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ANIMAL SCIENCE

Lipid profile and reproductive performance of female offspring of SWISS mouse females supplemented with resveratrol or canjiqueira (*Byrsonima cydoniifolia* A Juss) during gestation

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Abstract: This study aimed to resveratrol supplementation (at 5 or 10 mg/kg) and a hydroethanolic extract of canjiqueira fruits (150 mg/kg) on female SWISS mice. Total cholesterol, high-density lipoprotein (HDL), triglyceride levels, gestation rates, and embryonic implantation rates in their female Offspring was evaluated. In conclusion, the consumption of canjiqueira fruit extract altered the lipid profile of their female offspring, and did not impact their reproductive performance. Supplementing female SWISS mice with 10 mg/kg of resveratrol increased total cholesterol, triglycerides, and HDL levels, thereby enhancing the reproductive efficiency of their offspring.

Key words: antioxidants, lipids, mouse, Pantanal.

INTRODUCTION

The developmental plasticity is related to signals from the early environment, with heightened risk of disease if the induced phenotype does not match the later environment (Gluckman & Hanson 2007). Experimental studies evaluating maternal nutritional aspects suggested as fetal adaptations commonly occur in response to a failure to provide nutrients from the maternal placental system to meet the needs of the fetus (Godfrey 2002). Maternal body composition and diet influence nutrient supply through direct effects on substrate availability to fate and indirectly through changes in placental function and structure (Godfrey et al. 1999). Experimental work shows that the rat that has been an undernourished foetus has changes in its appetite control, with a higher set point for satiety and a preference for high fat diets (Vickers et al. 2000, 2003).

Cholesterol is a lipid molecule metabolic precursor of bile acids and steroid hormones, besides being an important component of plasma membranes that makes the lipid bilayer more rigid, decreasing the permeability. It is also associated with the success of embryonic development (Yoshida & Wada 2005). It has believed that most of the fetal cholesterol is synthesized in the liver(Baardman et al. 2013) although evidence indicates that during the first few weeks of life, when most organs are formed, the fetus depends largely on maternal cholesterol. The placenta plays an important role in transporting this cholesterol from mother to fetus (Woollett 2011, Van Montfoort et al. 2014).

Similarly, high density lipoprotein (HDL) levels are directly correlated with positive reproductive results (Fujimoto et al. 2010), as HDL and low density lipoproteins (LDL) are the major carriers of cholesterol for progesterone synthesis in the corpus luteum, influencing the establishment and the maintenance of the early phase of pregnancy (Baardman et al. 2013).

Triglyceride synthesis occurs in the intestinal mucosa cells, adipocytes, hepatocytes, epithelial cells of the mammary glands, and kidneys. Once within the intestinal mucosa cells, dietary fatty acids and monoglycerides are re- esterified to form triglycerides, being the control of triglyceride synthesis by enterocytes largely dependent on the availability of dietary fatty acids (Thrall et al. 2015).

Increased triglycerides in maternal blood is a typical finding during pregnancy that although they do not directly cross the placenta, may benefit the fetus in many ways. Maternal triglycerides represent a fluctuating energy deposit that under fasting are being efficiently used by the maternal liver to synthesize ketone bodies and save glucose for the fetus (Herrera 2000). They are being considered reservoirs of maternal fatty acids derived from the diet, and their uptake depends on the concentration in food (Ghio et al. 2011).

Resveratrol (3,5,4'-trihydroxystilbene) is a phytoalexin that belongs to the stilbene family. It is considered the most biologically effective phenolic compound (Frémont 2000). This polyphenol is a nutraceutical that has received the attention of different researchers due to its pharmacological potential for the treatment of different diseases (Berman et al. 2017). It exhibits antioxidant activity, modulates inflammatory response, and has a phytoestrogenic effect, acting on the ovary, slowing its aging and, thus, positively contributing to the reproductive efficiency of females (Liu et al. 2013).

Maternal intake of resveratrol in pregnancy brings benefits to the mother and her offspring. Although the mechanisms involved in these effects has been not yet fully elucidated, it is believed that the fetal development programming may explain the relationship between maternal nutrition and antioxidant consumption and offspring metabolic health (Costa-Silva et al. 2016).

The *Byrsonima cydoniifolia* A. Juss (Malpighiaceae) species, popularly known as canjiqueira or canjicão, is widely distributed in the Pantanal Sul Mato-Grossense region and it is a source of bioactive compounds such as phenolic acids, ascorbic acid, and piceatanol (resveratrol analog). It has recognized effects on metabolic and reproductive health, which may allow the discovery of a natural source of antioxidants with the potential to prevent or minimize deleterious effects on female reproduction (Prates et al. 2015, Santos et al. 2017).

The objective of this study was to evaluate if resveratrol (RV) and canjiqueira (CJ) consumption by F0 females of SWISS mice, from early reproductive life-span to first delivery (40 to 84 days old), influences total cholesterol, HDL, and triglyceride levels, pregnancy rate, and quantity and rate of embryonic implantations of their F1 female offspring.

MATERIALS AND METHODS

Animals

F1 females of SWISS mice were used, descendants of F0 mothers supplemented with resveratrol or hydroethanolic extract of canjiqueira from early reproductive life-span to first delivery (40 to 84 days old). All animals were obtained from the Central Vivarium of the Institute of Biosciences of the Mato Grosso do Sul Federal University (UFMS). F0 females of conventional sanitary standard were housed in individual

cages, kept in a ventilated shelf, under light and dark photoperiod (± 12h), and temperature (21 ° C ± 2 ° C) and humidity (60%) control, with ad libitum access to water and a commercial feed (moisture: 125 g/kg, crude protein: 220 g/kg, ether extract: 4 g/kg, mineral matter: 90 g/kg, crude fiber: 70 g/kg, calcium: 10-14 g/kg, and phosphorus: 8,000 mg/kg). The precedures involving laboratory animals were approved by the Ethics Committee for the Use of Animals (CEUA) of the Federal University of Mato Grosso do Sul (UFMS) (Protocol No. 831/2016).At 21 days of age (at weaning), F1 females were housed in cages with four animals and kept under the same conditions as females F0, until they were 60-day-old.

Antioxidant substance

Resveratrol (3,4,5-trihydroxy-trans-stilbene) used in F0 females was obtained from the Sigma-Aldrich laboratory (St. Louis, MO, USA). The antioxidant was diluted in normal saline immediately before use, as described by Ozcan et al. (2015).

Raw material collection and preparation for the canjiqueira extract

Canjiqueira fruits were collected around the city of Coxim, MS (18°30'24"S, 54°45'36"W), in January and February of 2016, during the harvest period, beingan exsiccate deposited in the UFMS herbarium, under registration number 59035.

At the Mineral Metabolism Laboratories of the Medicine School (FAMED) and the Food Technology and Public Health Unit of the Pharmaceutical Sciences, Food and Nutrition School of UFMS(UTA-FACFAN-UFMS), the fruits were washed with water, sanitized with bleach (150 ppm), naturally dried, and weighed in dark environment so that there was no light interference on the antioxidant content of the fruits.

Fruits were fully used, stored in a dark environment and frozen (-18 °C) in a freezer until analyzed. The samples were dehydrated in a circulating oven (40 °C), homogenized and stored in a freezer (-18 °C).

Extract preparation for the animal study

The canjiqueira extract was prepared with the whole fruits homogenized and dehydrated. Fruits were percolated in hydroethanolic solution (30:70), dripped (20 drops/min) for 72 hours and then lyophilized in an industrial lyophilizer topreserve the bioactive compounds of the fruit (Chiu et al. 1970, Ley et al. 2005).

Experimental design

Twenty 40-day-old F0 females of SWISS mice were randomly assigned to four groups that received, respectively, 0.2 mL of saline solution (Control group), 5 mg/kg of resveratrol (RV5 group), 10 mg/kg of resveratrol (RV10 group), or 150 mg/kg of canjiqueira fruit hydroethanolic extract (group CJ). Resveratrol concentrations (5 and 10 mg/kg) chosen for this experiment were based on previous studies with this antioxidant (Ara et al. 2005, Ozcan et al. 2015, Sharma et al. 2017). The 150 mg/kg dose for canjiqueira extract was chosen to assess whether the concentration lower cited in the literature (200 and 400 mg/kg; Gutierrez and Flores 2014) also had a therapeutic effect. The antioxidant substance and canjiqueira extract were dissolved in 0.2 mL of saline solution. Treatments were administrated by gavage, once a day, at 08h, between 40 and 84 days of age (pre-supplementation and post-supplementation, respectively).

F1 females weaning occurred at 21 days of age. A total of sixty-three F1 females were obtained, being eighteen females from the Control group, fifteen from RV5group, sixteen from RV10 group, and fourteen from CJ group. The nomenclature

F1 female groups was the same of the maternal groups (F0) (Figure 1).

Mating

At 60 days old, F1 females were housed in cages, previously used by males for estrous cycle induction and synchronization, known as the Whitten effect (Whitten 1958), in which the male pheromone odor influences and modifies female sexual behavior of rodents (Braga 2017). For mating, healthy males of the same age as F1 females, descendants from parents with proven fertility, were used in the proportion of two females for each male (2:1). Females were observed daily for vaginal plug and mating confirmation, which was considered day 1 of pregnancy. After mating confirmation, the females were kept in the cages for eightdays, period necessary for embryonic implantation to occur.

Biological material collection and quantity of embryonic implantation

Eight days after pregnancy confirmation, F1 females were euthanized byinduction chamber anesthesia with volatile anesthetic (isoflurane 3-5%). After death confirmation, blood was collected by posterior vena cava puncture to obtain serum and measurement of total cholesterol, triglycerides, and HDL, through commercial kits (LabTest®, Lagoa Santa 47 - GO, Brazil) and quantified byspectrophotometer

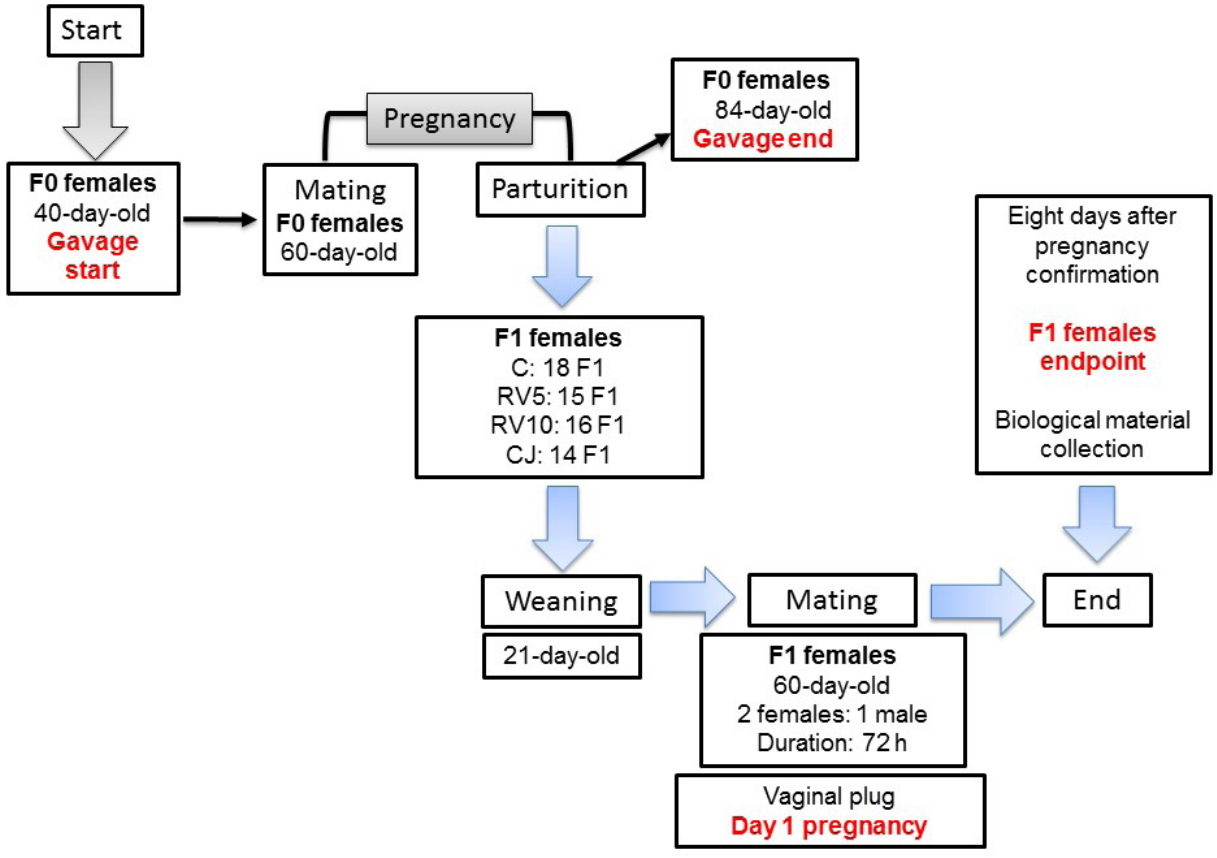

Figure 1. Experimental design schedule of females Swiss mice without supplementation or with supplementation of resveratrol or canjiqueira, from early reproductive life-span to first delivery and evaluation of F1 female offspring.

(BioTek® – PoweWave XS). Serum biochemical values obtained from females of SWISS mice, at 60-day-old, from the Central Vivarium UFMS (Restel T.I., unpublished data) were considered as the reference standard for this experiment.

Ovarian and uterine tissues were removed and conditioned in 10% formaldehyde solution for subsequent histological analysis and counting of the quantity of corpus luteum in the ovaries, and evaluation of the quantity of embryonic implantation sites in the uterus. After formalin fixation, tissues were submitted to paraffin embedding and then microtome 7 µm thick sections were mounted on glass slides. Each slide had a total of four sections taken from the paraffin block and then stained with hematoxylin and eosin. The analysis was performed at the INBIO / UFMS Image Capture Laboratory under a microscope coupled to a digital camera at a 200x magnification (Leica Application Suite® – Version 4.0.0). Representative sites were selected in the section, in which morphological alterations were observed in the evaluated organs (Abbas et al. 2010).

Reproductive function

The quantity of corpus luteum and embryonic implantation sites were recorded and, from these data, pregnancy rate was determined by the equation: [(quantity of pregnant females / quantity of females covered by males) x 100]; and implantation rate was determined by the equation: [(quantity of embryonic implantation sites / quantity of corpus luteum) x 100] (Spadotto et al. 2012).

Statistical analysis

The comparisons among experimental groups related to total cholesterol, triglyceride, and HDL fraction rates of F1 females were performed by the non- parametric test Kruskal-Whallis, followed by the Dunn post-test, since the samples did not pass the Shapiro-Wilk normality test. The same test was used in the comparisons among experimental groups, regarding the variables of uterine histological evaluation and average pregnancy rates and quantity and rate of embryonic implantation. The evaluation of the association between the experimental group and the variables pregnancy rate and implantation rate was evaluated using the X^2 test, with Bonferroni correction in the multiple comparisons of the other groups with the Control group. The remaining results of this study were presented as descriptive statistics or tables. Statistical analysis was performed using the statistical program SigmaPlot, version 12.0, considering a significance level of 5% (Rowe 2007).

RESULTS AND DISCUSSION

In this study, the supplementation of the F0 females of the RV10 group, from early reproductive life-span to first delivery (40 to 84 days old), resulted, in adult F1 females, in higher levels of total cholesterol compared to the Control and CJ groups, but with no difference compared to that of the RV5 group. The RV10 group also presented higher serum triglyceride concentrations compared to the RV5 and CJ groups. However, this difference was not maintained compared to the Control group. Regarding HDL levels, females F1 of the RV10 group presented higher concentrations compared to those of the CJ group, but did not differ from the Control and RV5 groups, as shown in Table I.

The total cholesterol concentrations the four evaluated groups were lower than values found by Restel T.I. (unpublished data) for 60-days-old SWISS female mice (116.33 mg/dL), considered as standard for the UFMS Central Vivarium animals. Even though F1 females of the RV10 group

Table I. Total cholesterol (mg/dL), triglycerides (mg/dL), and high density lipoproteins – HDL (mg/dL) concentrations in F1 females of SWISS mice descendants of F0 females without supplementation or with supplementation of resveratrol or canjiqueira.

Group	n	Total cholesterol	Triglycerides	HDL
Control	18	96.79±3.32[b]	302.42±14.97[ab]	86.74±2.91[ab]
Resveratrol 5 mg (RV5)	15	102.33±3.55[ab]	280.06±15.40[b]	83.17±2.52[ab]
Resveratrol 10 mg (RV10)	16	113.00±4.24[a]	367.10±15.18[a]	94.24±3.84[a]
Canjiqueira	14	96.32±4.42[b]	256.16±10.68[b]	76.37±3.49[b]
P value		0.007	<0.001	0.006

Results are presented as mean ± mean deviation error. P values from one way Kruskal-Whallis test. Different letters in the same column indicate significant difference among experimental groups (Dunn post-test, p <0.05).

presented higher concentrations thanthose from groups C and CJ, hypercholesterolemia was not established, since the results remained below the expected biochemical reference standard for these animals.

Resveratrol is a polyphenol that has multiple functions, low cytotoxicity, and recognized anti-inflammatory, antioxidant, antitumor, and cardio protective effects (Park et al. 2012, Riccioni et al. 2015, Haghighatdoost & Hariri 2018). During pregnancy, resveratrol consumption may indirectly affect the litter by improving the metabolic status of the mothers or it may present direct effects on the fetus due to its recognized ability to cross the placenta (Bourque et al. 2012,Ros et al. 2018). The higher serum total cholesterol concentration presented by F1 females of the RV10 group suggests that resveratrol consumption by F0 females was not able to improve the metabolic status of their daughters, contrary to what Bourque et al. (2012) and Ros et al. (2018) have suggested. However, F1 females from this experiment were fed a commercial isoenergetic diet and did not suffer any metabolic challenge, such as the consumption of hypo- or hyper- energetic diets, which may have minimized the antiobesogenic resveratrol effects.

Resveratrol concentrations (5 and 10 mg/kg) chosen for this experiment were based on previous studies with this antioxidant (Ara et al. 2005, Ozcan et al. 2015, Sharma et al. 2017). However, unlike these authors who investigated the effect of resveratrol associated with metabolic imbalances, these concentrationsmay not have been able to induce antiobesogenic effects in healthy animals.

Cholesterol is essential for mammalian development, as its presence determines membrane fluidity (Yoshida & Wada 2005, Willnow et al. 2007, Woollett 2008). It also acts as a precursor to steroid hormones, essential for ovarian follicular maturation. Therefore, substantial amounts of this lipid need to be transported to follicular cells or locally synthesized by teak and granulosa cells (Van Monfoort et al. 2014). Serum cholesterol concentrations in F1 females of RV10 group, although higher than in other groups, may have brought reproductive benefits, since these concentrations remained within the reference parameters, not triggering hypercholesterolemia in these females.

Serum triglyceride concentrations of F1 females in groups C, RV5, and RV10 were higher than those found by Restel T.I. (unpublished data) for 60-day-old female SWISS mice (273.67

mg/dL). Triglycerides act as a source of cellular metabolic energy, stored in adipose tissue, from which they are recruited in response to demands of the body (Evans 2009). In women, an increase in triglycerides is common during pregnancy, and even if they do not cross the placenta, they bring benefits to the fetus because they are considered fatty acid reservoirs from the diet, and the hydrolysis by the lipoprotein lipase (LPL) and other lipases, releases free fatty acids (FFA) to the fetus (Ghio et al. 2011). Therefore, it is possible that the higher concentration of triglycerides in F1 females of RV10 group is due to gestational period, since the females used by Restel T.I. (unpublished data) were not pregnant.

Higher HDL levels were also observed in the RV10 group when compared to the CJ group. However, there were no differences to the other groups. HDL is the main transporter of cholesterol and cholesterol esters to the liver in rodents (Thrall et al. 2015) and, when there is a higher concentration of lipids in the blood, high concentrations of HDL are required to transport these lipids as an attempt to compensate, since this lipoprotein has the ability to incorporate excess cholesterol from extrahepatic tissues by a process called reverse cholesterol transport (Fujimoto et al. 2010). In this study, F1 females of the RV10 group had different serum HDL levels from group CJ and, even though they did not differ in relation to Control and RV5 groups, this higher concentration can be explained as a physiological response of the organism, through the release of more HDL to compensate for the higher total cholesterol concentration in these females.

Resveratrol consumption by F0 females significantly influenced the lipid profile of F1 females. However, this difference was not able to prevent hypercholesterolemia. These females were not subjected to any nutritional challenge, so their use for antiobesogenic purposes should not be disregarded, since the positive effects of this antioxidant on the metabolic health of F1 offspring may have been attenuated. Still considering the data in Table I it was noted that the F1 females of the CJ group presented lower total cholesterol, triglycerides and HDL concentrations than the RV10 group, but their lipid profile did not differ from the results observed in the RV5 and Control groups. In addition, their lipid concentrations were lower than the biochemical reference standard considered for these animals (Restel T.I., unpublished data), revealing a positive effect of canjiqueira extract supplementation on mothers (F0 females) on the maintenance of metabolic homeostasis of their daughters, indicating a probable performance of bioactive compounds of the plant.

Several genus belonging to the *Malpighiaceae* family have nutraceutical fruits, such as the genus *Byrsonima*. Fruits of this genus have anti-inflammatory activity and are marketed throughout Brazil (Guilhon-Simplicio & Pereira 2011). Canjiqueira (*Byrsonima cydoniifolia* A. Juss) presents high levels of bioactive compounds in green fruits, rich in ascorbic acid (198.01 mg), tannins (179.15 mg), and phenolic compounds (124.26 mg) (Prates et al. 2015).

In a study conducted by Gutierrez & Flores (2014), with the objective to investigate the effects of the extract of *Byrsonima crassifolia* fruit and seed (same genus as canjiqueira), obtained with hexane, chloroform, and methanol in diabetic Wistar mice induced by streptozotocin (STZ), there was a decrease in total cholesterol, triglycerides, and HDL in the groups supplemented with *B. crassifolia* hexane extract. These authors concluded that the chronic administration of this extract attenuates pancreatic dysfunction in these animals, even without identifying which bioactive compound present in the plant was able to induce

these beneficial effects. It was similar to the observations of this study,where it was possible to identify positive effect of canjiqueira on the metabolic health of F1 females, but without establishing which bioactive compounds of the plant were able to verify these results.

In the same study, those authors used 200 and 400 mg of *B. crassifolia* hexane extract and found positive results of these concentrations on the lipid parametersof diabetic rats (Gutierrez & Flores 2014). However, in the present experiment, a lower concentration (150 mg/kg) was used in order to verify lower concentration with therapeutic results for the genus *Byrsonima*, and it was observed that it also presented positive effects on the lipid profile of F1 females.

The ascorbic acid present in canjiqueira fruits was related to several metabolic activities. Its presence may reduce serum cholesterol concentration in rodents, possibly due to the activation of 7α-hydroxylase enzyme that increase the conversion of cholesterol to bile acids and, consequently, decreasing its serum concentration (Chatterjea & Shinde 2002, Eteng et al. 2006). Therefore, its action on rodent lipid metabolism may justify the concentrations of cholesterol, triglycerides, and HDL observed in F1 females of the CJ group, even with numerically lower values compared to F1 females of the other groups. Piceatanol (3,40,30,5-trans-trihydroxystilbene), another bioactive compound present in canjiqueira fruit, is a resveratrol hydroxylated analogue, considered a potent antioxidant (Kukreja et al. 2013).

Santos et al. (2017) observed higher amounts of trans-piceatanol (16.34 µg/mg)in *B. cydoniifolia*fruits than in some grape varieties (Vincenzi et al. 2013), known for accumulate these compounds. They also identified resveratrol (1.86 µg/mg), being the first description of the presence of this compound in the genus *Byrsonima*. Piceatanol plays a vital role in adipogenesis inhibition, by regulate the expression of pro-adipogenic transcription factors (C/EBPα – binding enhancerproteinαand PPAR – peroxisome proliferator-activated receptor), as well as inhibiting phosphorylation and kinase activity of signaling pathways, including the IR (insulin signaling pathway) and PI3K/Akt (phosphatidylinositol-3- kinase/ serine-threonine kinase) pathway, similarly to resveratrol, giving these polyphenols antiobesogenic capacity (Kwon et al. 2012). Thus, the presence of these stilbenes in *B. cydoniifolia* fruit may also justify the results observed in the lipid profile of F1 females descendants of F0 females supplemented with canjiqueira extract. It also may indicate a possible synergistic action of bioactivecompounds present in the plant.

Evaluating the uterine histological sections of F1 females, it was noted that the quantity of embryonic implantations differed among groups. However, the test ofcomparison between means was not able to define this difference, because these differences were not great enough to be determined by the most powerful statistical tests.However, in the numerical observation, it was possible to identifya greater quantity of implantations in the females of the RV10 group, followed bythe RV5 and CJ groups compared to Group C. By calculate pregnancy and embryonic implantation rates, it was possible to confirm the best performance of F1 females from group RV10, which differed from group C in the evaluation of pregnancy and implantation rates. The RV5 group differed from group Control only in relation to implantation rate similar the pregnancy rate. The CJ group presented similar results to the other groups Table II.

Resveratrol beneficial effects on female reproductive processes have been widely recognized in recent years (Wang et al. 2018). Resveratrol can improve ovarian damage

Table II. Embryonic implantation quantities and pregnancy and embryonic implantation rates (%) in F1 females of SWISS mice descendants of F0 mothers without supplementation or with supplementation of resveratrol or canjiqueira.

Group	n	Embryonic implantation quantities	Pregnancy rate	Implantation rate
Control	18	0.89±0.50[a]	16.66[b]	16.49[b]
Resveratrol 5 mg (RV5)	15	2.00±0.56 [a]	53.33[ab]	40.00[a]
Resveratrol 10 mg (RV10)	16	2.56±0.42 [a]	75.00[a]	59.42[a]
Canjiqueira (CJ)	14	1.57±0.61 [a]	42.86[ab]	24.72[ab]
P value		0.049	0.007	<0.001

Results are presented as mean ± mean deviation error. P values from one way Kruskal-Whallis and χ^2 tests. Different letters in the same column indicate significant difference among experimental groups (Dunn and Bonferroni post-tests, p <0.05).

induced by radiation, chemotherapeutic agents, and endocrine disruptors (Ozcan et al. 2015, Said et al. 2016, Liu et al. 2017); increase ovarian reserve associated with aging, obesity, and diabetes mellitus (Kong et al. 2011, Liu et al. 2013, Erbas et al. 2014, Cabello et al. 2015); and improve ovarian dysfunction in an animal model of polycystic ovary syndrome and ovarian hyper stimulation (Ergenoglu et al. 2015, Kasap et al. 2016). In this study, supplementation of F0 females with 10 mg/kg of resveratrol resulted in F1 offspring, better percentages in gestation and implantation rates despite their actions on lipid profile, probably due to the positive effects of this antioxidant on ovarian reserve which begins its formation during intrauterine development, since resveratrol is able to cross the placental barrier and act directly on the fetus (Bourque et al. 2012).

At the beginning of embryonic development, the embryo is dependent on the maternal supply of cholesterol. Changes in maternal cholesterol levels may have an adverse effect on its development and growth (Baardman et al. 2013). F1 females from RV10 group had higher total and HDL cholesterol concentrations compared to the groups C and CJ, and similarly, they were different from these groups in the percentages of pregnancy and implantation rates, indicating that higher serum lipid levels may provide a better reproductive performance.

Maternal cholesterol levels may be important to meet fetal cholesterol demands during organogenesis. In women, maternal total cholesterol levels rise by 30 to 50% during pregnancy as a result of increased liver cholesterol synthesis, which begins during the first trimester but is higher in the third trimester of pregnancy (Amundsen et al. 2006, Edison et al. 2007). Curiously, during the first trimester of pregnancy, HDL is significantly increased, probably due to the increased need for cholesterol for corpus luteum synthesis of progesterone (Baardman et al. 2013). From these data, it can be inferred that the decrease in total cholesterol has an adverse effect on pregnancy, as observed in this study, in which F1 females from RV10 group, which had higher total cholesterol and HDL concentrations, also shown a better reproductive performance.

Knockout female mice, homozygous for ABCA1 protein (Apolipoprotein 1), had reduced fecundity, reduced number of pups, and decreased number of secondary pregnancies due to reduced serum HDL levels (Christiansen-Weber et al. 2000, Aiello et al. 2003), confirming

that the lipid profile presented by F1 females, descendants of F0 females supplemented with 10 mg/kg resveratrol, was probably determinant for the reproductive performance observed in these females.

On the other hand, F1 females descendants of F0 supplemented with canjiqueiraextract had a lipid profile close to the reference standard for these animals. However, they had lower reproductive performance than females F1 of the RV10group, indicating that their total cholesterol and HDL levels may have influenced these results.

In a study to evaluate the effects of gestational exposure to *Byrsonima verbascifolia* (same genus as canjiqueira) on reproductive parameters of SWISSfemale mice, it was observed that the plant did not alter the reproductive function and the embryonic development (Gonçalves et al. 2013), similar to the result verified in this experiment with canjiqueira fruit extract.

Finally, although the maternal supplementation with canjiqueira fruit extract did not promote a better reproductive performance in F1 females, the observed lipid profile indicates that the plant can be widely explored by determining which bioactive compounds can improve animal reproductive efficiency and its action on farm animals, bringing new perspectives for animal reproduction, contributingto the preservation of canjiqueira species in their habitat and to the sustainable development of Pantanal region. On the other hand, the supplementation of F0 females of SWISS mice with resveratrol, especially at a concentration of 10 mg/kg, resulted in a better reproductive performance in F1 females, indicating a possible role of resveratrol on the ovarian reserve of these females during their intrauterine development, and differed in the lipid profile of these females, but with a probable attenuation of their antiobesogenic effects on their lipid metabolism, corroborating to the action of this polyphenol for the reproductive success of females.

REFERENCES

ABBAS AK, FAUSTO N & KUMAR V. 2010. Robbins e Cotran: Patologia - Bases patológicas das doenças, 8ª ed., Rio de Janeiro: Elsevier, p. 1026-1032.

AIELLO RJ, BREES D & FRANCONE OL. 2003. ABCA1-deficient mice: insights into the role of monocyte lipid efflux in HDL formation and inflammation. Arterioscler Thromb Vasc Biol 23: 972-980.

AMUNDSEN AL, KHOURY J, IVERSEN PO, BERGEI C, OSE L, TONSTAD S & RETTERSTOL K. 2006. Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. Atherosclerosis 189: 451-457.

ARA C, KIRIMLIOGLU H, KARABULUT AB, COBAN S, AY S, HARPUTLUOGLU M, KIRIMLIOGLU V & YILMAZ S. 2005. Protective Effect of Resveratrol Against Oxidative Stress in Cholestasis. J Surg Res 127: 112-117.

BAARDMAN ME, KERSTJENS-FREDERIKSE WS, BERGER RMF, BAKKER MF, HOFSTRA RMW & PLOSCH T. 2013. The role of maternal-fetal cholesterol transport in early fetal life: current insight. Biol Reprod 88(24): 1-9.

BERMAN AY, MOTECHIN RA, WIESENFELD MY & HOLZ MK. 2017. The therapeutic potential of resveratrol: a review of clinical Trials. Precis Oncol 1: 1-9.

BOURQUE SL, DOLINSKY VW, DYCK JR & DAVIDGE ST. 2012. Maternal resveratrol treatment during pregnancy improves adverse fetal outcomes in a rat model of severe hypoxia. Placenta 33: 449-452.

BRAGA LMGM. 2017. Controle reprodutivo em biotérios de criação de animais de laboratório com ênfase em roedores Rev Bras Reprod Anim 41: 105-109.

CABELLO E, GARRIDO P, MORAN J, GONZALEZ DEL REY C, LLANEZA P, LLANEZA- SUAREZ D, ALONSO A & GONZALEZ C. 2015. Effects of resveratrol on ovarian response to controlled ovarian hyperstimulation in ob/ob mice. Fertil Steril 103: 570-579.

CHATTERJEA MN & SHINDE R. 2002. Textbook of Medical Biochemistry, 5th ed., India: AYPE, 800 p.

CHIU CJ, MCARDLE AH, BROWN R, SCOTT HJ & GURD FN. 1970. Intestinal mucosal lesion in low flow states.

I. A morphological, hemodynamic, and metabolic reappraisal. Arch Surgv 101: 478-483.

CHRISTIANSEN-WEBER TA, VOLAND JR, WU Y, NGO K, ROLAND BL, NGUYEN S, PETERSON PA & FUNG-LEUNG WP. 2000. Functional loss of ABCA1 in mice causes severe placental malformation, aberrant lipid distribution, and kidney glomerulonephritis as well as high-density lipoprotein cholesterol deficiency. Am J Pathol 157: 1017-1029.

COSTA-SILVA JH, SIMOES-ALVESAC & FERNANDES MP. 2016. Developmental origins of cardiometabolic diseases: Role of the maternal diet. Front Physiol 7: 1-8.

EDISON RJ, BERG K, REMALEY A, KELLEY R, ROTIMI C, STEVENSON RE & MUENKE M. 2007. Adverse birth outcome among mothers with low sérum cholesterol. Pediatrics 120: 723-733.

ERBAS O, PALA HG, PALA EE, OLTULU F, AKTUG H, YAVASOGLU A & TASKIRAN D. 2014. Ovarian failure in diabetic rat model: nuclear factor-kappaB, oxidative stress, and pentraxin-3. Taiwan J Obstet Gynecol 53: 498-503.

ERGENOGLU M, YILDIRIM N, YILDIRIM AG, YENIEL O, ERBAS O, YAVASOGLU A, TASKIRAN D & KARADADAS N. 2015. Effects of resveratrol on ovarian morphology, plasma anti-mullerian hormone, IGF-1 levels, and oxidative stress parameters in a rat model of polycystic ovary syndrome. Reprod Sci 22: 942-947.

ETENG MU, IBEKWE HA, AMATEY TE, BASSEY BJ, UBOH FU & OWU DU. 2006. Effect of vitamin c on serum lipids and electrolyte profile of albino wistar rats. Niger J Physiol Sci 21: 15-19.

EVANS GO. 2009. Animal Clinical Chemistry. A practical handbook for toxicologists and biomedical researchers. 2nd ed., Boca Raton, Florida: CRC Press, Taylor and Francis, 368 p.

FRÉMONT L. 2000. Biological effects of resveratrol. Life Sci 66: 663-673.

FUJIMOTO VY, KANE JP, ISHIDA BY, BLOOM MS & BROWNE RW. 2010. Highdensity lipoprotein metabolism and the human embryo. Hum Reprod Update 16: 20-38.

GHIO A, BERTOLOTTO A, RESI V, VOLPE L & DI CIANNI G. 2011. Triglyceride metabolism in the pregnancy. In: Makowski GS (Ed), Advances in Clinical Chemistry, San Diego: Elsevier, San Diego, USA, p. 133-153.

GLUCKMAN PD & HANSON MA. 2007. Developmental plasticity and human disease: research directions. J Intern Med 261(5): 461-471.

GODFREY KM, BREIER BH & COOPER C. 1999. Constraint of the maternoplacental supply of nutrients: causes and consequences. In: O'Brien PMS, Wheeler T & Barker DJP (Eds), Fetal Programming: Influences on Development and Disease in Later Life. Londres: RCOG Press, Londres, England, p. 283-298.

GODFREY KM. 2002. The Role of the Placenta in Fetal Programming - A Review. Placenta 23: 20-27.

GONÇALVES CM, SIQUEIRA JM, CAROLLO CA, MAURO MA, DAVI N, CUNHA-LAURA AL, MONREAL ACD, CASTRO AH, FERNANDES L & CHAGAS RR. 2013. Gestational exposure to Byrsonima verbascifolia: Teratogenicity, mutagenicity and immunomodulation evaluation in female Swiss mice. J Ethnopharmacol 150: 843-850.

GUILHON-SIMPLICIO F & PEREIRA MDM. 2011. Chemical and pharmacological aspects of Byrsonima (Malpighiaceae). Quim Nova 34: 1032-1041.

GUTIERREZ RMP & FLORES JMM. 2014. Effect of chronic administration of hexane extract of byrsonima crassifolia seed on β-cell and pancreatic oxidative parameters in streptozotocin-induced diabetic rat. Afr J Tradit Complement Altern Med 11: 231-236.

HAGHIGHATDOOST F & HARIRI M. 2018. Effect of resveratrol on lipid profile: An update systematic review and meta-analysis on randomized clinical trials. Pharmacol Res 129: 141-150.

HERRERA E. 2000. Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. Eur J Clin Nutr 54: S47-S51.

KASAP E, TURAN GA, ESKICIOGLU F, CENGIZ H, GUR EB, SIVRIKOZ ON, GENC M & YILMAZ O. 2016. Comparison between resveratrol and cabergoline in preventing ovarian hyperstimulation syndrome in a rat model. Gynecol Endocrinol 32: 634-640.

KONG XX, FU YC, XU JJ, ZHUANG XL, CHEN ZG & LUO LL. 2011. Resveratrol, an effective regulator of ovarian development and oocyte apoptosis. J Endocrinol Investig 34: e374-e381.

KUKREJA A, MISHRA A & TIWARI A. 2013. Source, production and biological activities of piceatannol: a review. Int J Pharm Sci Rev Res 4: 1000-1007.

KWON JY, SEO SG, HEO YS, YUE S, CHENG JX, LEE KW & KIM KH. 2012. Piceatannol, a natural polyphenolic stilbene, inhibits adipogenesis via modulation of mitotic clonal expansion and insulin receptor-dependent insulin signaling in the early phase of differentiation. J Biol Chem 287: 11566-11578.

LEY RE, BÄCKHED F, TURNBAUGH P, LOZUPONE CA, KNIGHT RD & GORDON JI. 2005. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA 2(102): 11070-11075.

LIU M, YIN Y, YE X, ZENG M, ZHAO Q & KEEFE DL & LIU L. 2013. Resveratrol protects against age-associated infertility in mice. Hum Reprod 28: 707-717.

LIU Y ET AL. 2017. Protective effects of resveratrol against mancozeb induced apoptosis damage in mouse oocytes. Oncotarget 8: 6233-6245.

OZCAN P, FICICIOGLU C, YILDIRIM OK, OZKAN F, AKKAYA H & ASLAN I. 2015. Protective effect of resveratrol against oxidative damage to ovarian reserve in female Sprague-Dawley rats. Reprod BioMed Online 31: 404-410.

PARK SJ ET AL. 2012. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting Camp phosphodiesterases. Cell 148: 421-433.

PRATES MFO, CAMPOS RP, SILVA MMB, MACEDO MLM, HIANE PA & RAMOS FILHO MM. 2015. Nutritional and antioxidant potential of canjiqueira fruits affected by maturity stage and thermal processing. Cienc Rural 45: 399-404.

RICCIONI G, GAMMONE MA, TETTAMANTI G, BERGANTE S, PLUCHINOTTA FR & D'ORAZIO N. 2015. Resveratrol and anti-atherogenic effects. Int J Food Sci Nutr. 66: 603-610.

ROS P, DIAZ F, FREIRE-REGATILLO A, ARGENTE-ARIZON P, BARRIOS V, ARGENTE J, BARRIOS V, ARGENTE J & CHOWEN JA. 2018. Resveratrol intake during pregnancy and lactation modulates the early metabolic effects of maternal nutrition differently in male and female offspring. Endocrinology 59: 810-825.

ROWE P. 2007. Essential statistics for the pharmaceutical sciences. Chichester, England: John Wiley & Sons Ltda, 440 p.

SAID RS, EL-DEMERDASH E, NADA AS & KAMAL MM. 2016. Resveratrol inhibits inflammatory signaling implicated in ionizing radiationinduced premature ovarian failure through antagonistic crosstalk between silencing information regulator 1 (SIRT1) and poly (ADPribose) polymerase 1 (PARP-1). Biochem Pharmacol 103: 140-150.

SANTOS VS, NASCIMENTO TV, FELIPE JL, BOARETTO AG, DAMASCENO-JUNIOR GA, SILVA DB, TOFFOLI-KADRI MC & CAROLLO CA. 2017. Nutraceutical potential of Byrsonima cydoniifolia fruits based on chemical composition, anti-inflammatory, and antihyperalgesic activities. Food Chem 237: 240-246.

SHARMA R, SHARMA NK & THUNGAPATHRA M. 2017. Resveratrol regulates body weight in healthy and ovariectomized rats. Nutr Metab 14: 1-6.

SPADOTTO R, DAMASCENO DC, GODINHO AF, AMORIM EMP, PEROBELLI JE & KEMPINAS WG. 2012. Reproductive physiology, and physical and sexual development of female offspring born to diabetic dams. Arq Bras Endocrinol Metab 56: 96-103.

THRALL MA, WEISER G, ALLISON RW & CAMPBELL TW. 2015. Hematologia e bioquímica clínica veterinária. 2ª ed., São Paulo: Roca, 1590 p.

VAN MONTFOORT APA, PLÖSCHA T, HOEKA A & TIETGE UJF. 2014. Impact of maternal cholesterol metabolism on ovarian follicle development and fertility. J Reprod Immunol 104-105: 32-36.

VICKERS MH, BREIER BH, CUTFIELD WS, HOFMAN PL & GLUCKMAN PD. 2000. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol 279: E83-E87.

VICKERS MH, BREIER BH, MCCARTHY D & GLUCKMAN PD. 2003. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol 285: R271-R273.

VINCENZI S, TOMASI D, GAIOTTI F, LOVAT L, GIACOSA S, TORCHIO F, SEGADE SR & ROLLE L. 2013. Comparative study of the resveratrol content of twenty-one Italian red grape varieties. SAJEV 34: 30-35.

WANG Y, ZHANG M, CHEN ZJ & DU Y. 2018. Resveratrol promotes the embryonic development of vitrified mouse oocytes after in vitro fertilization. In Vitro Cell Dev Biol Anim 54: 430-458.

WHITTEN WK. 1958. Modification of the oestrous cycle of the mouse by external stimuli associated with the male; changes in the oestrous cycle determined by vaginal smears J Endocrinol 17: 307-313.

WILLNOW TE, HAMMES A & EATON S. 2007. Lipoproteins and their receptors in embryonic development: more than cholesterol clearance. Development 134: 3239-3249.

WOOLLETT LA. 2008. Where does fetal and embryonic cholesterol originate and what does it do? Annu Rev Nutr 28: 97-114.

WOOLLETT LA. 2011. Review: transport of maternal cholesterol to the fetal circulation. Placenta 32: S218-S221.

YOSHIDA S & WADA Y. 2005. Transfer of maternal cholesterol to embryo and fetus in pregnant mice. J Lipid Res 46: 2168-2174.

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