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TRABALHO DE CONCLUSÃO DE CURSO:

Efeito dos polifenóis e complicações materno-fetais: uma Revisão Sistemática

PORTO ALEGRE
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Orientadora: Dra Simone Morelo Dal Bosco

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PORTO ALEGRE

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Sumário

Siglário

TNF: tumor necrosis factor

PICO: Population, Intervention, Comparison, Outcomes

TSH: thyroid stimulating hormone

TGF-β: Transforming growth factor beta

qPCR: Real Time Quantitative PCR

GH: Growth Hormone

IGF-II: Insulin Like Growth Factor 2

VEGF**:** Vascular endothelial growth fator

MCP-1: monocyte chemoattractant protein-1

RKW: Rhodiola kirilowii aqueous

EGC: higher glomeruli diameter (EGC)

RKW-A: Rhodiola kirilowii 50% hydro-alcoholic

SRBC: sheep red blood cells

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Efeito dos polifenóis e complicações materno-fetais: uma Revisão Sistemática

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

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We declare that there is no funding for this study.

Resumo

Objetivo: realizar uma revisão sistemática para verificar a influencia da ingestão dos polifenóis na gestação em animais e as complicações materno-fetais que podem ocorrer.

Métodos: Foi realizada busca sistemática da literatura em bases de dados (PubMed, Scopus e Web Of Science), com os termos MeSH: Polyphenols, Pregnancy and Pathology, sem uso de filtros. Foram incluídos estudos em animais, suplementação de polifenóis, animais prenhes, avaliação de desfechos maternos ou fetais, ensaios clínicos e intervenção controlada, desfechos negativos. exclusão: estudos em humanos, estudos in vitro, revisão sistemática, livros, cartas, metanálises, risco de gravidez, resultados positivos. Após a seleção, 8 artigos foram elegíveis para revisão. Os dados principais dos artigos foram extraídos em uma tabela de resultados.

Resultados: Malformações fetais, interrupção da atividade tireoidiana fetal e materna, aumento da adiposidade, anormalidades no fator de crescimento endotelial vascular sérico, alterações nos níveis de uréia, creatinina e cistatina C, que influenciaram negativamente na celularidade do baço e na formação de sua progênie . Os fetos do sexo masculino apresentaram piores padrões de desenvolvimento quando comparados ao grupo controle e irmãos da mesma ninhada. Houve também um aumento significativo nos níveis de ureia e creatinina.

Conclusões: Esta revisão sistemática sugere que o consumo de polifenóis pode ter resultados materno-fetais negativos em modelos animais. Mais estudos são necessários para elucidar o consumo de polifenóis e seus possíveis efeitos.

Summary

Objective: To realize a systematic review to verify the influence of polyphenol ingestion during pregnancy in animals and the maternal and fetal complications that could occur.

Methods: A systematic literature search was carried out in databases (PubMed, Scopus and Web Of Science), with the MeSH terms: Polyphenols, Pregnancy and Pathology, without using filters. Animal studies, polyphenol supplementation, pregnant animals, assessment of maternal or fetal outcomes, clinical trials and controlled intervention, negative outcomes were included. Exclusion: human studies, in vitro studies, systematic review, books, letters, meta-analyses, risk of pregnancy, positive results. After selection, 8 articles were eligible for review. The main data of the articles were extracted into a table of results.

Results: Fetal malformations, interruption in fetal and maternal thyroid activity, increased adiposity, abnormalities in serum vascular endothelial growth factor, changes in urea, creatinine and cystatin C levels, which negatively influenced in the cellularity of the spleen and in the formation of its progeny. Male fetuses showed worse developmental patterns when compared to the control group and littermates. There was also a significant increase in urea and creatinine levels.

Conclusions: This systematic review suggests that the consumption of polyphenols may have negative maternal-fetal outcomes in animal models. More studies are needed to elucidate the consumption of polyphenols and their possible effects.

Palavras-chave

Gestação, Polifenóis, Patologia, Nutrição, Complicações gestacionais, Complicações Fetais

Keywords

Pregnancy, Polyphenols, Pathology, Nutricion, Pregnancy Complications, Fetal Complications.

Introduction

Maternal nutrition is an essential and modifiable environmental factor influencing 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) The most studied polyphenols and their relationship with pregnancy are caffeine, hydroxytyrosol, procyandin, polyphenol from the African fruit Treculiaafricana, proanthocyanidin and Epigallocatechin.

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. 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.(3)

The consumption of these polyphenols can 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.(4 - 11) The aim of this work was to realize a systematic review to verify the influence of polyphenol ingestion during pregnancy in animals and the maternal and fetal complications that could occur.

Methods

Protocol and Registration

The systematic review protocol was reported in accordance with the Protocol of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P), where the current review was registered in the Internacional Prospective Record of Systematic reviews (PROSPERO), under the number of 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 until May 2021, according to the DeCS/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. The PICO (Population, Intervention, Comparison, Outcomes) criteria used to define our research question are summarised in Table 1.

Table 1. PICO criteria employed to define our research question.

Criteria	**Description**
Participants	Pregnant healthy animals
Intervention/exposure	Oral supplementationwith polyphenols
Comparisons	Inert placebo / control
Outcome	Different maternal and fetal complications

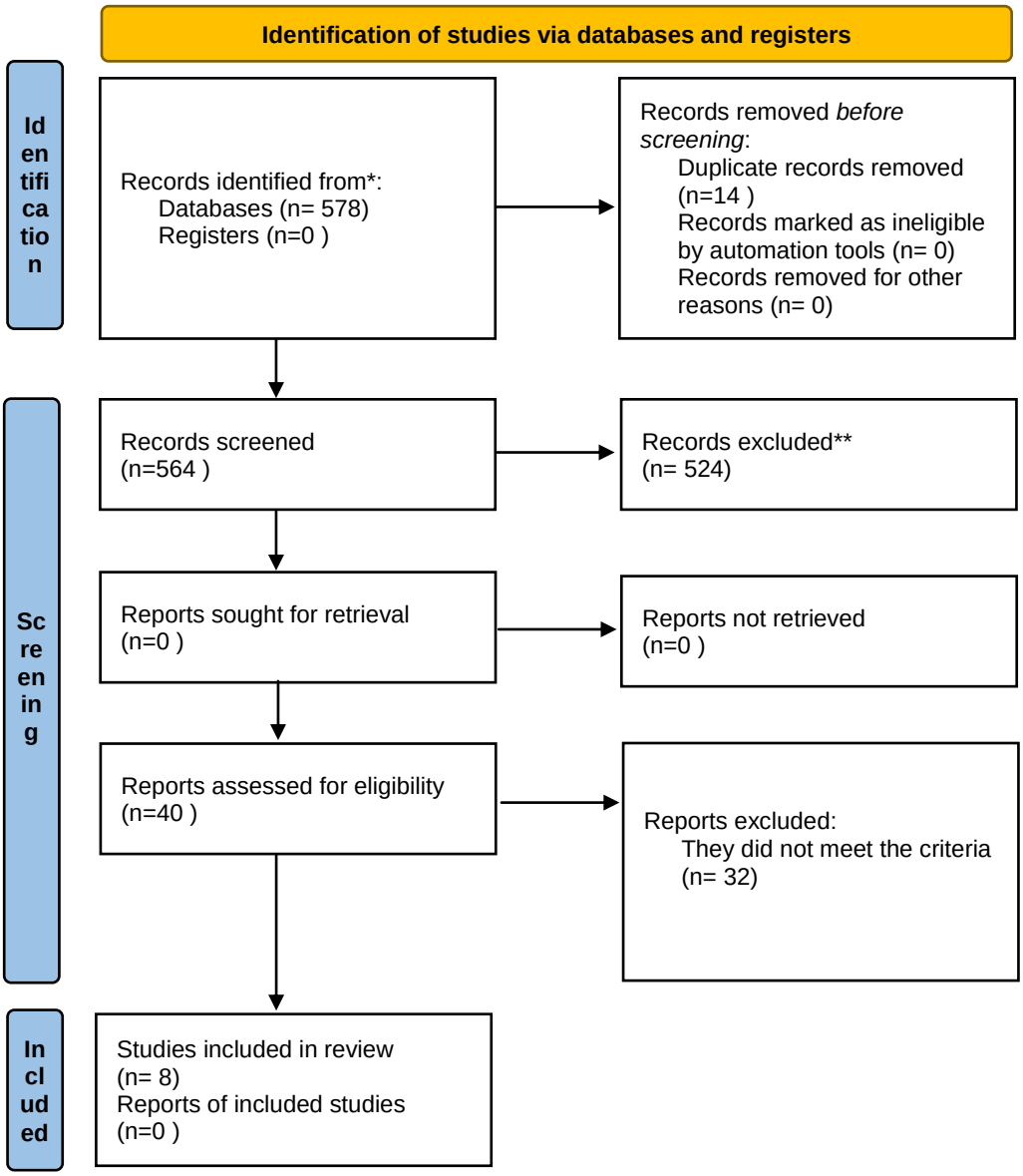
Inclusion criteria were: animal study, polyphenol supplementation, pregnant animals, assessment of maternal and/or fetal outcomes, controlled intervention, negative outcomes, and description of possible negative outcomes.

Exclusion criteria were: human studies, in vitro studies, systematic reviews, books, letters, meta-analyses, risk of pregnancy, and positive results.

Selection of studies

The articles were classified into 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. (Figure 1)

Figure 1 – Flowchart



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Data extraction

Data extraction was independently completed by four authors. All were placed and recorded in a Microsoft Excel spreadsheet designed for specific purposes, where data from each study was added and organized by various categories in order to maintain a standard in the extraction of data from the studies. Meetings were held periodically to maintain the standard of analysis. The data extracted from the articles were: article title, authors, year of publication, study objective, population (type of animal), dose, control, polyphenol, route of administration, time of administration, outcomes, and results. (Table2)

Results

Table 2 - Design characteristics of the included stu

Table 2. Table 2 - Design characteristics of the included studies.

Study	Population	Intervention groups	Control group	Route of administration	Exposure time	Objective	Outcome	Relevant results
Lawal, R. O. (1997Nigeria)	90 female Wistar rats	1 ml/100 g of body weight (2.5 mg/kg of Treculiaafricana)	Untreated animals + G1 animals: injections with appropriate volume of solvent	Subcutaneous injections	13 weeks (virgin rats) + 20 days (gestation)	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	Fetal, visceral and skeletal malformations	Polyphenol-treated animals maintained on a normal protein diet and a 5% normal protein diet had statistically significant reductions in fetal body weight compared to the respective controls ($p < 0.01$). Polyphenol induced several gross, visceral, and skeletal malformations in rat fetuses maintained at different protein levels. None of the control rat fetuses maintained on a 10% protein diet and a 5% normal protein diet showed any malformations. The main malformations after treatment with polyphenol were hydrocephalus and anophthalmia. Rat fetuses from treated animals in groups I and III showed significant increases in the percentage of visceral anomalies (12% and 30%, respectively).
Ahmed, R.G. et al (Egypt, 2019)	24 pregnant Wistar rats (Rattus Norvegicus)	Caffeine 120 and 150 mg per kg	Sterile Distilled Water	Intraperitonial	From day 1 to day 20 of pregnancy	To examine the impact of gestational caffeine administrations on the maternal-fetal thyroid axis and on the fetal thyroid-cytokine axis	Thyroid activity. Both doses of gestational caffeine induce a significant disruption in thyroid activity in both mothers and their fetuses by day 20 of gestation. .	Caffeine significantly increased serum free triiodothyronine (FT3) and free thyroxine (FT4) levels and decreased thyroid stimulating hormone (TSH) ($p<0.01$) in mothers. Mothers showed an increase in body weight and food consumption ($p<0.01$). Serum FT4 and FT3 levels and fetal body weight decreased in both supplemented groups and TSH levels increased ($p<0.01$). QPCR analysis showed activation of BAX, Bcl-2, Cox2 expression, NF-κB, and caspase-3 in the fetal thyroid gland ($P < 0.01$). The use of caffeine decreased levels of fetal serum GH, IGF-II, VEGF, TGF-β, TNF-α, IL-1β, IL-6, leptina, and MCP-1 and increased the level of adiponectin ($p<0.01$).

Del Bas, J M (Spain, 2014)	32 mice	Grape Seed Extract - Procyanidin (GSPE) - (25mg/kg bodyweight/day)	Standard diet and high fat diet (HFD)	Oral supplement	During pregnancy and breastfeeding	To evaluate low-dose GSPE supplementation during the pre- and postnatal period on the health of young offspring .	The treatment with grape seed procyanidin supplementation in rats induced a clear effect of metabolic programming in the offspring, increasing adiposity, but also decreasing circulating levels of MCP-1 and altering gene expression in EWAT towards a better inflammatory profile.	The animals in the HFD-GSPE group exhibited significantly higher levels of adiposity and higher rates of weight in the different deposits of white adipose tissue compared to the animals in the HFD group, with the EWAT group showing the greatest increase in deposits. This increase was significant in the number of EWAT cells in this group, to the detriment of the HFD group. Furthermore, plasma levels of MCP-1 and glycerol significantly decreased in HFD-GSPE animals compared to those in the HFD group. A total of 238 unique genes were significantly altered ($P<0.05$) in the EWAT of the HFD-GSPE animals compared to the animals in the HFD group, most of which (81.9%) were up-regulated. These effects of GSPE were not observed in animals on a standard diet.
Lewicki, S et al (Poland, 2017)	20 mothers and 288 baby mice of the Balb strain	Rhodiolakirilowii Extract (Proanthocyanidin) (20 mg/kg of weight/day)	Distilled water	Gavage	From the moment of copulation until the 28th day after delivery	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.	Children of mothers fed with RKW-A or EGC had 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 were also found in relation to the control group.	Significant results were found by the composition of polyphenols in the serum of mice (salidroside and kaempferol) from the RKW and RKW-A groups ($P<0.05$) and lower in the EGC group ($P<0.05$), compared to the control group. . The concentration of VEGF was lower in the RKW-A group than in the control group ($P = 0.031$), and higher in the EGC group ($P = 0.085$). The TNF-alpha content was significantly lower in the serum of the offspring of the EGC group and higher in the RKW-A group compared to the control group. Morphometric analysis revealed a statistical difference in the number of glomeruli and glomerular atrophy between RKW-A kidneys, with this group being the highest number and control kidneys, EGC and RKW. The results of the offspring's mean body mass were not significant.

Balan, B.J. et al (Poland, 2017)	134 mice from the offspring of the Balb/c strain (n=20)	Epigalocatequina 0,2 mg/kg/ dia	Distilled water	Gavage	From the copulatory plug to the 28th day of the offspring's life	To investigate the effect of epigallocatechin on spleen morphology and immune function parameters of the offspring.	Feeding mothers of mice with EGC had a negative influence on spleen cellularity and on the architecture of their progeny. However, EGC did not significantly influence the humoral (after immunization with SRBC), and cellular (splenocyte proliferation after stimulation with mitogens) immune response.	The intervention group had offspring with lower weight (p=0.0106), lower spleen cellularity with lymphocytes with NK cell markers CD335 (p<0.001), CD19 (p<0.01), and CD4 (p<0.05). Microscopically, enlarged white pulp, fewer lymph nodes in the spleen (p<0.01), and larger diameter (p<0.001). In mated females without offspring, litter size, spleen mass and relative spleen mass index, proliferative response of cell, humoral response to SRBC immunization and macroscopic abnormality were not significant (p>0.05).
Garcia-Contreras, C et al (Espanha, 2019)	13 iberian sows	1 hydroxytyrosol 1.5 mg / kg / day	Control group fed a standard grain-based diet	Gavage	From day 35 of pregnancy to day of sampling (day 100 of pregnancy).	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 improves fetal antioxidant status and glucose metabolism in a sex-dependent manner. However, male fetuses showed worse developmental patterns when compared to control counterparts and littermates.	The evaluation of the antioxidant status showed a higher total antioxidant capacity (TEAC) in the fetuses of the HTX group than in the fetuses of the control group (p <0.0001), with higher values in the females than in the males (p <0.0005).). Supplementation of the maternal diet with hydroxytyrosol resulted in the fetuses with the lowest mean body weight (p < 0.005). Males in the HTX group had lower values than males in the control group for biparietal diameter and chest circumference (p < 0.01 for both), body weight (p < 0.05) and total viscera and liver weights (p < 0 .05 for both) and intestine (p < 0.001). In the control, males had a lower number of secondary muscle fibers and smaller fiber area (p < 0.005 for both). Significantly lower values in the HTX group than in the C group for glycemic indices (p<0.05 for glucose and p<0.01 for fructosamine) were found. DNA methylation analysis showed significantly higher values in the HTX group than in the C group (4.3 ± 0.1 vs. 4, 0 ± 0.1, respectively; p <0.01).

Zdanowski, R et al (Poland, 2014)	96 adult inbred females of the Balb/c strain	Rhodiola kirilowii Crassulaceae 20 mg / kg /dia	Distilled water	Oral. The substances were applied to corn chips .	From the time the copulatory plug was observed, until the 28th day after delivery	The aim of the present study was to establish whether aqueous and hydroalcoholic extracts of R. kirilowii given to pregnant mice will change the course of pregnancy and the number of offspring. .	The aqueous and hydroalcoholic extracts affected litter size (significant increase after RKW-A supplementation) as well as the number of childless females (significant increase after supplementation of both extracts).	The mice in the RKW-A group had a longer pregnancy time, being abnormal (42 days). The progeny (2 mice) survived for only four days. The intervention group (both RKW and RKW-A) significantly increased the number of mated females without offspring ($p < 0.05$). The hydroalcoholic extract of Rhodiolakirilowii caused a significant increase in litter size compared to the group that received RKW ($p<0.01$) and the control group ($p<0.05$). There was mortality within the first 5 days postpartum in the offspring of mothers fed RKW-A extracts; approximately 8.5% (6 of 71 newborns). In the RKW (54) or control group (105), all newborns survived.
Fareed, S.A. & Mostafa, H.E.-S. (Egypt 2020)	40 pregnant albino rats (10 for each group) and 10 pups per group	Caffeine 80 mg/ kg/ dia	Control group without treatment	Oral gavage	From the first day of pregnancy to the 30th day of lactation	This study aimed 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.	The caffeine group (III) showed a significant increase in MDA levels accompanied by a significant decrease in GSH, SOD and GSHPx levels when compared to the control group (I). The caffeine group (III) showed a significantly higher increase in urea and creatinine levels ($p < 0.001$) when compared to the control group (I) and the combined group (IV).	Rats exposed to coffee (group III) showed a statistically significant decrease in the number of normal glomeruli ($p<0.05$) compared to other groups, but showed a highly significant decrease in mean cortical thickness ($p<0.001$) when compared to other groups. with the control and combined groups (I and IV, respectively). A large significant increase in the percentage of renal smooth muscle actin expression area was observed in the caffeine (III) and combined (IV) groups ($p < 0.001$) versus groups control (I) and ASP (II), while the ASP (II) group showed no significant difference when compared to the control group, but showed significant difference when compared to caffeine and combined groups (III and IV; $p < 0.05$) . The caffeine group (III) showed a significantly higher increase in urea and creatinine levels ($p < 0.001$) when compared to the control group (I) and the combined group (IV).

Abbreviations: POMS - Profile of Mood States; GHQ - General Health Questionnaire; PSQI - Pittsburgh Sleep Quality Inventory; CVR - Cerebrovascular Responsiveness; CES-D - Epidemiologic Studies Depression Scale; MRS - Menopause Assessment Scale; SF-36 - Short Form-36; R = repetition and TxR = treatment x repetition

Risk of bias assessment and assessment of methodological quality

The tool used to assess the risk of bias and quality of evidence was SYRCLE's, which 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 a high risk of bias, and “UNCERTAIN”, which indicates a risk of bias. uncertain. It is not recommended to calculate the sum score. (12). Tabel 3. 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**
Lawal, R. O. (1997)	?	+	?	+	?	?	+	?	?	?
Ahmed, R.G. et al (2019)	?	+	?	+	?	?	+	+	-	+
Del Bas, J M 2014	?	+	?	+	?	?	+	+	-	+
Lewicki, S et al 2017	?	+	?	+	?	?	+	?	+	-
Balan, B.J. et al 2017	?	+	?	+	?	?	+	?	+	?
Garcia-Contreras, C et al 2019	?	+	?	+	?	?	+	+	+	?
Zdanowski, R et al 2014	?	?	?	+	?	?	+	+	+	+
Fareed, S.A., Mostafa, H.E.-S 2020	+	+	+	+	-	+	+	+	+	+

Abbreviations:SB:Selection Bias; PB: Performance Bias; DB: Detection Bias; AB: Attrition Bias; RB: Reporting Bias; O: Other

+ : low risk - : high risk ?: unclear

1) Was the allocation sequence adequately generated and applied?
2) Were the groups similar at baseline or were they adjusted for confounders in the analysis?
3) Was the allocation to the different groups adequately concealed?
4) Were the animals randomly housed during the experiment?
5) Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?
6) Were animals selected at random for outcome assessment?
7) Was the outcome assessor blinded?
8)) Were incomplete outcome data adequately addressed?
9) Are reports of the study free of selective outcome reporting?
10) Was the study apparently free of other problems that could result in a high risk of bias?

Discussion

The eight articles selected through the inclusion and exclusion criteria were articles dated between 1997 and 2020, all being case-control studies, always having an intervention group, which received the polyphenol, and a control group, which did not receive any type. of intervention. 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 *Rhodiolakirilowii*.(4,5,7,11) Polyphenol, dose and intervention time varied according to each article. You can see this data in the results table (Table 2).

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 and causing a significant increase after Rhodiolakirilowii 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.(4) 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, which 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/weight/day of polyphenol, obtained from the outer covering of the fruit of T. Africana. As the 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.(4)

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.(5) A study that used caffeine supplementation at doses of 12.5, 25, and 50 mg/kg body weight/day in broilers also found a reduced ratio of T3 and T4 after 42 days, this study by Kamely, Met al also showed a correlation negative difference between thyroid hormone concentrations and birth weight on day 42 ($P < 0,05$).(13)

The use of caffeine (60mg/kg body weight/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.(14) 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 Basetal, the use of grape seed procyanidin extract (GSPE), being 20mg/kg of weight/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.(6) Contrasting this result, the study by Caimariet 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.(15)

In the same study plasma levels of MCP-1 and glycerol were significantly decreased in HFD-GSPE animals compared to those in the HFD1 group. In view of these results, an in vitro study by Chacónet 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 Baset al.(6,16)

In the study by Lewickiet at a dosage of 20 mg/kg of body weight/day per day in intervention groups of mice, the significant results were the composition of polyphenols in the serum of mice, salidrosidep 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 Zdanowskiet study where a 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*.(7,17)

The study by Balan et al. showed changes in rats born to mothers fed epigallocatechin during pregnancy.(8) A great similarity was observed in the study by Balan et al. 2017, who supplemented 8 female Balb/c strain rats with cranberry extract (44mg/kg body weight/day), from the day of copulation to the 28th day postpartum of the offspring.(18) 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 ($p<0.0001$), 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 Rhodiolakirilowii extract (20mg/kg body weight/day) for the same period as the aforementioned study.(19)

Supplementation of the maternal diet of hiberian sows with hydroxytyrosol at a dose of 1.5 mg/kg body weight/day resulted in fetuses with lower mean body weight ($p<0.005$).(9) The present study by Garcia-Contreras, C 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 RhodiolakirilowiiCrassulaceae (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 also significantly increased the number of females mated without offspring ($p < 0.05$). The hydroalcoholic extract of Rhodiolakirilowii caused a significant increase in litter size compared to the group that received RKW ($p<0.01$) (10). Converging with this finding, another study using the same dose in BALB mice demonstrated that there is no toxic effect on pregnant female 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 ($p < 0.001$).(22)

Contributing to this finding, a study that evaluated pregnant Wister 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 nephrin protein expression.(23)

Conclusion

It is concluded with this systematic review that the consumption of polyphenols can have negative maternal-fetal outcomes in animal models, among the main outcomes found were fetal, visceral, and skeletal malformations, interruption in fetal and maternal thyroid activity, increased adiposity, morphometric abnormalities in the structure of the kidneys, 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 in the architecture of their progeny when studied in animals. However, the current published studies are limited, requiring continuity and improvement of the intervention methodology used. Therefore, more studies are needed to investigate the negative effects of polyphenols ingestion during pregnancy resulting in maternal-fetal complications in animals, possibly to study the effects of these polyphenols in humans.

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ANEXOS

I. Cadastro PROSPERO;

Número do PROSPERO: CRD42020210553, o qual pode ser localizado no pelo link: https://www.crd.york.ac.uk/prospero/#searchadvanced

II. Protocolo ComPesq;

Número do protocolo ComPesq 215-2022 para registro no SEI, protocolado em 08 /09 /2022: