptor 8; **GDM:** gestational diabetes mellitus; **GRS:** Genetic Risk Score; **GWG:** gestational weight gain; **hPL:** human placental lactogen; **IL-1:** Interleukin 1; **IL-6:** interleukin 6; **MAPK:** Mitogen-activated protein kinase; **MAPK ERK1:** Mitogen-activated protein kinase/extracellular signal-regulated kinase; **MAPK Erk1/2:** MAPK/ERK pathway also known as the Ras-Raf-MEK-ERK pathway; **MCP-1:** Monocyte chemoattractant protein-1; **mRNA:** messenger ribonucleic acid; **MSM:** Multiple Source Method; **NF-ϰB:** nuclear factor kappa B; **NGT:** normal glucose tolerance; **OGTT:** Oral Glucose Test; **ROS:** Reactive oxygen species; **SNPs:** Single-Nucleotide Polymorphisms; **TNF:** treated- tumor necrosis factor; **VAT:** visceral adipose tissue.

SUMMARY

Gestational diabetes mellitus (GDM) is a common metabolic disorder that occurs when a woman's body cannot produce sufficient insulin during pregnancy. Phytochemicals or secondary metabolites of plant origin like flavonoids help regulate and improve the pathogenesis of diabetes by increasing insulin-sensitivity. Studies suggest that diets high in flavonoids such as naringenin, nobiletin, and others have anti-inflammatory and antioxidant properties that can aid in blood sugar control and reduce placental inflammation. It was also revealed that a greater flavonoid intake of 718 mg per day is needed to reduce the incidence of gestational diabetes mellitus and obesity in pregnant women. However, the effects of flavonoids on the subject were not clearly administered since there has been a discrepancy in giving the right amount of dosage.

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