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FLAVONOIDS-A DIETARY SUPPLEMENT FOR TREATING PREGNANCY-INDUCED DISORDERS: A REVIEW

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ABSTRACT

Flavonoids, a group of plant-derived bioactive compounds, play a significant role during pregnancy in promoting maternal and fetal health. The multitude of health benefits that flavonoids are associated with, has resulted in increasing interest of it in pharmaceutical studies. As pregnancy is associated with several health risks in mother like preeclampsia related diseases, gain of weight, diabetes mellitus, etc., its implication is also seen in fetus which in some cases may result in morbidity or mortality later in the life of the child. To reduce such complications and the occurrence of diseases in the future, a healthy diet consumption by mothers is needed which can create a healthy in-utero nutritional environment for the normal development of the child. This review aims to identify the potential of flavonoids when consumed during pregnancy, in minimizing the pregnancy induced disorders as well as providing protective functions for the fetus

against a range of diseases. Flavonoids multi-prong benefits as anti-oxidative, anti-inflammatory agent, providing better cardiovascular support, metabolism regulation, immune support and proper fetal development makes it a potent dietary supplement during pregnancy. However, further research is needed to determine the optimal dosage of flavonoids, ensuring their benefits without any adverse effects on both the mother and the developing fetus.

Keywords: Flavonoids, Pregnancy-induced disorders, Cardiovascular diseases, Preeclampsia, Gestational diabetes, Anti-inflammatory effect

INTRODUCTION

Maternal nutrition, during pregnancy, is vital for a healthy pregnancy and a healthy start in life of the developing fetus as over- or under-nutrition can be deleterious to the developing fetus that in turn results in the increased health risks in adulthood [1-4]. Depending on mother’s supply of nutrients and the demand of nutrients by the fetus at the time of development, the fetus adapts to the in-utero environment of the mother as it is

programmed to adjust to the uterine nutritional status. When the supply of nutrients is insufficient for the fetus during its development, there is a high risk of disease contraction which may occur later in life and predicts the physiological alterations that persist into the adulthood which can be understood by “Fetal Programming Hypothesis” (Figure 1) [5]:

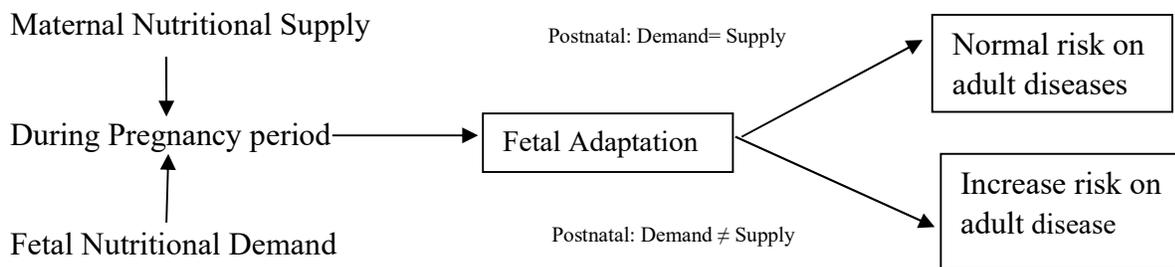


Figure 1: Overview of fetal programming

Reports suggest that nearly 78% of pregnant women consume some form of natural products as they are the good sources of micronutrients and are believed to be good for fetal development [6]. Over the past few decades, consumption of such supplements

have increased and flavonoid is one such supplement which is recommended for maternal intake during pregnancy [7]. Flavonoids are polyphenolic secondary metabolites of plants comprising approximately 4500 compounds [8]. Plant

flavonoids which is one of the most commonly found secondary metabolite are found in several medicinal plants belonging to nearly 10,000 species of plant families. Different preparations of the parts of these plants have exhibited wide range of activities like pharmacological activities, antioxidative, anti-inflammatory, tissue-protective, etc. [9, 10]. These flavonoids are found in both free forms (aglycones) or conjugated with sugar molecules (glycosides) [11].

According to Schaefer *et al.* [12], “Chemically flavonoids are based on a skeleton of fifteen carbon composed of two benzene rings connected by a heterocyclic pyran chain. Chemically the different classes of flavonoids vary in the degree of oxidation and the substitution pattern of the C ring, while individual compounds differ in the pattern of substitution of the A and B rings” (Figure 2).

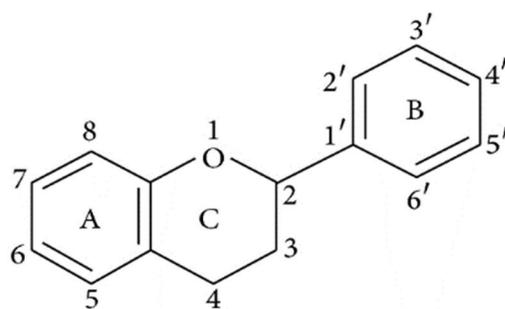


Figure 2: Chemical structure of flavonoid

Various studies have shown that flavonoid rich diets are wholesome food owing to their high nutritional content. Besides the

nutritional aspect, they are also known for their pharmacological activities in the treatment of certain diseases (Figure 3).



Figure 3: Some Natural Food Sources of Flavonoids

In general, plants and marine organisms possess the biosynthetic ability of the flavonoids and not animals [13]. The consumption of flavonoid-rich diet reduces the risk of diseases like diabetes, obesity, chronic inflammatory disorder, neurodegenerative disorder, cancer, cardiovascular diseases, and many more. In the case of cancer cell treatment, the tumor cells are targeted using nanoparticle-mediated delivery of flavonoids [14]. Studies have shown that flavonoids can cross the placental barrier and reach the fetal tissue [15] so a healthy diet rich in such supplements can help reduce the risk of developing several disorders in the fetus. Flavonoids also aid in treating pregnancy induced hypertension against inflammation and oxidative stress which are the prime cause of hypertension [16-19].

There are considerable number of benefits associated with the consumption of flavonoids during pregnancy, however, their detrimental effects on the developing fetus cannot be ruled out and these areas also need to be studied and addressed [20-21]. Studies have highlighted their detrimental effects in the form of anomalies in the development of limb and genitourinary tract, impaired metabolism and fetal development, childhood leukemia, etc. [22-24].

Pregnancy Induced Disorders

Pregnancy-induced disorders refer to health conditions that arise during pregnancy, affecting both the mother and the developing fetus. Proper prenatal care, a balanced diet and regular medical check-ups are essential for early detection and effective management of these conditions, promoting a healthy pregnancy. There are numerous studies which have proved the relationship between Hypertensive Disorders in Pregnancy (HDP) and the increased risk of Cardio Vascular Diseases (CVD) later in mother's life [25, 26]. HDP comprises Gestational Hypertension (GH), Preeclampsia (PE) and Chronic Hypertension. Studies reveal that women with PE during pregnancy show structural and functional cardiovascular changes, which include changes like impaired myocardial function, biventricular systo-diastolic chamber dysfunction, localized myocardial ischemia and fibrosis [27, 28]. In addition, cardiopulmonary complications associated with severe PE are again associated with increased maternal mortality [29].

HDP is also related to higher risk of developing peripheral artery disease (PAD) [30] affecting the vessels of the lower extremities [31]. It has been studied that most women with hypertension disorder have some metabolic risk factors like obesity, diabetes which causes abruption or infarction of

placenta from the womb due to obstruction of the blood supply to placenta. The study interpreted that the vascular obstruction of maternal placenta was associated with higher risk of early cardiovascular disease and hence there is a need for healthy lifestyle [32]. Subsequent studies have confirmed the increased association between the risk of PAD with HDP and between HDP with atherosclerosis in women at the pre-clinical stage [33]. HDP are also reported to show subsequent development of asymptomatic (stage B) or symptomatic (stage C) heart failure [34, 35] and coronary heart disease including (stable and unstable) angina pectoris, myocardial infarction, and sudden cardiac death [33].

Apart from HDP and related diseases, maternal excess weight also poses a considerable risk for both maternal and fetal health in the short- and long-term outcomes during pregnancy [36, 37] and according to “International Diabetes Federation” it is the main determinant of Gestational Diabetes Mellitus (GDM) which accounts for approximately 16% of pregnant women globally [38].

Flavonoids Treating Pregnancy Induced Disorder

Flavonoid compounds such as baicalin, quercetin, silibinin, vitexin are some of the

potential metabolites which have been reported as a new therapeutic solution to serious disorders for both expectant mother and the fetus. All of them have a beneficial anti-inflammatory, anti-oxidative and anti-hypertensive properties at the molecular and cellular level which are being discussed in the following section:

Baicalin

Baicalin, a flavonoid found in *Scutellaria baicalensis* Gerorgi (Lamiaceae), is a Chinese traditional medicine which has therapeutic properties showing anti-coagulant, anti-bacterial, anti-inflammatory, anti-oxidative, cardioprotective and anti-hypertensive effects [39-45]. This flavonoid extracted from the dried root of the plant is a glucuronide of baicalein, another flavonoid extracted from the same plant [46]. A number of studies relating to baicalin activity towards different diseases have shown healing effects against several disorders, which also includes pregnancy-related disorders.

In a study carried out in pregnant rat models by Wang *et al.* [47], baicalin showed protective functions against organ damage in PE, protecting the liver and kidney from related injuries by cell apoptosis. Baicalin intervention increased the expression of anti-apoptotic protein X-linked inhibitor of apoptosis protein (XIAP) and B- cell

lymphoma 2 (Bcl-2) and decreased the expression of apoptotic protein Caspase-9 in rat liver suggesting its therapeutic potential in preventing liver and kidney damage [48].

Another pregnancy-related disorder, Estrogen Induced Cholestasis (EIC) is marked by compromised bile flow and thus bile acids build-up in the liver, causing liver damage [49, 50]. Baicalin helped in maintaining the bile acid balance and averting liver injury by activating sirtuin 1 (Sirt 1) /hepatocyte nuclear factor-1 α (HNF-1 α) / farnesoid X receptor (FXR) signaling pathway which is beneficial against EIC [51].

The use of baicalin to alleviate pregnancy-induced hypertension along with preeclampsia, eclampsia and gestational hypertension, showed positive results [52, 53]. It suggested that the alleviation of damage to vascular endothelium and increase in the number of placental villi can be brought about with baicalin treatment, reducing vascular endothelial injury and harm to the placenta, thus, securing proper passage of nutrients through the placenta [53]. In cases of cardiovascular malformation of embryos caused by diabetes mellitus induced hyperglycemia during pregnancy, baicalin administration showed therapeutic effects by reducing risk of malformation during early embryonic development by subduing the

uncontrolled reactive oxygen species (ROS) production and preventing apoptosis; making it a possible contender as drug for GDM [54].

Quercetin

Quercetin is a broadly distributed flavonoid which is present in fruits, vegetables and different medicinal plants [55-58]. Quercetin or 3,3',4',5,7-pentahydroxyflavone is a flavanol also abundant in tea, red wine, honey and other fruit juices in the form of glycosidic derivatives [59]. In general, supplements of quercetin are promoted in the market to treat various conditions ranging from asthma, allergic reactions, infections, eye problems, arthritis and neurological problems [60].

There are many studies that focus on activity of quercetin and its impact in various in vitro and in vivo models [61-63]. The flavanol has healing properties mainly attributable to its anti-oxidative characteristic and anti-hypertensive effect [64, 60]. At a dosage of 50 mg/kg, quercetin is reported to exhibit antioxidant and anti-inflammatory properties, having the potential of treating diabetes mellitus when tested in streptozotocin (STZ)-induced diabetic Wistar rats [65]. As a flavonoid, quercetin has anti-hypertensive properties when used on patients having Stage 1 hypertension [55]. Quercetin has also proved to have restorative properties against cardiovascular diseases [66, 67]. It is a highly

efficient flavonoid as it can be used in treating pregnancy related disorders with no embryotoxic effect on the growing embryo [68]. As such, quercetin intake during early pregnancy, in the prenatal period, showed genetic up-regulation of enzymes involved in improved iron accumulation in the liver and lowered oxidative stress when the treated mice attained adulthood [69]. González-Esquivel *et al.* [61] used TiO₂ nanoparticles as vectors which resulted in oxidative stress in liver and kidney and quercetin counteracted the treatment in rats. Quercetin had a protective effect on renal function by elevating levels of glutathione reductase and peroxidase while reducing malondialdehyde (MDA) levels. The presence of TiO₂ significantly upregulates the expression of glutathione reductase, which can subsequently be downregulated by quercetin. Biochemical assessments of serum and urine revealed that the combination of quercetin and TiO₂ exhibited superior effectiveness in mitigating oxidative stress.

Li *et al.* [62], studied the effects of quercetin in vitro on VEGF using rhesus macaque choroid-retinal endothelial (RF/6A) cell line. Quercetin in a dose dependent manner inhibited RF/6A cell proliferation, VEGF-induced migration and tube formation of RF/6A cells by interfering VEGF induced targeting VEGFR-2 signaling pathways.

Thus, findings of the study suggest that quercetin is known as inhibitor of choroidal and retinal angiogenesis as it inhibits VEGF-induced choroidal and retinal angiogenesis of the cell line. According to a study reported by Khaksary-Mahabady *et al.* [57] quercetin through its anti-oxidative effect can defend the fetus against the teratogenic effect of a metabolite of retinoid, namely all trans retinoic acid (at RA), accountable for abnormal development of different organs of the embryo. The anti-inflammatory effect of quercetin in lipopolysaccharide (LPS) stimulated macrophages [63]. It was shown that quercetin had a marked effect in reducing the production of nitric oxide (NO), inducible NO synthase (iNOS) and interleukin 6 (IL6), and the nuclear translocation of nuclear transcription factor kappa B (NF K β). Additionally, LPS induced stimulation of extracellular signal regulated kinase (Erk1/2) and Jun N terminal kinase (JNK) was suppressed by quercetin implying that NF κ B, Erk1/2 and JNK could be potential molecular targets of quercetin in an LPS induced inflammatory response and thus decreased the inflammation.

Silibinin

Silibinin is a flavonoid extracted from dried fruits of *Silybum marianum*, commonly known as milk thistle [70]. It is the principal

constituent present in silymarin, the main extract of the plant [71] and is a mixture of two diastereomers, silibinin A and silibinin B [72]. Silibinin, also called silybin, in general is known to have anticancer [70], anti-oxidant properties [73] and exhibits hepato-protective properties [74]. Silibinin consumption, during pregnancy, is reported to decrease inflammation induced by bacterial endotoxin LPS and pro-inflammatory cytokine, IL- β in gestational tissues of human and thus, can prevent infection and preterm labor. When tested in vivo, in an infected fetus with inflammation, silibinin could also reduce inflammation and injury to fetal brain in a mouse model, proving to be an important and novel medicament that can not only reduce the adversaries of tissue inflammation but can also, help tissue recover [71].

In pregnant women with preeclampsia, silibinin has shown to hinder the release of ROS and tumor necrosis factor- α (TNF- α), thereby exhibiting its anti-oxidative and anti-inflammatory properties [75]. Silibinin, in another study, lowered monocyte basal activation in preeclamptic women causing the decline of activated NLR family pyrin1/3 (NLRP1/NLRP3) inflammasomes and the NF- κ B pathway that is predominantly triggered by the presence of uric acid crystals in blood of the patients [76]. Apart from

suppressing inflammatory cytokines, it also leads to polarization of monocytes in culture to M2 profile, thus showing its anti-inflammatory characteristic in preeclamptic sterile inflammation [77].

Vitexin

Vitexin belongs to the group of C-glycosylated flavonoids. The occurrence of this flavonoid is reported from different plant species of *Matricaria* sp. (L.) of Asteraceae [78], *Rosmarinus officinalis* (L.) of Lamiaceae [79] some species of *Passiflora* (L.) of Passifloraceae [80] and species of *Crataegus* (L.) and *Rosa* (L.) of the family Rosaceae [81]. Some of the derivatives of Vitexin are soviteixin, rhamnopyranosylvitexin, methylvitexin (isoembigenin), vitexin-2-O-rhamnoside (VOR) and vitexin-2-O-xyloside [82, 83].

Vitexin plays wide role in pharmacological activities such as in anticancer [84], antioxidant [85], anti-hypertensive and anti-inflammatory effects [80], protective properties in the cardiovascular system [86], antibacterial [87,88], antiviral [89], antinociceptive [90], cardioprotective [91] and neuroprotective effects [92]. Vitexin also possesses potent activities against preeclampsia pathogenesis during pregnancy which includes inflammation, oxidative stress, and angiogenic imbalance.

Experimentally, interesting results were obtained in an animal model of preeclampsia which was dose and time-dependent. In the study, vitexin was introduced to pregnant rats where experimental preeclampsia was induced.

Vitexin showed protective effect which opposed preeclampsia damage by lowering high systolic blood pressure, urinary protein in PE rats. High dose of vitexin helped to overcome pup weight, pups/placenta ratio leading to a normal pregnancy outcome. It also helped in reducing oxidative stress in the blood and placenta by the inhibition of tissue factor pathway inhibitor (TFPI-2), hypoxia inducible factor (HIF-1) and vascular endothelial growth factor (VEGF) in PE rats [93].

Recently Babaei *et al.* [94], reported that vitexin is an anti-oxidant molecule and provide protection against various ROS and lipid peroxidation involving pathophysiological pathways of preeclampsia. It decreased the expression levels of biomarkers soluble fms like tyrosine kinase (sFlt) and placental growth factor (PlGF) ratio which otherwise causes hypertensive pregnancy related disorder which led to pathogenesis of preeclampsia.

Anthocyanin

Anthocyanins are polyphenolic flavonoids composed of an anthocyanidin backbone with two aromatic benzene rings which are separated by an oxygenated heterocycle with sugar and acyl conjugates [95, 96]. Anthocyanins have a range of colors which ranges from orange, red and purple to blue in flowers, seeds, fruits and vegetative tissues [96]. Most common derivatives of anthocyanins in plants are cyanidin, petunidin, pelargonidin, malvidin, delphinidin, and peonidin [97].

Various *in vitro* and *in vivo* studies from animal models suggested that anthocyanins have anti-oxidant properties which promote health benefits and may play roles in reducing chronic and degenerative diseases [98-103]. During lactation, anthocyanins, the potent polyphenol in combination with high-fat diet protected the offspring against oxidative stress, body fat gain, hyper-triglyceridemia and insulin resistance in adulthood [104-106]. The same beneficial effects were also observed during gestation as well as lactation of rat model after polyphenol supplementation. The intake upregulates adenosine monophosphate activated protein kinase (AMPK) phosphorylation in young and adult offspring which may lead to decreased bodyweight, hepatic triacylglycerol levels and increased adiponectin levels by acetyl

coenzyme A carboxylase (ACC) phosphorylation and downregulation of sterol regulatory element -binding protein-1c (SREBP-1c) expression [107]. Research has shown that jussara (*Euterpe edulis* Mart.) fruit supplementation in maternal diet which is rich in anthocyanins have promising effects on the metabolic programming during pregnancy as well as lactation period and was also effective in lowering blood glucose and triacylglycerol levels in the offspring [108]. An in vitro study showed anti-obesogenic property of anthocyanins inhibiting the lipid accumulation by regulating the lipogenesis process resulting in effective weight reduction [109]. Similar results had been reported from animal model rat and rodent [107, 19]. Furthermore, anthocyanins are reported to activate the AMPK pathway which increases skeletal muscle glucose uptake, reduces lipogenesis, promotes lipolysis and reduces cholesterol synthesis [110]. Food rich in anthocyanins are found to have anti-inflammatory action by inhibiting the translocation of serum endotoxin levels NFkB to the nucleus [18, 19, 111]. A contradictory result from the anthocyanins of blue berries exhibited increase in pro-inflammatory genes like TNF in treated rodents [19]. Studies have shown that high fat-diet along with extracts rich in anthocyanins are potent polyphenol

against body weight gain. The regulation of weight gain and obesity can be balanced by energy expenditure in the brown adipose tissue (BAT) through thermogenesis and is mediated by uncoupling protein-1 (UCP-1) [112, 113, 108] resulting in reduction of fat/weight gain in fetus.

Catechin: epicatechin and epigallocatechin-3-gallate (EGCG)

Catechin, epicatechin and epigallocatechin-3-gallate (EGCG) are flavonoids of subclass of flavanols or flavan-3-ols present widely in apple, cocoa-based products, red grapes, red wines and teas. They are reported to show vasoprotective properties including anti-inflammatory and vasodilatory activities [114-117].

Green tea is rich in flavonoid catechin and among catechins most abundant is EGCG and studies suggest that polyphenolic compounds in the tea have anti-oxidant properties and reduce the risk of a variety of diseases [118-122].

Hachul *et al.* [123], reported that consumption of green tea increased IL-10/TNF- α ratio and IL-1 β in the mesenteric adipose tissue and decreased the catalase level; as well as it also lowered superoxide dismutase, higher adiponectin and LPS concentrations and inflammatory cytokines in adipose tissue in the offspring. The study demonstrated that

green tea consumption altered inflammatory status by increasing IL-10/TNF- α ratio and other related factors in mother and offspring by decreasing the risk during pregnancy and lactation period. Similar findings have been reported by Moreno *et al.* [124] and Okuda *et al.* [125] when comparing with lipidic (saturated fat from animal source) food ingestion with or without green tea extract in day-to-day life.

Shi *et al.* [126], performed a comparative clinical study on the PE pregnant women by administering either nifedipine with EGCG or with placebo effect. The study showed that the two groups of drugs combination (nifedipine+EGCG) and (nifedipine + placebo) in the study was synergistic and efficacious in controlling blood pressure, maternal and neonatal health. Moreover, epigallocatechin gallate reduced the side effects like vomiting and hypotension of nifedipine.

The flavonoid has potential health benefits in metabolism to the pregnant mothers and studies have shown that these flavonoids and flavonoid metabolites could reach the fetal tissue during development [127, 128]. Maternal catechin, epicatechin and EGCG diet helps in fetal growth and development. In vivo study in human showed that consumption of catechin has profound influence on absorption, metabolism and excretion which

help in biological activity by modulating cellular bioavailability [129-131]. But Tu *et al.* [132] reported high-dose of catechin, epicatechin and EGCG having adverse effects during implantation by inducing apoptosis in both their in vivo and in vitro study.

Genistein

Genistein is a naturally occurring phytoestrogen found in Leguminosae species like in soy products. This isoflavonoid like another general phytoestrogen intake has extensive antioxidant properties and other beneficial effects [133, 134]. Genistein also play important role by epigenetic alterations, blood cell development and other crucial event during pregnancy.

During fetal development, epigenetic alterations are crucial through methylation by some epigenetic markers involved in the proper imprinted gene expression to ensure proper development [135]. Study related to the induced changes in epigenome of fetus by giving genistein incorporated supplemental diet to maternal mice during gestation showed the uptake of the flavonoid by the fetus [136]. The genistein supplementation resulted in expression of heterozygous agouti mice having different coat color which reduced the ectopic agouti expression. The changed agouti phenotypes also called pseudo-agouti mice were associated with protection against

obesity of the offspring later in life which remained unaltered throughout the life.

Other studies have shown that pregnant female rats exposed to genistein diet exerts long lasting effects on the immune and endocrine system by having higher immune organ masses, lymphocyte subpopulations, cytokine concentrations and lower testosterone concentrations by Klein *et al.* [137] and Ohta *et al.* [138] respectively. The study reported about post weaning growth and altered stress response in which plasma concentration of corticosterone and ACTH were lower resulting in decrease anxiety to offspring. Genistein exposure also induced long-term effects on the uterine gene expression profile during development [139]. Vanhees [5] reported about prenatal exposure of mice to genistein leaves a permanent signature on the hematopoietic lineage by affecting fetal red blood cell development by inducing a distinct gene expression profile.

Luteolin

Luteolin is a flavone contained in many medicinal plants and in vegetables like celery, parsley, spinach, thyme, lettuce and peppers [140].

Though luteolin is only a minor flavonoid component recent research in vitro and in vivo has provided that luteolin has many medical applications as anti-bacterial, anti-

carcinogenic anti-oxidant, cardiovascular immunological, and other pharmacological mechanisms. Previous studies performed in gestational tissues have demonstrated that luteolin are two phytophenols exerting anti-inflammatory actions via inhibition of NF- κ B and AP-1 [141-143].

In the processes of inflammation and carcinogenesis luteolin which is an active inhibitor of intercellular adhesion molecule-1 (ICAM-1) has been implied. They were actively inhibiting the I-kappa-B-alpha (IK α) degradation, I kappa B kinase (IKK) activity, the NF- κ B DNA-protein binding and the NF- κ B luciferase activity. Using activator protein (AP-1) site deletion mutant TNF- α -induced ICAM-1 promoter activity was decreased indicating AP-1 association with ICAM-1 expression. It has been reported that AP-1 seems to play a more significant role than NF- κ B in the flavonoid-induced ICAM-1 inhibition [144]. It has also been studied that luteolin inhibited the expression and production of the inflammatory genes and mediators like NO, prostaglandin E2 (PGE2) as well as the expression of iNOS, cyclooxygenase-2 (COX-2), TNF- α and IL-6 in mouse alveolar macrophages stimulated with LPS by blocking NF- κ B and AP-1 activation [145].

Luteolin has shown to lower the inflammatory responses by inhibiting TNF- α , an inflammatory cytokine which caused multiple adverse effects on cardiac myocytes. Luteolin blocked LPS-induced I κ B- β degradation, NF- κ B p65 subunit nuclear translocation and NF- κ B DNA binding activity in neonatal rat cardiac myocytes. It also inhibited LPS-

induced production of TNF- α in myocytes by inhibiting NF- κ B signaling pathway showing the promising role of luteolin for the treatment of inflammation-related myocardial diseases [4].

The summarized broad benefits of flavonoid supplement consumption during pregnancy are given in **Figure 4**.



Figure 4: A summarized view of benefits of flavonoid supplements during pregnancy

Side Effects of Flavonoids

PE in pregnant woman is mainly caused due to their placental oxidative stress. During pregnancy, flavonoids and their derived metabolites consumption by pregnant woman play an important role to overcome this condition because of their anti-oxidant properties [146]. Despite their potential

benefits, it's essential to research and understand the optimal dosage of flavonoids. High doses of certain flavonoids may have adverse effects on fetal development, emphasizing the need for a balanced and varied diet. During pregnancy bioflavonoids consumption of mother easily exposed the infant in utero leading to onset of infant

leukemia [22, 147, 148] which may be result of several chromosomal abnormalities. The abnormalities seen in infant leukemia are thought to be the result of the inhibition of topoisomerase II (top II) by MLL gene rearrangement [22, 149]. Generally, pregnant women are advised to take cocoa contained food but, in a study, it has been reported that catechin containing chocolates caused abnormal morphology in the kidney structure specially the size and shape of glomerulus [23]. A clinical study has been reported about a disorder called fetal ductus arteriosus constriction due to pregnant women consumption of foods like tea, fruits, chocolates and others during the third trimester of pregnancy [24]. Different reports suggested that flavonoids act as protective antioxidants but at high concentrations these compounds attributed to pro-oxidant function by interfering the synthesis of thyroid hormone and action of estrogen [150]. At adult age, prenatal phytoestrogen flavonoid exposure to pregnant mice sometimes associated with hematopoietic lineage of the mice, increased granulopoiesis and erythropoiesis along with moderate macrocytosis and left a permanent effect on the mother [5]. Thus, during pregnancy there is a need for the assessment of flavonoid intake by mother that include safety doses and

orientation of flavonoid content food which should be evaluated based on their beneficial and adverse effect.

CONCLUSION

This review highlights the importance of flavonoids, a secondary plant metabolite, in treating various disorders related to pregnancy. This review provides new and important insights and trends in pharmacological studies and their future applications for introducing new therapeutic solutions for the pregnancy-induced disorders which are often fatal to both mother and fetus. Its antioxidant property helps in neutralizing harmful free radicals that can damage cells and DNA, protecting both the mother and the developing fetus from oxidative stress. Flavonoids, help mitigate inflammation during pregnancy, contributes in better blood circulation and vascular function, supporting the growing demands of the developing fetus, decreases the risk of gestational diseases, such as gestational diabetes and gestational hypertension, provides potential immune support, regulates glucose metabolism and in short, it results in promoting maternal well-being (**Figure 4**). Though there are studies combining in vitro and in vivo models to assess the efficacy of flavonoids on the pregnant mother as well as fetus but more clinical studies to assess their safety as well as

to understand the mechanism of their action is needed which will open new vistas for rational phytotherapy as a complementary therapy for the treatment of pregnancy-induced disorders. This will allow proper evaluation of the amount of dose to be administered to a pregnant woman to prevent any harm to the mother and fetus. Incorporating flavonoid-rich foods, such as fruits, vegetables, and certain herbs, into the maternal diet can contribute to a healthier pregnancy and support the well-being of both the mother and the growing baby. However, pregnant individuals should consult their healthcare providers before making significant dietary changes or taking flavonoid supplements.

Conflict of Interest

The authors report no conflict of interest.

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