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Maternal Polyphenol Consumption and Pregnancy Outcomes: Current Evidence and Perspectives

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ABSTRACT

Polyphenols are plant-derived compounds that we consume daily in large amounts through food. They have anti-inflammatory and antioxidant properties. Researchers have shown that these compounds affect the health of an expectant mother and her developing baby; however, their effects are twofold and can be both positive and negative. In this review, studies from the past 20 years listed in PubMed, Scopus, and Google Scholar were examined using terms such as "polyphenols in pregnancy," "oxidative stress," "fetal development," and "ductus arteriosus." The papers show that a moderate intake of certain polyphenols (especially resveratrol, EGCG (epigallocatechin gallate), and curcumin) may help lower the risk of pregnancy problems related to oxidative stress, including preeclampsia and gestational diabetes. However, very high doses can be harmful, for example, by triggering early closure of the ductus arteriosus in late pregnancy, and some polyphenol may disturb the first stages of pregnancy. While many authors focus on potential benefits, overuse could leave lasting adverse effects on the fetus. More human studies are needed to set safe polyphenols intake limits and create clear dietary guidelines for pregnant women.

Keywords: polyphenols, pregnancy, oxidative stress, ductus arteriosus, fetal development

1. INTRODUCTION

The mother's diet plays a role in promoting the health of both herself and the growing fetus at all stages of pregnancy. Such a varied diet of nutritious foods which is adequate for mother's physiological changes and needs, will also provide fetal normal growth and development (Hsu and Tain, 2019; Santangelo et al., 2014). Healthy diets contain bioactive substances, particularly polyphenols, which represent a widely studied category of phytochemicals. Polyphenols, naturally synthesized as secondary metabolites by plants, structurally contains at minimum

two phenyl rings and one or more hydroxyl groups. They occur extensively in common dietary sources such as foods and beverages, becoming an integral part of daily nutrition (Nacka-Aleksić et al., 2022; Tain and Hsu, 2024; Salinas-Roca et al., 2022). Fruits such as berries, grapes, oranges, and red fruits; vegetables (spinach, red onions, broccoli), teas (black, green, and herbal (e.g., mate, chamomile), coffee and chocolate/cocoa products (especially the dark variety), nuts, soybeans, and olive oil are the most abundant and important dietary sources of polyphenolics (Scalbert and Williamson, 2000). The amount and type of polyphenols can vary significantly according to the food source and processing methods. For example even the roasting of the beans has an effect on the polyphenol content of the cocoa beans, nibs, and chocolates (Żyżelewicz et al., 2016). Flavonoids are the largest group of dietary polyphenols and exhibit classes including anthocyanins, flavanols, flavonols, and isoflavonoids (Nacka-Aleksić et al., 2022). Polyphenols are widely known for their various biological functions and health-promoting benefit. One of their mechanisms of action is their antioxidant nature and they function as typical hydrogen or electron-donating antioxidants.This leads to an overall enhancement in plasma antioxidant status and oxidative stress derivatives. They also have significant anti-inflammatory action (Tsao, 2010; Rudrapal et al., 2022). Oxidative stress and inflammation are basic processes that, when disordered, are involved in a multitude of reproductive disorders and complications of pregnancy. For instance, oxidative stress stems from placental impairment, may lead to diminished efficacy of the antioxidant system, inhibited angiogenesis, impaired nitric oxide bioavailability, endothelial dysfunction, and an excessive inflammatory response. Flavonoids, as one of the subclass of polyphenols, are proposed to have modulating roles that may reduce oxidative stress-induced pregnancy damage and abnormal outcomes. It is proposed that a uterine environment rich in polyphenols and antioxidants during pregnancy may help prevent diseases that manifest later in adulthood (Hussain et al., 2017).

The protective effects of polyphenols in the prevention of chronic diseases (including CVD, DM, cancer, and neurodegenerative diseases) have been widely studied in the general population (del Bo et al., 2019), but their role during pregnancy is complex and should be especially considered. Dietary polyphenols are increasingly being consumed, often in large amounts by way of supplements and fortified foods, and this means pregnant women are exposed to them and their potential effects on maternal adaptation and fetal development pathways should be given serious consideration (Nacka-Aleksić et al., 2022). Evidence from research suggests that transport across the placenta is not very effective; however, polyphenols and their metabolites may cross the placental barrier, which may have biological effects on the offspring (Chu et al., 2006; Arola-Arnal et al., 2013).

This review serves to summarize the current evidence on polyphenol consumption in pregnancy using the available scientific evidence. It will also review evidence regarding both potential benefits, such as for pregnancy complications including preeclampsia and gestational diabetes, and potential harm, such as for fetal ductus arteriosus constriction. By critically analyzing the results from a number of these studies, this review aims to add depth to the current understanding of the role of polyphenols during pregnancy, highlight gaps in knowledge, and propose directions for future research.

2. REVIEW METHODS

This review article provides a detailed and organized description of the literature on the impact of polyphenols on pregnancy. The main objective was to collate and critically evaluate current knowledge, identify research gaps, and suggest future research directions. A systematic search of literature was carried out in various electronic databases which included PubMed, Google Scholar, and Scopus (Figure 1).

Inclusion criteria:

We included randomized controlled trials, clinical interventions, meta-analyses, and review articles published within the last 20 years. Relevant search terms included “polyphenols“ and "pregnancy", "oxidative stress” and "fetus", "constriction of arterial duct", "ductus arteriosus closure", "preeclampsia“, "gestational diabetes mellitus“, "resveratrol”, and "pregnancy“ among others.

Exclusion criteria:

We excluded studies with methodological weaknesses such as small sample sizes, lack of control groups, inadequate statistical analysis, and studies published in languages other than English.

All studies included in this review adhered to ethical guidelines, and relevant institutional review boards approved studies involving human participants.

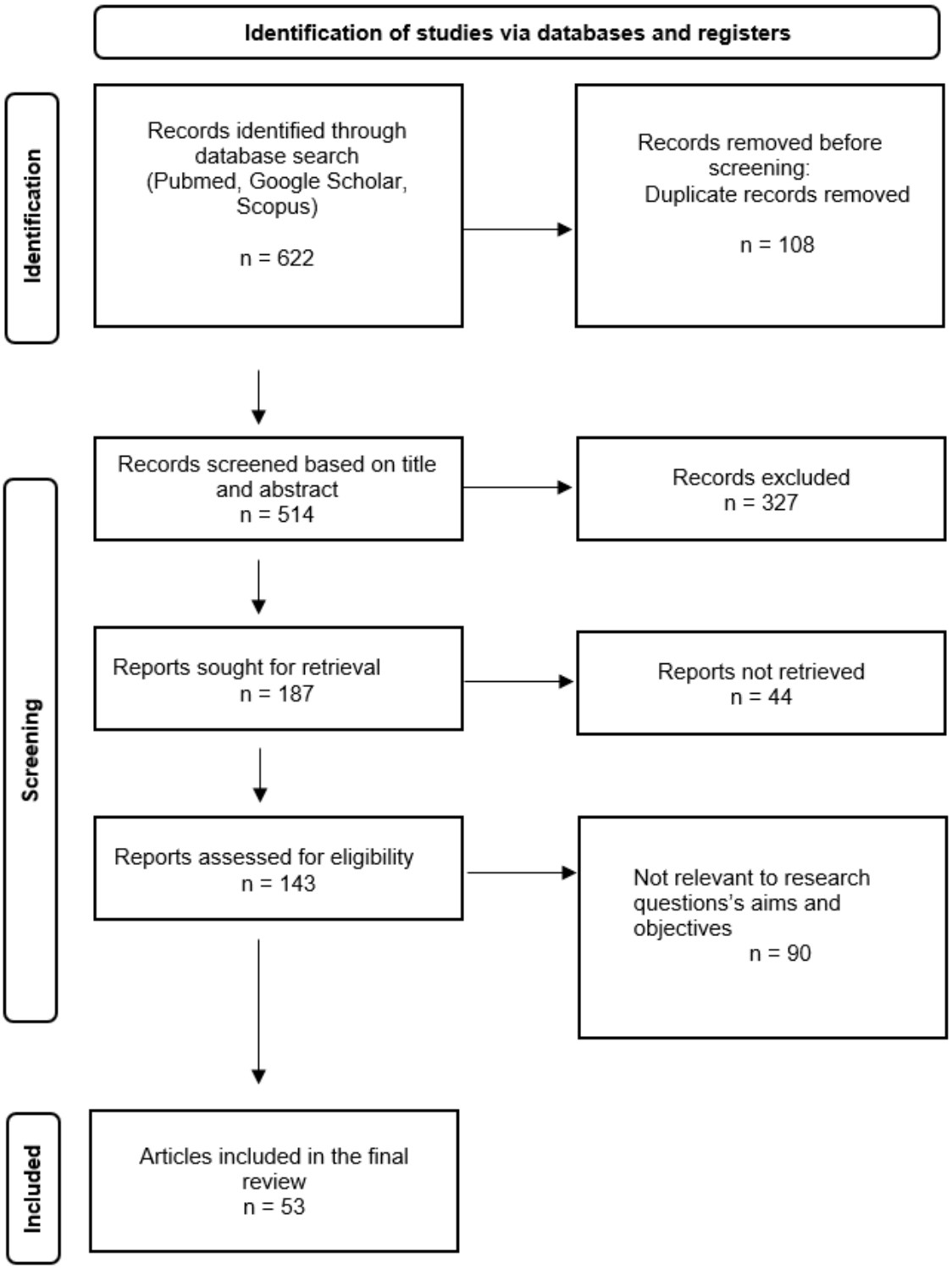

Figure 1 Prisma consort chart.

3. RESULTS AND DISCUSSION

The well-documented antioxidant and antiinflammatory features of polyphenols play a prominent role in studying their potential effects during pregnancy. Since oxidative stress and inflammation contribute to most of the pregnancy-related complications, the polyphenols are believed to be good candidates for attenuating these conditions (Ly et al., 2015), (Figure 2).

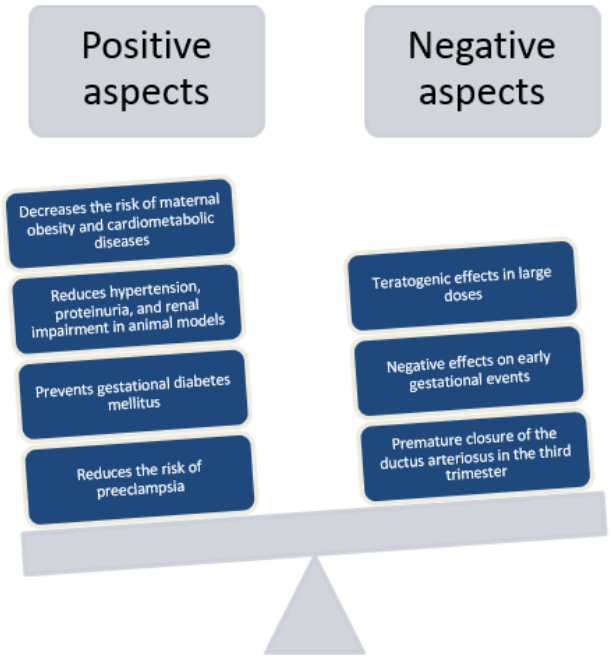

Figure 2. Positive and negative aspects of a polyphenol-rich diet during pregnancy

Potential Beneficial Effects

Preeclampsia (PE) presents as one of the most crucial research areas. Preeclampsia mainly appears as high blood pressure and proteinuria after the 20th week of pregnancy. It is often accompanied by inflammation in the body, oxidative stress, and impaired function of blood vessels. Treatment focuses mainly on reducing inflammation. One meta-analysis of randomized controlled trials included fourteen trials examining six putative polyphenol candidates – EGCG (epigallocatechin gallate), resveratrol, Salvia miltiorrhiza, PsBHr (Bryophyllum pinnatum), RE (raspberry extract), and CE (cranberry extract) – on preeclampsia-related outcomes (Nguyen et al., 2025). Another study showed that the administration of EGCG plus nifedipine (an antihypertensive) versus nifedipine alone may be effective in decreasing the onset time of blood pressure reducing (Mean difference (MD) = −14.10 min, 95% CI −18.46 to −9.74) and increasing the onset time (MD = 3.10 h, 95% CI 2.35 to 3.85) of the next hypertensive crisis in women with preeclampsia (Shi et al., 2018). Similarly, the concurrent intake of resveratrol and nifedipine in another trial had a potential impact on blood pressure control (MD = −15.50 min, 95% CI −19.83 to −11.17) and the time duration from hypertensive attacks (MD = 2.50 h, 95% CI 2.09 to 2.91 h) (Ding et al., 2017). Possible reasons for these effects are discussed. Research indicates resveratrol activates signaling pathways such as Nrf2, which increases the production of antioxidant enzymes, thereby reducing oxidative stress—a key contributor to the pathology of preeclampsia (Hussain et al., 2017).

Other polyphenols, such as curcumin, quercetin, baicalin, and punicalagin, exhibited beneficial outcomes in animal models with PE through the modulation of blood pressure, inflammation, oxidative stress, and apoptosis (Zielinsky and Busato, 2013). For example, curcumin reduced hypertension, proteinuria, and renal impairment in Lipopolysaccharide-(LPS)-administered pregnant rats and enhanced trophoblast invasion and the remodeling of spiral arteries. Quercetin exhibits antiabortive effects in LPS-induced abortion models by affecting T lymphocytes and cytokines. The polyphenolic compounds such as baicalein, wogonin from Radix Scutellariae and Rhizoma Atractylodis decreased fetal resorption in mice (Hussain et al., 2017).

Another key pregnancy-related disorder for which polyphenols have been studied is gestational diabetes mellitus (GDM) (Nacka-Aleksić et al., 2022; Salinas-Roca et al., 2022). GDM is the result of modified glucose metabolism associated with chronic sub-clinical inflammation and increased oxidative stress. Diet is a preferred method of GDM treatment. A systematic review showed a positive association between the intake of polyphenol and prevention and management of cardiometabolic complications in pregnancy, also in GDM (Salinas-Roca et al., 2022). One cohort study found that consumption of total polyphenols, probably flavonoids during mid-pregnancy, was inversely associated with GDM risk (Gao et al., 2021). Trials with individual polyphenol-rich foods such as blueberries

(ingested as two cups daily) and supplements like resveratrol or EGCG have demonstrated potential benefit. Blueberry intake coupled with soluble fiber prevented the increase of glucose, elevation of antioxidant markers reduced glutathione (RG), and total antioxidant capacity (TAC), and suppression of lipid peroxidation malondialdehyde (MD) plasminogen activator inhibitor 1 (PAI-1) in pregnant women at risk of GDM (Basu et al., 2021a; Batiha et al., 2022; Basu et al., 2021b). Blood glucose and lipid profiles in overweight pregnancy benefits following an intervention (80 mg trans-resveratrol + D-chiro-inositol/Myo-inositol). Addition of EGCG (500 mg/day) was reported to be effective in reducing diabetic symptoms in mothers and neonatal complications (low birth weight and hypoglycemia) in GDM patients (Zhang et al., 2017). Resveratrol, in particular, has been well researched for its antidiabetic properties, using animal models, associated with antioxidant, anti-inflammatory actions, effects on insulin sensitivity, and pancreatic function, possibly via AMP-activated protein kinase and SIRT1 (Szkudelski and Szkudelska, 2015). Although encouraging results have been reported, further evidence is needed to confidently develop recommendations regarding the prevention or treatment of GDM with polyphenols.

Polyphenols have also been associated with more general maternal health advantages with potential effects on pregnancy outcomes. For instance, they have been related to a decreased risk of maternal obesity and cardio-metabolic diseases. The possibility that maternal polyphenol supplementation may intervene in the development of cardiovascular–kidney–metabolic (CKM) syndrome in the offspring is a field of active research (Tain and Hsu, 2024; del Bo et al., 2019). However, some additional research would be needed to clarify those possible long-term benefits fully, and the science is still emerging.

Negative Aspects and Effects on the Fetus

Despite their possible merits, there are evident concerns about the dietary intake of polyphenols during pregnancy, particularly in late gestation, about the fetal ductus arteriosus (DA) (Zielinsky and Busato, 2013; Hahn et al., 2017; Zielinsky et al., 2013). In fetal development, the ductus arteriosus serves as a critical blood vessel, and premature narrowing or closure within the womb can result in serious adverse outcomes including fetal pulmonary hypertension, right-sided heart failure, fetal hydrops, and potentially fatal neonatal pulmonary hypertension (Abdel Mohsen and Amin, 2013; Babaoğlu et al., 2013). Although non-steroidal anti-inflammatory drugs have established associations with premature constriction of the fetal DA, increasing evidence supports a role for maternal ingestion of polyphenol-rich foods (PRF) in non-NSAID-induced cases of premature fetal DA constriction. As per one review, among 177 cases of NSAID-unrelated RPWs reported from 1946 to 2020, 58 could be attributed to polyphenol-rich foods (Hahn et al., 2017). It has been stated that certain foods are particularly involved in causing fetal DA constriction; these are mate tea, black tea, green tea, other homemade teas, black chocolate, black coffee, grape and its derivatives, orange, tangerine, red fruits, olive oil, and soybeans (Zielinsky et al., 2013). Specific associations have been made between premature constriction of the ductus arteriosus and excessive maternal intake of certain foods or beverages, particularly oranges (but notably not grapes) and chamomile tea.

Notably, a number of studies have demonstrated that inhibition of maternal PRF intake during the final third trimester can reverse fetal ductal constriction and its hemodynamic effects (Zielinsky et al., 2012; Zielinsky et al., 2021). An open clinical trial showed that when the third trimester of maternal consumption of polyphenol-rich foods was restricted for at least 2 weeks, there were improvements in fetal ductus arteriosus flow dynamics and dimension of the right ventricle (Zielinsky et al., 2012). The reversal of fetal ductal constriction after reducing polyphenol consumption was associated with an increase in plasma levels of prostaglandin E2 (PGE2) (Zielinsky et al., 2021). This observation strongly supports the hypothesis that polyphenols, similar to NSAIDs, interfere with prostaglandin synthesis or metabolism, as PGE2 is necessary for the ductus arteriosus in the fetus to stay open (Koren et al., 2006). Its mechanism is thought to be an inhibition of the prostaglandin metabolic pathway, particularly COX-2, leading to blockage of conversion of arachidonic acid to prostaglandin (Zielinsky and Busato, 2013). Some polyphenols, like quercetin and kaempferol, have demonstrated anti-inflammatory and antinociceptive effects that are comparable to or even stronger than those of indomethacin, a nonsteroidal anti-inflammatory drug (NSAID) known to cause constriction of the ductus arteriosus (DA) (Sadhu et al., 2006; Küpeli and Yesilada, 2007; Küpeli et al., 2007). These effects occur by blocking or altering the production of arachidonic acid and prostaglandins, especially prostaglandin E2 (PGE2). Nitric oxide (NO), another or a coexisting pathway of polyphenol-induced vasoconstriction, is also included as one of the second messenger pathways. High polyphenol intake in pregnant sheep also resulted in lower serum nitric oxide levels, which were associated with constriction of the ductus arteriosus. This may indicate that the polyphenols induce vasoconstriction via epicardial NO-mediated vasodilatation (Bubols et al., 2014).

Fetal sequelae to high maternal PRF ingestion and subsequent DA constriction are dilation, increased ductal systolic and diastolic velocities, a decrease in the pulsatility index, and dilation of the right ventricle. Hemodynamically significant premature Constriction of

the DA in its severe form can also lead to right ventricular hypertension and tricuspid regurgitation. Overall, these data emphasize a potential adverse effect of polyphenol intake, especially during late pregnancy (Zielinsky and Busato, 2013; Hahn et al., 2017; Zielinsky et al., 2013).

In addition to late pregnancy effects, there may be adverse effects of polyphenols on early pregnancy events. It has been reported in in vitro and animal studies that dietary polyphenols, particularly in high concentrations, could have adverse effects on fetal development and pregnancy outcome through effects on early gestation events (Nacka-Aleksić et al., 2022). This includes the possibility of affecting endometrial receptivity, embryo development/survival, and processes of implantation and placentation (Shahzad et al., 2017). Mechanisms are assumed, in part, through interference with the inflammatory cascade, inhibition of COX-2 activity, suppression of the NF-κB signal transduction pathway, and/or embryotoxicity (Karunaweera et al., 2015; Khan et al., 2020). For instance, curcumin at high concentrations has been proposed to be a teratogen by evoking a pro-apoptotic mechanism and inducing ROS production in early embryos (Chen and Chan, 2012; Huang et al., 2013). Experiments at a very high dose induced uterine receptivity molecules and sex steroid levels in rats and induced neural tube defects and other injuries in mouse embryos (Shahzad et al., 2017; Pérez-Pastén et al., 2010). Naringenin and a Ginkgo biloba extract component also slowed growth and caused developmental abnormalities in mouse embryos in culture (Chan, 2006).

It is important to note that specific inflammatory and redox signaling pathways establish pregnancy, and any intervention that interferes with these pathways in early pregnancy may be detrimental.) Medium levels of ROS, for example, have been shown to promote processes in early pregnancy such as decidualization, embryogenesis, trophoblast invasion, and vascular remodeling (Wu et al., 2015; Huppertz et al., 2009; Pereira et al., 2015). Scavenging ROS during placentation in mice compromised trophoblast invasion and placental development, causing PE-like symptoms (Yang et al., 2021). This emphasizes the fine balance that there is and the potential for excess polyphenol intake, for instance through supplementation which can provide 100-fold higher amounts than the typical western diet, to disrupt these critical early stages (Mennen et al., 2005).

Finally, the potential that polyphenols might in some way perturb subsequent fetal developmental trajectories via epigenetic mechanisms (such as DNA methylation) is suggested. Although some epigenetic modifications may be beneficial or adaptive, such pleiotropic effects may be deleterious. These points are currently studied using animal models (Rigacci and Stefani, 2016; Chango and Pogribny, 2015).

Proposals for Future Research

Although it is certain that polyphenols certainly have effects on human health (Table 1), some issues remain to be addressed to make clear what the role of polyphenol consumption during pregnancy is:

Table 1 Polyphenol Overview

Key Point	Explanation
Polyphenol Overview	Polyphenols are natural plant-derived compounds, that contain at minimum two phenyl rings and one or more hydroxyl groups.
Dietary Sources	Found in fruits (berries, grapes, oranges, and red fruits) and vegetables, teas, coffee and dark chocolate products, nuts, soybeans, and olive oil.
Mechnism of Action	Their mechanisms of action are primarily related to their antioxidant nature. They function as typical hydrogen- or electron-donating antioxidants; moreover, they also exhibit anti-inflammatory properties.
Benefits	Diet rich in polyphenols improves blood pressure management in preeclampsia and glycemic control in gestational diabetes. Furthermore decreases risk of maternal obesity and cardio-metabolic diseases.
Disadvantages	In studies, high polyphenol intake in the third trimester of pregnancy may have been associated with ductus arteriosus constriction and could have adverse effects on fetal development and pregnancy outcome through effects on early gestation events.
Unresolved Issues	More research is needed on supplementation guidelines, their influence on early pregnancy events, long-term effects, and transgenerational health.

Clinical effectiveness and safety in pregnancy disorders: Despite promising preclinical results and limited clinical trial data,there is a significant need for more high-quality, adequately powered randomised controlled trials to evaluate the clinical effectiveness and safety of specific polyphenol supplements and extracts for preventing and treating preeclampsia and gestational diabetes in humans. Ideally, interventions should take place earlier in pregnancy (i.e., earlier than 12 weeks) to evaluate a possible preventive effect on preeclampsia. The risk of adverse effects and organ toxicity must be carefully evaluated in GDM trials

Dose-response and safety studies: We need to carefully study how different doses of polyphenols affect safety and effectiveness during pregnancy. Considering the potential risks posed by high doses—particularly from supplements that can significantly exceed normal dietary levels—comprehensive safety assessments must precede nutritional recommendations for pregnant women.

Influence on early pregnancy events: More in vivo research is needed to clarify the conflicting data on the effects of polyphenols on oocyte maturation, fertilization, embryonic development, implantation, and placentation, as well as to help translate findings from animal models to humans when possible.

Long-term effects and transgenerational health: Understanding the lasting impact of maternal polyphenol consumption on offspring health is critical. These include the mechanism of effect on the offspring's metabolic risk (e.g., by CKM syndrome) and on neurodevelopmental outcomes.

4. CONCLUSION

Undoubtedly, polyphenol intake during pregnancy influences its course. A diet rich in polyphenols may contribute to the reduction of gestational hypertension and hypertensive crises in preeclampsia. Their beneficial effects on the course of gestational diabetes have also been demonstrated. Moreover, the consumption of these phytochemicals may help prevent maternal obesity and cardiometabolic diseases. Unfortunately, any substance in excessive amounts can become a poison. Studies have shown that excessive consumption of polyphenol-rich products in the third trimester of pregnancy may cause constriction or closure of the ductus arteriosus, which in the worst-case scenario can even lead to fetal death. Fortunately, this phenomenon appears to be reversible through dietary modification. In addition, high concentrations of polyphenol derivatives in early pregnancy may impair implantation and exert pro-apoptotic or teratogenic effects; however, these issues require further investigation. Since polyphenols are widely present in our daily diet, no safe intake guidelines have been established yet during pregnancy. One thing is sure: clinicians should be aware of the risks associated with excessive polyphenol consumption, particularly in the third trimester, and advise their pregnant patients accordingly.

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Informed consent

Not applicable.

Ethical approval
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Conflict of interest
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Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author

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