Review Article
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Effect of polyphenols and maternal-fetal complications: a systematic review

Abstract

Maternal nutrition is a crucial and modifiable environmental factor that influences both short-term and long-term health outcomes for mothers and their offspring. Consequently, the increasing consumption of natural products during pregnancy warrants special attention due to the complexity of the largely unknown processes underlying maternal adaptation and fetal development. This study aimed to perform a systematic review of the consumption of polyphenols during pregnancy and its association with maternal-fetal complications in animal models. A systematic search was conducted in databases (PubMed, Scopus, and Web of Science), using the MeSH terms: Polyphenols, Pregnancy, and Pathology, without filters. The outcomes selected included fetal malformations, interruptions in fetal and maternal thyroid activity, increased adiposity, abnormalities in serum vascular endothelial growth factor levels, and changes in urea, creatinine, and cystatin C levels, which negatively affected the cellularity of the spleen and the formation of its progeny. Male fetuses exhibited worse developmental patterns compared to the control group and their littermates, along with a significant increase in urea and creatinine levels. This systematic review suggests that the consumption of polyphenols may increase the risk of adverse maternal-fetal outcomes in animal models. Further studies are needed to elucidate the effects of polyphenol consumption and its potential impact.

Keywords: pregnancy, polyphenols, pathology, nutricion, pregnancy complications

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Introduction

Maternal nutrition is an essential and modifiable environmental factor that influences short- and long-term maternal and offspring health.[1] Therefore, the increasing consumption of natural products during pregnancy requires special attention, considering the complexity of the largely unknown processes underlying maternal adaptation and fetal development.[2] In the present study, we sought to verify whether there are harmful effects of polyphenol consumption during pregnancy. The most studied polyphenols and their relationship with pregnancy are: caffeine, hydroxytyrosol, procyandin, polyphenol from the African fruit *Treculia africana*, proanthocyanidin, and Epigallocatechin.[3–10] Polyphenols or phenolic compounds are several groups of molecules found in vegetables, fruits, teas, coffee, wines and soy. The chemical structure of polyphenols is simply derived from benzene attached to a hydrophilic group and depending on their structure the polyphenolic rings bond to each other they are classified into four categories: flavonoids, phenolic acids, lignans and stilbenes. They are known for their biological activities such as scavenging oxygen radicals and modulating enzymatic activities, in addition to having potential antibiotic, antiallergenic and anti-inflammatory action.[11] The consumption of these polyphenols may not always have positive effects during pregnancy and should be consumed with caution, studies have already suggested significant changes in pregnancy such as fetal, visceral and skeletal malformations, interruption in fetal and maternal thyroid activity, increased adiposity, morphometric abnormalities in the structure of the kidneys, abnormalities in the serum vascular endothelial growth factor, alteration in the tumor necrosis factor (TNF) -alpha, and in the levels of urea, creatinine and cystatin C, these negatively influenced the spleen cellularity and the formation of their progeny when studied in animals.[3–10] The objective of this systematic review was to verify whether the consumption of polyphenols during pregnancy can lead to maternal-fetal complications in animal models.

Methods

Protocol and registration

The protocol for this systematic review was developed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. Additionally, this review has been registered in the PROSPERO Systematic Review Registry with the record ID CRD42020210553.

Search strategy and eligibility criteria

To identify studies potentially relevant to the present review, a systematic literature search in databases (PubMed, Scopus and Web of Science) was performed, according to the MeSH terms: Polyphenols, Pregnancy and Pathology. All terms were searched in the title, abstract and keyword. No restrictions were applied regarding language or publication date. Inclusion criteria were related to animal study, polyphenol supplementation, pregnant animals, assessment of maternal and/or fetal outcomes, controlled intervention, negative outcomes, and description of possible negative outcomes. Exclusion criteria were selected based on human studies, in vitro studies, reviews, books, letters, meta-analyses, risk of pregnancy, and positive outcomes.

Selection of studies

The articles were classified in two phases. First, duplicate and triplicate articles were removed. In the first phase, two reviewers (M.C.V. and I.M.) independently analyzed the titles and abstracts in the electronic database and selected the articles that appeared to be potentially eligible. In the second phase, two reviewers (M.C.V. and I.M.) independently analyzed and read the full text of each article selected in the first phase, excluding all articles that did not meet the eligibility criteria. At all stages, a third reviewer (K.K.P.)

was consulted in case of doubts or disagreements among the other researchers, and conflicts were resolved by the third reviewer and by consensus.

Data extraction

Data extraction was independently carried out by four authors. All data were entered and recorded in a *Microsoft Excel spreadsheet,* which was specifically designed for this purpose. Data from each study were added and organized by categories to ensure consistency in the extraction process. Periodic meetings were held to maintain the standard of analysis. The extracted data included: article identification, population (animal, sample size, and general characteristics), characteristics of the intervention (source of polyphenols, route of administration, and exposure time), control, objective, and main results.

Risk of bias assessment and assessment of methodological quality

The tool used to assess risk of bias and quality of evidence was SYRCLE's, that assesses the risk of bias for animal studies.[12] This tool contains the following assessment categories: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Ten questions are applied to articles included in the systematic review, whose answers can be "YES", which indicates low risk of bias, "NO", which indicates high risk of bias, and "UNCERTAIN", which indicates risk of bias. uncertain. The questions domains are (1) allocation; (2) similarity; (3) concealment; (4) housing; (5) blinding; (6) selection; (7) assessor blinding; (8) Completeness; (9) Reporting; (10) Integrity. It is not recommended to calculate the sum score.[12]

Results

Study selection

The electronic search through databases and registers led to the identification of 578 records. After removing 14 duplicate records, 564 studies were screened for relevance. This initial screening resulted in the exclusion of 524 records for various reasons, leaving 40 studies to be assessed for eligibility. Upon further review by the assessment team, 40 studies were excluded because they did not meet the predefined criteria for inclusion in the systematic review. Consequently, 8 studies were ultimately included in the review for qualitative synthesis (Figure 1).

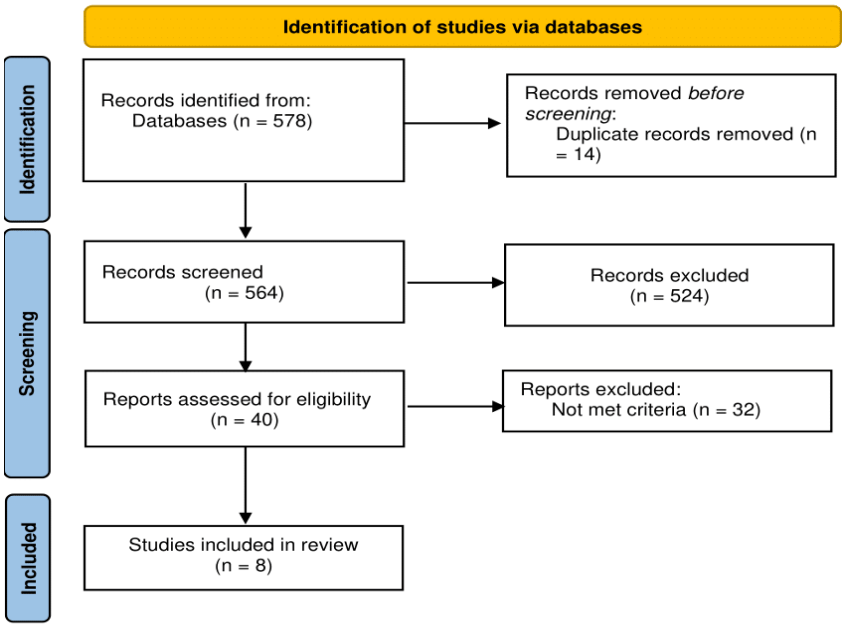

Figure 1 Flow diagram of the systematic review.[13]

Study characteristics

Among the studies included in the systematic review, a diverse range of interventions and populations were examined to understand the effects of polyphenols on animal models (Table 1). The review highlighted studies that utilized different forms and concentrations of polyphenols, including Treculia africana, caffeine, grape seed extract procyanidin, Rhodiola kirilowii extract, epigallocatechin, and hydroxytyrosol, showcasing the variety in experimental approaches. The exposure times varied significantly, ranging from the early gestational period to several weeks post-delivery, emphasizing the critical windows for potential polyphenol impact. The population studied predominantly consisted of female Wistar rats and mice, with sample sizes ranging from 13 to 90 maternal progenitors, indicating a wide spectrum of research scales. The routes of administration varied across studies, including subcutaneous injections, intraperitoneal injections, oral gavage, and dietary supplementation, reflecting the versatility in delivery methods employed in these experiments. Objectives across the studies were aimed at exploring the teratogenic effects, impact on maternal-fetal thyroid axis, metabolic programming in offspring, abnormalities in renal morphology or function, and effects on antioxidant status and fetal development. The outcomes focused on fetal malformations, disruptions in thyroid activity, alterations in adiposity and gene expression, renal morphometric abnormalities, and antioxidant capacity among others, offering a comprehensive overview of polyphenol effects. The main results on the qualitative synthesis included reductions in fetal body weight, induction of visceral and skeletal malformations, significant disruptions in thyroid activity, increased adiposity with better inflammatory profiles in offspring, and sex-dependent improvements in fetal antioxidant status.

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Table 1 Synthesis of experimental studies on the effects of polyphenol consumption during pregnancy on maternal-fetal health outcomes

Study	Population	Intervention			Control group	Objective	Main findings
		Polyphenol Source(concentration)	Route of administration	Exposure time			
3	90 female Wistar rats	Treculia africana (2.5 mg/kg/Body Weight (BW))	Subcutaneous	13 weeks (virgin rats) + 20 days (gestation)	Untreated animals and Group I (5% Protein (ptn) Diet) solvent injection	To know the teratogenic effects of polyphenol obtained from the outer layer of the fruit of T. africana when administered to pregnant rats with protein deficiency.	Polyphenol treatment in rats on both normal and reduced (5%) protein (ptn) diets significantly decreased fetal body weight ($p < 0.01$) and induced malformations, including hydrocephalus and anophthalmia, across various protein levels. Control groups on 10% and 5% ptn diets exhibited no fetal abnormalities. Treated groups I (5% ptn diet) and III (normal ptn diet) experienced significant increases in visceral anomalies, with rates of 12% and 30%, respectively.
4	24 pregnant Wistar rats	Caffeine (120 and 150 mg/kg/BW)	Intraperitoneal	Day 1 to day 20 of pregnancy	Sterile Distilled Water	To examine the impact of gestational caffeine administrations on the maternal-fetal thyroid axis and on the fetal thyroid-cytokine axis.	Both doses of gestational caffeine induced a significant disruption in thyroid activity in both mothers and their fetuses by the day 20 of gestation.
5	32 male rats (Offspring)	Grape Seed Extract Procyanidin (GSPE) (25mg/kg/BW)	Oral fed supplementation	Pregnancy and breastfeeding	Standard diet and high fat diet (HFD)	To evaluate low-dose GSPE supplementation during the pre- and postnatal period on the metabolism of their offspring in youth.	The treatment induced a clear effect of metabolic programming in the offspring, increasing adiposity, but also decreasing circulating levels of monocyte chemoattractant protein-1(MCP-1) and altering gene expression in epididymal white adipose tissue (EWAT) towards a better inflammatory profile.
6	20 pregnant Balb/c mice & 288 Offsprings	Rhodiola kirilowii extract 50% hydro-alcoholic (RKW-A) -proanthocyanidin (20 mg/kg/BW)	Oral Water-Mixed Feeding	From copulatory plug to the 28th day of the offspring's life	Distilled water	To analyze whether the daily diet of pregnant and lactating mice with RKW can lead to abnormalities in renal morphology or function in adult offspring.	Offspring of female mice fed with RKW-A had morphometric abnormalities in the structure of the kidneys as a significantly higher number of glomeruli/mm2 and a lower diameter of glomeruli compared to control. It was also found abnormalities in serum vascular endothelial growth factor, tumor necrosis factor (TNF)-alpha, urea, creatinine and cystatin C levels in relation to the control group.
7	124 Balb/c mice (Offspring)	Epigallocatechin (EGC) (0.2 mg/kg/BW)	Oral Water-Mixed Feeding	From copulatory plug to the 28th day of the offspring's life	Distilled water	To investigate the effect of epigallocatechin on spleen morphology and immune function parameters of the offspring of mice that were fed this compound during pregnancy and nursing.	Spleen morphometry in EGC treated offspring showed fewer, but larger, lymphatic nodules compared to control, along with reduced spleen cellularity. Cytometric analysis indicated a significant decrease in lymphocytes expressing CD335 (Natural Killer Cell Receptor, $p<0.001$), CD19 (B Cell Marker, $p<0.01$), and CD4 (T Cell Marker, $p<0.05$) markers in EGC offspring. No differences in antibody production following immunization with Sheep Red Blood Cells (SRBC) or in the splenocytes' proliferative response to mitogens Phytohemagglutinin (PHA), Concanavalin A (ConA), and Lipopolysaccharide (LPS).

Table 1 Continued...

Study	Population	Intervention			Control group	Objective	Main findings
		Polyphenol Source(concentration)	Route of administration	Exposure time			
8	13 primiparous Iberian sows	Hydroxytyrosol (1.5 mg/kg/feed)	Oral Food-Mixed Feeding	From day 35 to day 100 of pregnancy	Standard grain-based diet	To determine the possible effects of maternal supplementation with hydroxytyrosol on placental expression of genes involved in antioxidant homeostasis, vascularization and fetal growth and, therefore, on antioxidant status, DNA methylation and phenotypic characteristics (morphology and homeostasis) of the fetus.	Hydroxytyrosol during pregnancy improved fetal antioxidant status, placental gene expression and glucose metabolism in a sex-dependent manner, which males were favored. However, these male fetuses showed worse developmental patterns when compared to control counterparts and female littermates. DNA hypomethylation associated with oxidative stress was prevented by hydroxytyrosol without sex-related effects.
9	96 pregnant Balb/c mice	Rhodiola kirilowii aqueous and hydroalcoholic extracts (20mg/kg/BW)	Oral Food-Mixed Feeding	From copulatory plug to the 28th day of delivery	Distilled water	To establish whether aqueous and hydro-alcoholic R. kirilowii extracts given to pregnant mice changed the course of pregnancy and the number of progenies.	The addition of RKW or RKW-A extract did not alter the duration of pregnancy. Concurrently, both RKW and RKW-A extracts significantly increased the number of mated females that did not produce offspring, but neonatal deaths within the first 5 days after delivery were observed only in the RKW-A group.
10	40 pregnant albino rats (10 for each group) & 40 Offsprings	Caffeine (80mg/kg/BW)	Oral gavage	From the first day of pregnancy to the 30th of lactation	Distilled water	To evaluate the effect of maternal exposure to caffeine and the sweetener aspartame during pregnancy and lactation on the development of the kidneys of the offspring of rats.	Caffeine group showed a significant increase in Malondialdehyde (MDA) levels accompanied by a significant decrease in Glutathione (GSH), Superoxide Dismutase (SOD), and Glutathione Peroxidase (GSHPx) levels when compared to the control group. Caffeine group also exhibited a significantly higher increase in urea and creatinine levels ($p < 0.001$) when compared to the control and combined group (caffeine + aspartame)

BW, body weight; CD19, B-cell Marker; CD335, natural killer cell receptor; CD4, T-cell marker; ConA, Concanavalin A; EGC, epigallocatechin; EWAT, epididymal white adipose tissue; GSPE, grape seed extract procyanidin; HFD, high fat diet; LPS, lipopolysaccharides; MCP-1, monocyte chemoattractant protein-1; PHA, phytohemagglutinin; Ptn, protein; RKW, rhodiola kirilowii Extract; RKW-A, rhodiola kirilowii extract 50% hydro-alcoholic; SRBC, sheep red blood cells; TNF, tumor necrosis factor

Assessment of risk of bias

Using SYRCLE's Risk of Bias tool for assessment, Table 2 provides a detailed overview of potential biases in the selected studies. In general, the studies exhibited a low risk of bias in several critical areas, notably in maintaining baseline characteristics between groups (marked with a positive sign) and in selective outcome reporting. Most studies managed to ensure similarity at baseline and integrity in reporting outcomes, indicating conscientious efforts to mitigate biases that could affect the study outcomes significantly. However, there were notable gaps in the reporting and management of other biases. A common trend across the studies was the unclear or unreported methods of sequence generation and blinding procedures, which raises questions about the allocation concealment and the potential for performance bias. Additionally, few studies provided detailed information on allocation concealment, random housing, and random outcome assessment, which are crucial for preventing selection bias and ensuring the reliability of the results. The blinding of researchers and outcome assessors was another area where information was frequently missing or unclear. Despite these concerns, the overall assessment suggests that the main variables with the potential to significantly compromise study quality were adequately controlled in most studies. The less well-controlled variables, according to the analysis, have a comparatively lesser impact on animal studies. Consequently, it was considered that the quality of the selected studies to be reasonably intact, with a low overall risk of bias.

Table 2 Risk of bias

Risk of bias (SYRCLE's tool)										
Study	**SB**			**PB**		**DB**		**AB**	**RB**	**O**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
3	?	+	?	+	?	?	+	?	?	?
4	?	+	?	+	?	?	+	+	-	+
5	?	+	?	+	?	?	+	+	-	+
6	?	+	?	+	?	?	+	?	+	-
7	?	+	?	+	?	?	+	?	+	?
8	?	+	?	+	?	?	+	+	+	?
9	?	?	?	+	?	?	+	+	+	+
10	+	+	+	+	-	+	+	+	+	+

Discussion

The eight articles selected through the inclusion and exclusion criteria were articles dated between 1997 and 2020, with an intervention group which received the polyphenol, and a control group, which received a placebo. In total, 449 females were used to gestate. In all studies, females received the intervention during pregnancy, most of them from the first day of pregnancy, the most frequent polyphenols were caffeine and the proanthocyanidin provided by *Rhodiola kirilowii*.[3,4,6,10] Polyphenol source, concentration and exposure period varied according to each article.

The results obtained after research in the main databases show that the consumption of polyphenols during pregnancy in animals showed that they can cause different fetal complications, namely: Fetal, visceral and skeletal malformations, interruption in fetal and maternal thyroid activity, increased adiposity, morphometric abnormalities in the structure of the kidneys, abnormalities in serum vascular endothelial growth factor, tumor necrosis factor (TNF)-alpha, urea, creatinine and cystatin C levels, negatively influenced spleen cellularity and architecture. of your progeny. Male fetuses showed worse developmental patterns when compared with the control group and littermates, affecting litter size causing a significant increase after *Rhodiola kirilowii* supplementation as well as the number of childless females and a significant increase after supplementation of both extracts. There was also a significant increase in urea and creatinine levels.

Dietary composition is a very important factor in the gestational period, since it influences the development of the fetus. In this sense, a study was conducted to investigate the teratogenic effects of polyphenol obtained from the outer layer of the fruit of *Treculia africana*, when administered to pregnant Wistar rats with protein deficiency.[3] Thus, the animals were divided into three groups: group I, which received a 5% protein diet for 4 weeks, followed by a normal protein diet for the remainder of the experimental period; group II, who received a 10% protein diet throughout the experimental period; and group III, animals fed a normal protein diet containing 27% casein during the entire experimental period. When sexual maturity was reached, the rats were mated with mature males of the same lineage. On the 6th day of pregnancy, the rats that became pregnant received a subcutaneous injection containing 2.5 mg/kg/BW/day of polyphenol, obtained from the outer covering of the fruit of *T. africana.* As main findings, the study suggests that dietary protein deficiency may increase the animal's susceptibility to the teratogenic effects of polyphenol obtained from the outer layer of the *T. africana* fruit, with emphasis on the impairment of skeletal development. Furthermore, it was observed that rats fed a normal protein diet treated with polyphenol showed a significant increase in the percentage of fetal resorptions, a corresponding decrease in the percentage of live fetuses and a depression in fetal body weight when compared to the corresponding controls. Polyphenol induced several malformations such as visceral and skeletal in all three groups fed different levels of protein.[13] The study, conducted by Ahmed, RG et al, showed the impact of administration of gestational caffeine at a dose of 120 or 150 mg/kg body weight/day in rats on the maternal-fetal thyroid axis during pregnancy. Both doses of gestational caffeine induced a significant dysregulation in the thyroid activity of mothers and their fetuses.[4] A study that used caffeine supplementation at doses of 12.5, 25 and 50 mg/kg/BW/day in broilers also found a reduced ratio of T3 and T4 after 42 days, this study by Kamely et al. also showed a correlation negative difference between thyroid hormone concentrations and birth weight on day 42 ($p<0.05$).[14]

The use of caffeine (60mg/kg/BW/day) in pregnant Wistar rats resulted in an increase in the expression of interleukin (IL)-1β, IL-8, IL-6 and TNF-α in the offspring's lungs, suggesting that the Caffeine intake harms offspring.[15] However, another study by Ahmed, R.G. et al showed that caffeine use decreased serum levels of TNF-α, IL-1β, IL-6, leptin and MCP-1.[4] According to the study by del Bas et al, the use of grape seed procyanidin extract (GSPE), being 20mg/kg/BW/day, obtained significant results in the group that consumed a high fat diet (HFD) and GSPE, thus exhibiting greater adiposity and body weights in addition to different white adipose tissue deposits than HFD animals.[5] Contrasting this result, the study by Caimari et al., supplementation with GSPE at (25mg kg of weight/day) for 15 days concluded that the use of GSPE at low doses protects against fat accumulation and improves the plasma lipid profile in hamsters, for this reason it can be understood that the use of GSPE did not bring significant benefits in the accumulation of fat in the offspring, when supplemented in the mothers.[16] In the same study plasma levels of MCP-1 and glycerol were significantly decreased in HFD-GSPE animals compared to those in the HFD group. In view of these results, an in vitro study by Chacón et al suggested that the use of GSPE used in human adipocytes (SGBS) and macrophage-like cell lines (THP-1) modulated the gene expressions of the cytokines IL-6 and MCP-1, also reducing its gene expression, consonant with the work of del Bas et al.[5,17]

In the study by Lewicki et al. a dosage of 20 mg/kg/BW/day per day in intervention groups of mice, the significant results were the composition of polyphenols in the serum of mice, salidroside and kaempferol, from the groups *Rhodiola kirilowii* aqueous (RKW) and 50% hydroalcoholic RKW-A ($p<0.05$), intervention groups, results that were similar to the Zdanowski et al. study where chemical analysis revealed higher concentrations of salidroside and kaempferol in pregnant Balb/c mice, using the same dosage as in the study by Lewicki et al.[6,18] The study by Bałan et al. showed changes in rats born

to mothers fed epigallocatechin during pregnancy [7]. A great similarity was observed in another study by Bałan et al. 2017, who supplemented 8 female Balb/c strain rats with cranberry extract (44mg/kg/BW/day), from the day of copulation to the 28th day postpartum of the offspring.[7] The results corroborate the lack of macroscopic alterations in the anatomy of the spleen, in the presence of lymph nodes in smaller numbers and larger diameters ($p<0.01$), in contrast, observed decreased white pulp. Significantly decreased cellularity of mothers' spleens ($p<0.01$) was observed by Lewicki et al. who supplemented 128 adult female inbred rats of the Balb/c strain with alcoholic and aqueous *Rhodiola kirilowii extract* (20mg/kg/BW/day) for the same period as the afore mentioned study.[19]

Supplementation of the maternal diet of hiberian sows with hydroxytyrosol at a dose of 1.5 mg/kg/BW/day resulted in fetuses with lower mean body weight ($p<0.05$).[8] The present study by Garcia-Contreras et al. demonstrated that the group supplemented with hydroxytyrosol had an increase in methylation compared to the control group, and the intervention group also avoided the hypomethylation of DNA Deoxyribonucleic Acid associated with oxidative stress, corroborating this finding, a study with wild mice showed that hydroxytyrosol is an efficient maternal nutrient that protects neurogenesis and cognitive function in prenatally stressed offspring, in addition, oxidative stress and mitochondrial dysfunction in prenatally stressed mice were confirmed with alterations in protein oxidation, SOD activity, expression of mitochondrial complexes and mitochondrial DNA copy number.[20] The study by Zdanowski et al evaluated the consumption of *Rhodiola kirilowii Crassulaceae* (RWA) at a dose of 20 mg/kg/day in pregnant mice. The mice in the intervention group, that is, those that consumed RKW had a longer pregnancy time, being abnormal (42 days). The progeny (2 mice) survived for only four days and significantly increased the number of females mated without offspring ($p<0.05$). The hydroalcoholic extract of *Rhodiola kirilowii* caused a significant increase in litter size compared to the group that received RKW ($p<0.01$).9 Converging with this finding, another study using the same dose in BALB mice demonstrated that there is no toxic effect for pregnant women in animals.[21] In another landmark study looking at the effect of caffeine, 63 pregnant women who drank one cup of instant coffee a day showed that after coffee consumption, the amniotic fluid index significantly increased six hours after ingestion ($p<0.01$).[22] Contributing to this finding, a study that evaluated pregnant Wistar rats administered caffeine at a dose of 30 to 120 mg/kg/day, during the 9th and 20th day of gestation, showed that caffeine consumption induces toxicity in the development of glomerular podocytes in male offspring, leading to a marked decrease in nephron protein expression.[23]

Conclusion

This systematic review concludes that the consumption of polyphenols can lead to negative maternal-fetal outcomes in animal models. Among the primary outcomes observed were fetal, visceral, and skeletal malformations; disruptions in fetal and maternal thyroid activity; increased adiposity; and morphometric abnormalities in kidney structure. Additionally, abnormalities in serum vascular endothelial growth factor, tumor necrosis factor (TNF)-alpha, urea, creatinine, and cystatin C levels were found to adversely affect spleen cellularity and the architecture of offspring in animal studies. However, the existing published studies are limited and call for further research with improved intervention methodologies. Thus, more studies are necessary to explore the negative impacts of polyphenol consumption during pregnancy on maternal-fetal health in animals and, potentially, to examine the effects in humans.

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Conflicts of interest

The author declares that there is no conflicts of interest.

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