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INVESTIGATING THE EFFECT OF GINSENG TERATOGENIC ON THE FETUS OF A FEMALE MICE BALB/C / C DURING THE 7, 8,9,10 DAYS OF PREGNANCY

Soheila Azad Beigi¹, *Parvin Torabzadeh¹ and Monire Movahedi²

¹Department of Biology (Cellular -Developmental Biology), Karaj Branch, Islamic Azad University, Karaj, Iran

²Department of Biology, Tehran North Branch, Islamic Azad University, Tehran, Iran

*Author for Correspondence

ABSTRACT

It is more than 5,000 years that the ginseng plant is being use in East Asian countries, especially Korea and China as a healing agent to increase memory power, physical and sexual stamina, enhancing strength, happiness and excitement and coping with aging Also this plant is used by athletes in the combination of diet supplements to enhance their physical strength. For this reason, it was decided to study the eratogenic effects of this plant on adult female Balb / C during pregnancy. The objective of this research work was to investigate teratogenic effects of ginseng plant on small mice embryos during pregnancy. Considering that the Ginseng does not have lethal dose, Injection at a dose of 0/4 mg / kg intraperitoneally on days 7, 8,9,10 pregnancy after vaginal plug in adult female mice Balb / C with a weight of 28+_2 gr was done. Along with the control group, the two experimental group and control group were considered to compare answers. All rats were anesthetized by chloroform in day of 15 of pregnancy and the embryos were removed. The results of both the macroscopic and microscopic were analyzed. In microscopic study abnormalities in embryos examined and the following results were obtained: Bleeding in more than 40% of embryos in different areas of the body, anencephaly, asymmetric orientation of the limb, exohepatic, defective growth of limb and C shape body. Conclusion: The ginseng plant has great medical and therapy properties most parts of the world use as a medicinal tonic for everyday applications but its use during pregnancy is dangerous.

Keywords: Ginseng, Female Rat, Teratogenic, Pregnancy

INTRODUCTION

Extensive research has been done about Ginseng in various fields but about its consumption during pregnancy and its risks in this period and impact of this plant on embryo no research work has been done. In this study it was attempt to investigate the effect of an aqueous solution prepared from 500 mg capsules of this herb during pregnancy on fetal mouse of Balb / C. Iran due to its appropriate conditions to grow a variety of plants has adequate coverage of plants and exotic plants that among these plants that many of them are known as a medicinal plant used in traditional medicine and people use them for treatment of different disease in different ways such as boiled vegetables, edible, and dried.

Ginseng is a native plant in China and Korea, which any species of that have not found in Iran yet.

About many properties of this plant and involved mechanisms and effective doses during pregnancy and its effects on the fetus enough animal study have not done yet. The objective of this study was to determine the teratogenic effects of this herb on mice embryos of Balb / C and comparing its complications at higher levels, such as a human. The reason to select this subject of study is due to lack of national and international studies in this field. It is hoped that by doing this research to understand the effects of this herb during pregnancy. Russian scientists have done more than 400 researches on healing effects of Siberian ginseng. The results of all investigations have shown that subjects who used brewed ginseng are usually healthier, fresher, and in coping with adversity of live is endurance. A research group affiliated with Tufts University of Washington in 2010 extracted quinonereductase from American ginseng which is effective in the prevention of premature aging in people (Chen and Ribaya, 2009). In 2006, Japanese scientists extracted several substances from the root of this plant which are;

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Panksyn: increases the strength of muscles in the face of pain and pressure.

Panaks acid: modify the metabolism.

PANA Colin: effect on the endocrine glands.

Panasn : stimulates the central nervous system because of having the Panoxid (Park *et al.*, 2006).

In 2010, Japanese scientists have found that using oral ginseng to improve mood and anxiety in postmenopausal women. This group believed that the main medical ingredients of ginseng are related to ginsinoid PPDS (Proto Panax Adiol) and PPTS (Proto Panax Atriol) that both dissolved in water well and orally have a better effect (Xuet *et al.*, 2010).

A research group in 2013 with experiments on animal models has concluded that anti-fatigue effects of ginseng are related to the impact of ganoids on the central nervous system (Kim and Park, 2013). In 2013 Karwah mentioned that red ginseng has a positive impact to treat erectile dysfunction in men (Leung and Wong, 2013). Also in 2009, reported that ginsinoid Rb2 improve the capacity of spermatogenesis in human through Yesn anti oxygen pathway (Choon and Junglimlee, 2009). Ebrahimi *et al.*, (2011) in a research work in the treatment of cancer rats with busulfan in combination with ginseng and after preceding the treatment phases realized that taking ginseng during treatment with the drug, improve spermatogenesis. So that shows increase in stem cells of spermatogonial and spermatozoa. In this study it was observed that ginseng as a plant contains phytoestrogens gincinoid, the disorders of busulfanas a chemotherapy drug with alkylating properties in germinal epithelium and reduces semen parameters.

Pak and Lim (2005) have studied the effect of red ginseng on polycystic ovary syndrome in rats and concluded that ginseng increases induced growth factor (NGF) in the ovaries (Sawirens and *et al.*, 2011). Studied the effect of ginseng on testicular function in rats with diabetes and concluded that inducing ginseng diabetic rats prevents the degenerations of somniferous tubules.

MATERIALS AND METHODS

In order to prepare Ginseng solution and study its teratogenic effects on the fetus mice of Balb / C was performed according to the following steps:

Ginseng capsules were purchased from pharmacies. To prepare ginseng solution for Intra Peritoneal injection, 500 mg of each capsule distilled in 10ml of distilled water is poured into the flask and solved. Because ginseng hardly dissolves in water, put the prepared suspension in a shaker for 2 hours until well dissolved. Then the solution is passed through a filter, pour the similar amount of solution into the Falcon tubes and centrifuges at 4000 rpm for 15 minutes. After the centrifugation, the solution is ready for injection. Laboratory rats were purchased from the Institute of Razi Vaccine and Serum Research Institute of Hisarak. Then they were kept in animal room with controlled conditions of light, temperature and humidity. Using the automatic timer, light frequency of 12 hours light and 12 hours of darkness was restored. Room temperature using heaters and heating during the winter and cooler in summer was adjusted at 21±2 °C at normal humidity (RH 50-40%). Rat cages each three days cleaned and washed and once a month it was autoclaved and fine wood chips were cast. Their water glasses were controlled and cleaned daily. Prepared rat food purchased from Livestock and Poultry Company and is controlled on a daily basis. In order to determine the specific days of pregnancy, adult female and male rats 2.5-3 month; weighing 24- 28 g were placed in special cages for intercourse with polygamy method. Through observing Vaginal Plug the zero day of pregnancy determined. Intercourse was between 10 pm to 1 am. Therefore, the bases of starting pregnancy considered at 12 midnight. In this way, for injection during determined days of pregnancy after observing vaginal plug, separate male and female rats and were kept in individual cages.

To study the biological effects, prepared aqueous solution of plant and injecting it to the pregnant female rats, determine the LD50 dose at first and multiple doses of 24 to 26 mg injected into rats but there was no mortality in any of the rats. Then, according to the rat weigh the amount of 0.4 g/kg is considered for injection. Before injection, the rats were separated into 4 separate groups of 10.

Group 1 (control) consisted of 10 animals that did not receive any drug or solvent during the experiment.

Group 2 (sham): consisted of 10 animals that distilled water were injected

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Group 3 (experiment 1) considered of 10 animals that consecutively in day of 7 of pregnancy 0.4g/kg aqueous solution was injected.

Group 4 (experiment 2) included 10 animals that consecutively was injected 0.4g/kg aqueous solution in 8th day of pregnancy

Group 5 (experiment 3) of 10 animals that consecutively was injected 0.4g/kg aqueous solution in 9th day of pregnancy

Group 6 (experiment 4) was of 10 animals that consecutively was injected 0.4g/kg aqueous solution in 10th day of pregnancy

All the rats were killed by chloroform in 15th day of pregnancy and dissected.

Injection Method

Prepared solution was injected Intra Peritoneal to pregnant female rats. The reason for this choice was fast absorption of injected substances and their entry into the circulatory system. Before the injection, the rats were weighed carefully. A total of 60 adult female rats put into 6 groups of 10. After we recognize that Ginseng doesn't have LD50 with 0.4 dose applied the injection on experimental groups. All injections were performed at 10-11 am.

Exiting the embryos and fixation process:

After the injection in 15th day of pregnancy, dissection was performed. The rats were killed by chloroform and immediately after death, dissection embryos into the uterus with the help of special equipment exited and placed in normal saline. Then amniotic sac surrounding the fetus was removed carefully.

After washing the embryos in physiological saline solution, with help of caliper the length of Crown-Rump (CR) measured and through precise balance the weight of embryos and placentas determined and recorded. After initial morphological studies, embryos and pairs of experimental and control group were fixed in 10% formalin fixative solution for 24-18 hours.

Methods of Fetal Tissue Sections

Prepared fetal samples were stored in formalin. Then for sectioning and staining was referred to the TMU laboratory.

The fourth step is the preparation of slides:

Slides were placed into the oven for 10 minutes until paraffin melted completely.

Samples were fixed on slides.

Histological and cytological methods of studying sample:

For more accurate study, the Effects of ginseng solution on embryos and control, prepared slides examined carefully with stereo photomicroscope and microscope.

In macroscopic study some abnormalities were observed in embryo. The desired sections were photographed.

Applied Statistical Methods

Since in all the experiments, experimental samples were compared with control and sham groups. For statistical analysis of the results, One Way ANOVA with repeat was used. Tables were prepared. SPSS software was used for data analysis. Statistical analysis of data obtained from the operation was carried out with the help of computers. Desired parameters including mean, standard deviation and variance analysis. In this series of experiments dosage of 0.4 g/kg aqueous solution of Ginseng were injected Intra Peritoneal to pregnant rats in days of 7, 8,9,10 with hygiene. To compare experimental samples and controls with 3 times repeating which means 15 pregnant female rats were considered as control and witness. So that a series of rats without any injection considered as a control and the other series (witness group) were injected with distilled water. Experimental, control and witness rats were dissection in the 15th day of pregnancy. Macroscopic examination revealed that all embryos of control and witness group were healthy. However, the experimental rats that aqueous solution of plant in days 7 to 10 of pregnancy was injected, fetuses with abnormalities was obtained.

The results of injecting ginseng in days of 7, 8, 9, and 10 of pregnancy

The results of injecting ginseng in 7th day of pregnancy

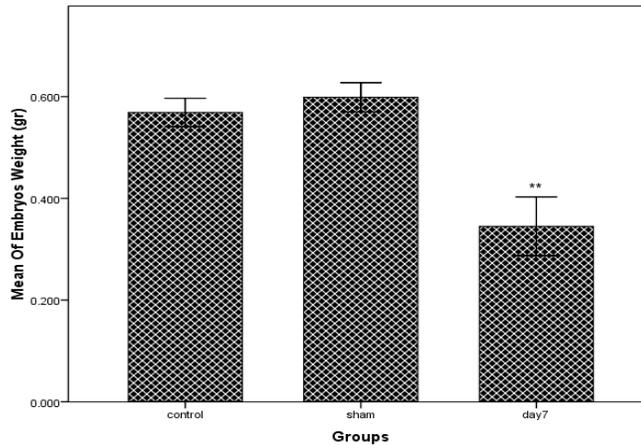
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30 of experimental embryo at 7th day of injection 10 fetuses were apparently healthy (33.4%). A total of 20 embryos had various anomalies (66.6%) which include 7 fetal that showed exohepaticab normality (23.3%) 1 fetus showed exence phalus (3.03%).

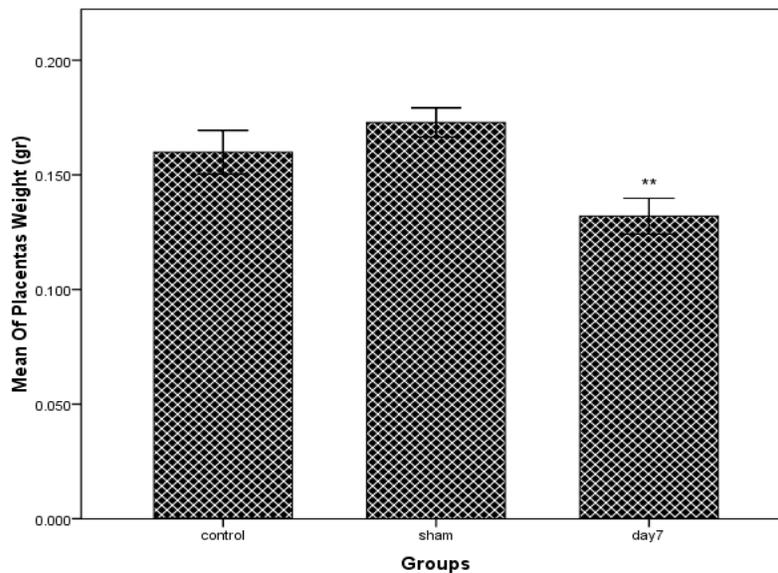
5 embryos showed bleeding under the skin(16.6%) and 5 fetus had umbilical hernia(16.6%) and 2 embryos showed a C-shaped body(6.06%) and 4 rats had uterus with atrophicfetus (40%) and 2 rats had thicken uterus (20%).

The results of Ginseng Injection on Day 7th of Pregnancy

According to the table, it can be said that injecting Ginseng Intra Peritonially in the 7th days of pregnancy causesfetal weight, placental weight, CR embryo and placenta diameter decreases significantly with p value <0.001. It is clear in 1-3 to 3-4 histograms. In histograms of 1 to 4 it is completely clear.

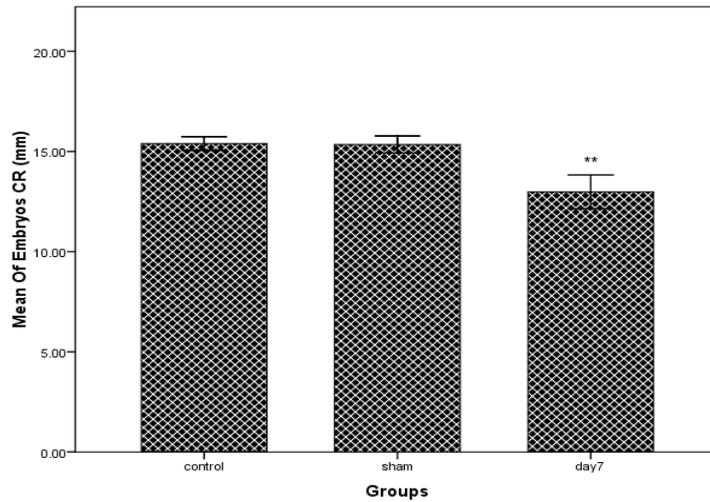


Histogram 1: Comparing the weight of experimental embryos, sham and control in the 15th day of pregnancy of the 7th day of pregnancy experiment series (gr) (P <0.001))

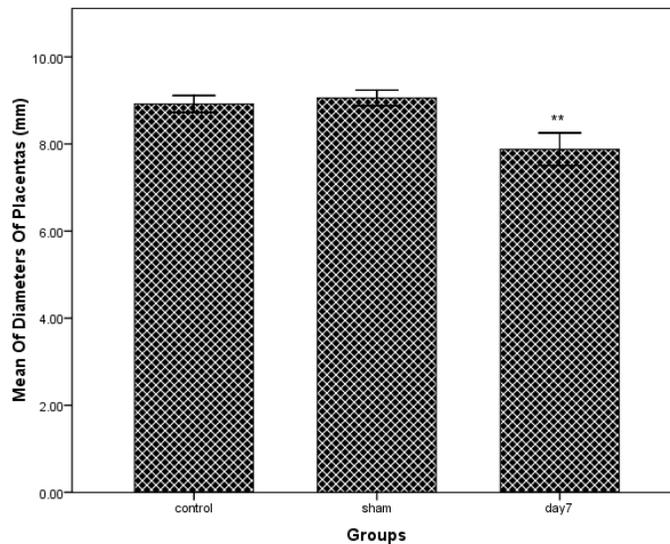


Histogram 2: Comparing the weight of experimental embryos, sham and control in the 15th day of pregnancy of the 7th day of pregnancy experiment series (gr) (P <0.001))

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Histogram 3: Comparing the size of CR in experimental, sham and control embryos in the 15th day of pregnancy of the 7th day of pregnancy experiment series (mm) (P <0.001)



Histogram 4: Comparison of the experimental pairs in diameter, sham and control in the 15th day of pregnancy of the 7th day of pregnancy experiment series (mm) (P <0.001)

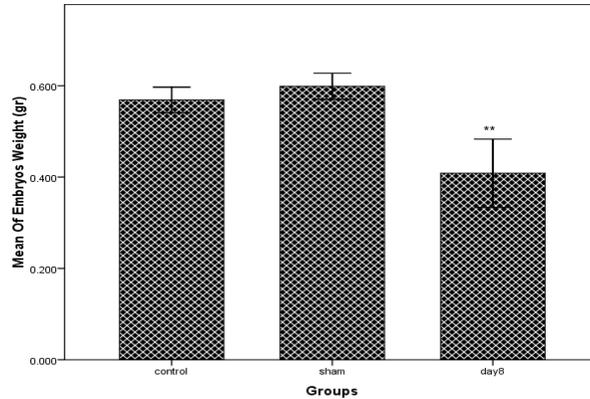
The Results of Ginseng Injection on 8th Day of Pregnancy

In this series of experiments dosage 0.4 mg/kg.bw was injected to the pregnant rats on 8th day of pregnancy. For comparative analysis, experimental samples with the same number of controls, the control rats considered as sham. So that control rats didn't injected and distilled water was injected sham group. Embryos of experimental, control and sham were isolated on the 15th day of pregnancy from the mother womb. Initial macroscopic examination revealed that all embryos of sham and control were healthy. A total of 38 experimental embryos on the 8th day of injection 7 embryos were apparently healthy(18.43%), 31 fetuses had various abnormalities (81.57%) that include; 6 fetuses had exohepatic abnormalities (15.78%) 1 embryo had Exencephalus (2.63%), 1 fetus had a C-shaped body(2.63%) . 8 fetuses showed bleeding under the skin(21.02%) and 6 embryos had inguinal hernias (15.78%) and 6 rats had thickened uterus and atrophic embryo (60%).

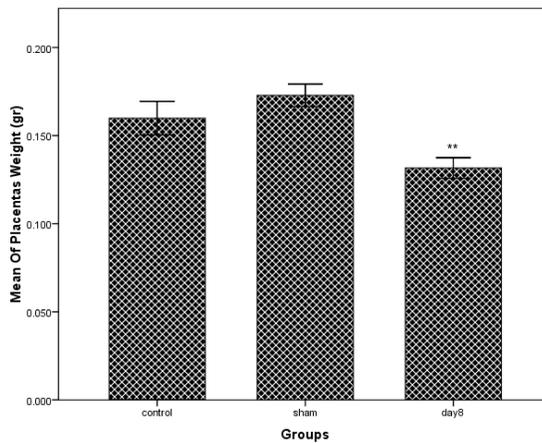
The Results of Ginseng Injection on 8th Day of Pregnancy

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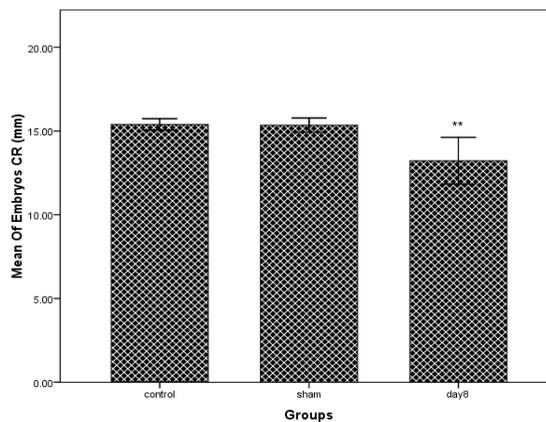
According to the table, we can say that injecting ginseng Intra Peritonically on the 8th day of pregnancy causes fetal weight, placental weight, embryo CR fetal placental diameter significantly decrease with p value <0/001. In histogram of 5 to 8 it is clear.



Histogram 5: Comparing the experimental fetus weight, sham and control on the 15th day of pregnancy of the 7th day of pregnancy experiment series (gr) (P <0.001)

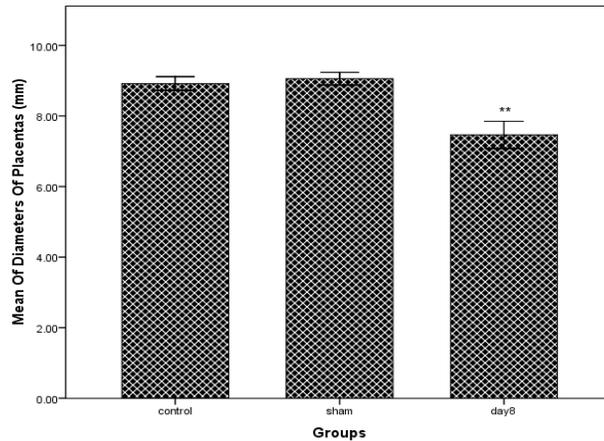


Histogram 6: Comparing the weight of experimental pairs, sham and control on the 15th day of pregnancy of the 7th day of pregnancy experiment series (gr) (P <0.001)



Histogram 7: Comparing the size of CR in experimental, sham and control embryos on the 15th day of pregnancy of the 8th day of pregnancy experiment series (mm) (P <0.001)

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Histogram 8: Comparing diameters of experimental, sham and control embryos on the 15th day of pregnancy of the 8th day of pregnancy experiment series (mm) (P <0.001)

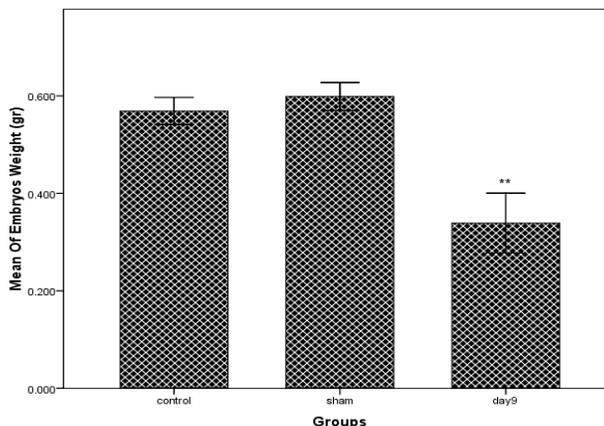
The Results of Injecting Ginseng on 9th Day of Pregnancy

In this series of experiments dosage of 0.4mg/kg.bw were injected intraperitoneally to pregnant rats on 9th day of pregnancy. In order to comparative analysis experimental samples with the same number of controls were considered as sham in rats. So that the control rats didn't inject and the distilled water was injected to sham group. Experimental, control and sham were isolated from the mother womb on the 15th day of pregnancy. Initial macroscopic examination revealed that all embryos of control and sham were healthy. A total of 35 experimental embryos of 9th day of injection, 7fetuseswere apparently healthy (20%), 28 of foetuses had various anomalies (80%) that are;

7 of embryos showed exohepatic abnormality (20%) 3 foetus showed exencephalus (8.57%). 2 fetuses had a C-shaped body (5.71%).8 fetuses showed bleeding under the skin (22.58%) and 6 embryos had inguinal hernias (17.14%) and 2 fetuses had asymmetric navigation of foot and hand and lack of foot formation (5.71%) and 1 rat with thickened uterine and 5 rats had uterine with atrophic fetus that they were 6 infertile uterine (60%).

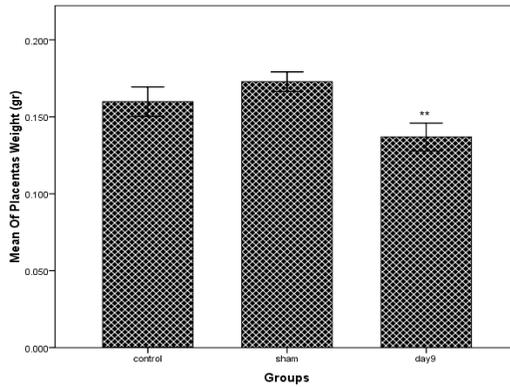
The Results of Ginseng Injection on 9th Day of Pregnancy

According to table (6-3) it can be said that injecting ginseng intraperitoneally on 9th day of pregnancy cause decrease significantly in the Fetal weight, Placental weight, fetus CR, and placenta diameter with p value <0/001. It is obvious in histograms of 9 to 12.

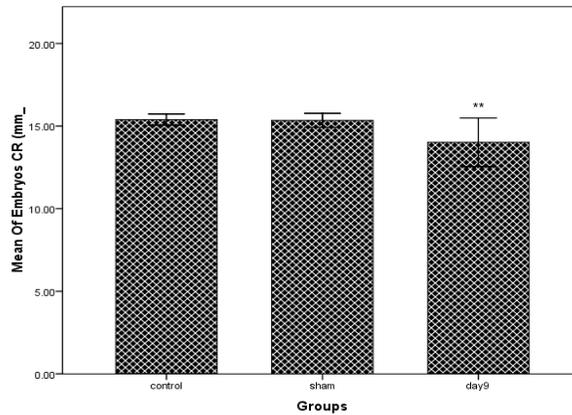


Histogram 9: Comparing the weight of experimental, Sham and control embryo, on the 15th day of pregnancy of experiments of 9th day of pregnancy (gr) (p value <0/001)

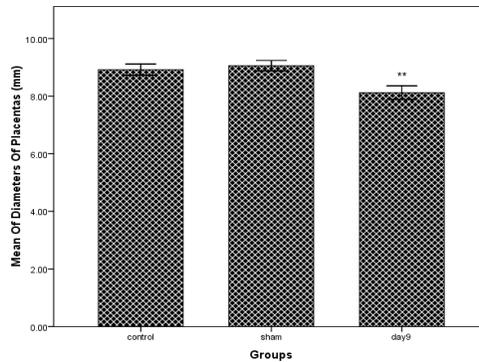
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Histogram 10: Comparing the weight of experimental, Sham and control embryo, on the 15th day of pregnancy of experiments of 9th day of pregnancy (gr) (p value <0/001)



Histogram 11: Comparing the size of CR in experimental, Sham and control embryo on the 15th day of pregnancy of experiments of 9th day of pregnancy (mm) (p value <0/001)



Histogram 12: Comparing diameters of experimental, Sham and control pairs on the 15th day of pregnancy of experiments of 9th day of pregnancy (mm) (p value <0/001)

The Results of Ginseng Injection on 10th Day of Pregnancy

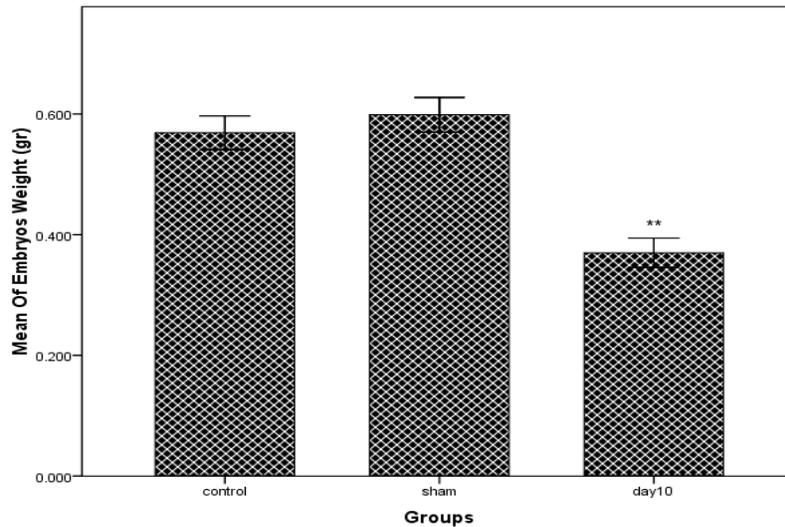
In this series of experiments dosage of 0.4mg / kg.bw soluble ginseng, intraperitoneally into pregnant rat were injected on day 10 of pregnancy. Comparative analysis of experimental samples with the control, with the same numbers control rats considered as sham. So that nothing were injected to control rats and distilled water was injected into sham. Experimental, control and sham embryos were isolated on the 15th day of pregnancy from the mother womb. Initial macroscopic examination revealed that all embryos of control and sham were healthy. 17 of experimental embryo on the 10th day of injection, and 2 fetus were

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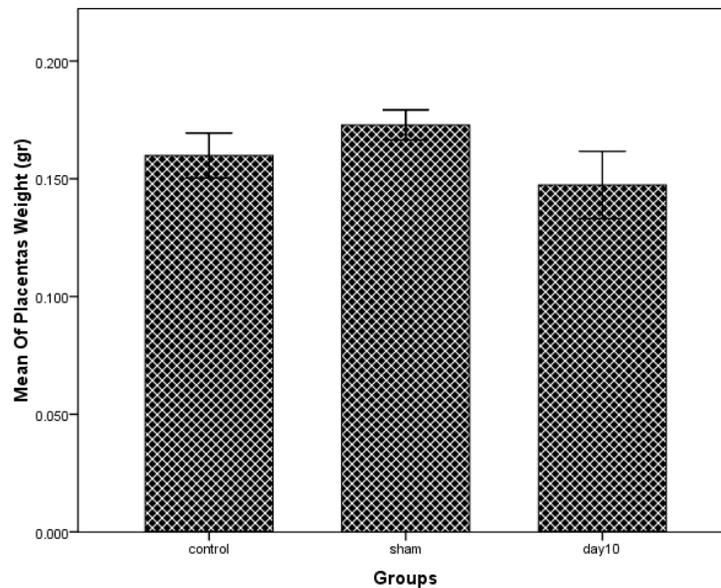
apparently healthy (11.76%) 15 of the embryos had various abnormalities (88.24%) that include; 3 fetus showed exohepatic abnormalities (17.64%), 3 fetuses were with a small placenta (17.64%), 5 fetus showed bleeding around the ears and spine (29.41%) 3 fetuses were with umbilical hernia (17.64%) and also 1 fetus showed tilt of the head from the axis of body (5.88%) and 5 fetus were with thickened uterus and had atrophic embryo (50%).

Examine the Results of Ginseng Injection on 10th Day of Pregnancy

Injecting ginseng intraperitoneally on the 10th day of pregnancy causes significant decrease in Fetal weight, fatal CR, and placenta diameter with $p < 0/001$ (Histopathology grams, 13, 15, 16). Placental weight decreased but it was not significant (histogram 14).

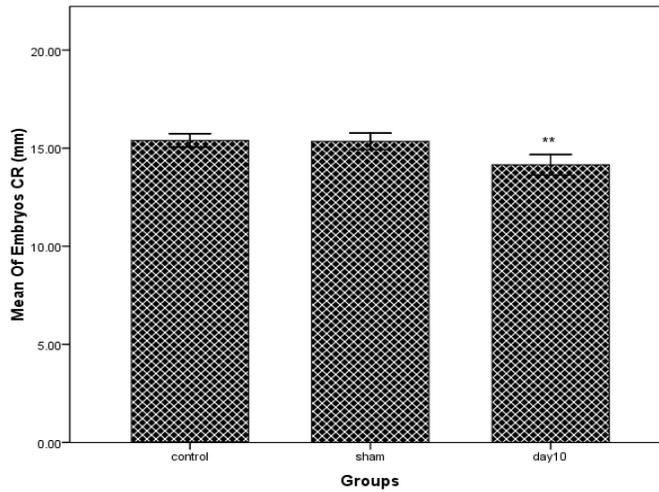


Histogram 13: Comparing the weight of experimental, Sham and control embryo, on the 15th day of pregnancy of experiments of 10th day of pregnancy (gr) (p value <0/001)

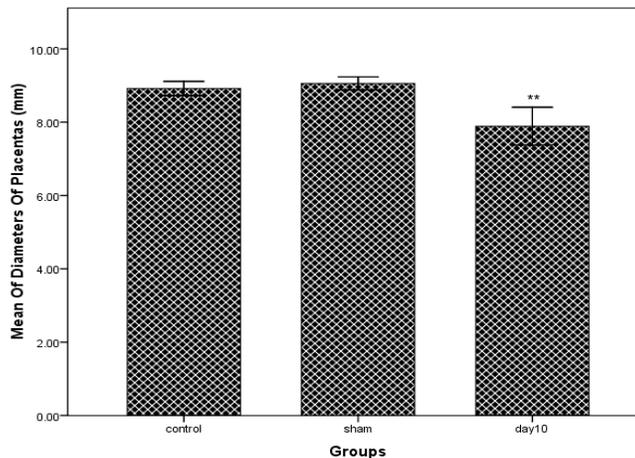


Histogram 14: Comparing the weight of experimental, Sham and control embryo, on the 15th day of pregnancy of experiments of 10th day of pregnancy (gr)

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Histogram 15: Comparing the size of CR in experimental, Sham and control embryo on the 15th day of pregnancy of experiments of 10th day of pregnancy (mm) (p value <0/001)



Histogram 16: Comparing the diameter of pairs of experimental, Sham and control on 15th day of pregnancy of experiments of 10th day of pregnancy (mm) (p value <0/001)

The Results of Studies on Fetuses with Exohepatic Abnormalities (Herniated Liver)

Macroscopic and microscopic examinations of fetuses with exo hepatic abnormalities in comparison with control embryos reveals that liver enlarged, abdominal wall from the chest to the abdomen and flank area is opened and the abdominal wall from the chest to the abdomen and flank area is opened and the liver is seen out of the body. This abnormality observed in each 4 days of pregnancy. Of course with different percentages, on the 7th day of pregnancy (23.3%) which is the highest percentage in the injection of 7th day. 8th day of pregnancy (15.78%), 20th day of pregnancy (20%) and 10th day of pregnancy (17.64%) was observed.

Examine the Results of Studies on Fetal with Abnormalities in the Limb

It was observed in macroscopic examination that there is asymmetric orientation in limbs of hand, foot and also the feet are not formed in experimental embryos which were observed on 9th day of pregnancy.

Examine the Results of Studies on Embryos with Subcutaneous Hemorrhage

It was observed in the macroscopic examination, that there are subcutaneous hemorrhages in different parts of the body including the scalp, face, and ears, lumbar and so on. Sometimes there is bleeding in the leg and tail. The bleeding was observed on different days with different percentages so that on the 7th day

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of pregnancy (16.6%), on the 8th day of pregnancy (21.02%), on the 9th day of pregnancy (22.85%), and on the 10th day of pregnancy (29.41%) that these abnormalities were more than the other days in the injection of 10th day of pregnancy.

Examine the results of studies on embryos with xencephalus (protrusion of the brain):

Examine the embryos with exencephalus through stereomicroscope revealed the brain protrusions. For more detailed analysis, Microscopic sections were prepared from the exencephalus embryos that the abnormality observed on different days of gestation with different percentages so that on the 7th day of pregnancy (3.03%), on the 8th day of pregnancy (2.63%) and on the 9th day of pregnancy (8.57%) was observed. This abnormality was not observed on the 10th day of pregnancy. The highest percentage of this abnormality was on the 9th day injection.

Examine the performed studies on fetuses with umbilical hernia:

In the macroscopic and microscopic examination experimental embryos, had a hiatal hernia so that different percentages observed on different days. On the 7th day of pregnancy (16.66%), 8th day of pregnancy (15.78%), 9th day of pregnancy (17.14%) and on the 10th day (71.64%) was observed.

Examine the performed studies on fetuses with C- Shape body:

In macroscopic and microscopic examination, some of the experimental embryos had c- shape body so that different percentages observed on different days. On the 7th day of pregnancy (6.06%), on the 8th day of pregnancy (2.63%), on the 9th day of pregnancy (5.71%) and on the 10th day of pregnancy this abnormality did not observe.

RESULTS AND DISCUSSION

Ginseng solution was injected intra peritoneally into adult rats. In this method the substance is rapidly absorbed into the visceral peritoneum and then entered to the liver and bloodstream. In the present research several abnormalities observed due injecting ginseng on 7, 8, 9, 10 days of pregnancy which include;

In this series of experiments, injecting ginseng with dosage of 0.4 mg / kg.bw causes abnormal embryos in the nervous system with Exencephalus, so that abnormalities observed as follow; on the 7th day of pregnancy (3.03%), on the 8th day (2.63%), on the 9th day (8.57%). Probably meningeal membrane is not formed in different parts of the brain and protrusion of the brain has occurred (5).

According these results, ginseng can be introduced as a neurotropic teratogen.

Compare the size of the crest- rump (CR) in 15 days experimental embryos revealed a decrease in comparison with other groups of control and sham so that significant decrease in embryos CR observed on days of 7, 8 and 9 of pregnancy ($p < 0.001$) and on 10th day of pregnancy ($p < 0.05$).

Probably, ginseng had inhibitory effect on the growth hormone of the pituitary gland. The pituitary gland has a buff form structure and located at the basis of brain. This gland is called the leader. The pituitary gland secretes several hormones.

The hormone that plays an important role in growth of organ is Somatropin or growth hormone. This hormone has an important role in growth and bone formation (height, arm and leg length) (4) that with reduction of height, weight and organs in experimental rats we conclude that ginseng has a significant impact on growth hormone and causes the CR reduction. In a series of experiments of injecting ginseng with dosage of 0.4 mg/kg.bw on days of 7, 8, 9 and 10 the exohepatic abnormality observed, so that on the 7th day of pregnancy (23.3%), on the 8th day (15.78%), on the 9th day of pregnancy (20%) and on the 10th day of pregnancy was (17.64%) due to the non formation of the peritoneal membrane from the chest to the end of abdominal area caused the herniated liver.

Also it was observed that abnormalities in limb or non formation of limb or Incomplete formation of organs, so that on the 9th day (5.71%) this abnormality were observed that according to these results ginseng can be introduced as a kind of teratogene for the growth and development of limb. Ginseng directly effects on the fetus during organogenesis (rat embryo). Limb development begins when mesenchymal cells of the partial layer or somatic mesoderm of lateral plate and xylotomy mesoderm (part of the spine) with the each other accumulate under the ectodermic.

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Tissue and creates a spike named limb bud. Most of the limb bud cells after performing its function undergo apoptosis and only the expressing cells of BMP remains. These cells preferentially convert to bone, muscle and the skin of the posterior limb. In fact the posterior limb of rats is created by the BMP-secreting cells. So we can mention that ginseng make damage to the limb bud and the genes that should be expressed on that part for the formation of limbs and fingers and inhibit expression of genes and causes the creation of fetus with limb abnormality (not forming organs, defective formation of organs, not the formation of the fingers or toes) (13). When there is a defect in the expression of Chordin and Noggin genes in rat, the formation of eye, ear and limb faces problem (3) probably ginseng affect the expression of these genes and their expression faces the problem. In macroscopic studies, some experimental fetuses after injecting ginseng with dosage of 0.4 mg/kg had severe bleeding under the skin on the scalp, face, ears, body, and tail so that on the 7th day of pregnancy(16.6%), on the 8th day of pregnancy(21.02%), on the 9th day of pregnancy(22.85%) and on the 10th day of pregnancy(29.41%) of this abnormality was observed which is probably due to the non formation of the Platelets or defective formation of them severe subcutaneous bleeding occurred. Platelets are the spherical or elliptical form

Bodies which are produced from the segmentation of large cells cytoplasm in the bone marrow that called megakaryocytic. Mega karyocytes are the stem cells of the platelets and their non- differentiation cause decrease of platelet and consequently severe bleeding under the skin can occur. Platelets are non-core. Platelets are not only through the contraction of vascular smooth blood clotting but also help prevention of bleeding(13) Studies show that injection of Ginseng reduces blood platelets and results in severe bleeding under the skin and placenta.

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