

Original Research Article

Effect Study of *Verbena Officinalis* Medicinal Herb on Sex Hormones Level of NMRI Female Rats During Pregnancy

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ABSTRACT

The use of medicinal herbs in the treatment of diseases has become increasingly widespread, in this regard the *Verbena officinalis* is considered as one of the herbs that affects pregnancy. The present study was conducted to investigate the *Verbena officinalis* herb on the level of sex hormones of NMRI female rats during pregnancy. This is an experimental study which divided 40 rats into 5 groups of 8 each and the groups included control, sham, and experimental with 5, 10, and 15 mM alcoholic extract of *Verbena officinalis*. The serum levels measurement of FSH and LH hormones was done using ELISA (Biotech) method. After blood sampling, the ovaries were stained with hematoxylin eosin for histological examination. Cell count and thickness measurement of different ovarian cells, primitive follicles, primary follicles, growing follicles, graph follicles, lymph nodes, blood vessels, atretic follicles, and abnormal follicles (1 or 2 oocytes in one follicle) were examined microscopically in 6 segments of tissue segments from different groups. The statistical analysis was performed using SPSS23 software.

The findings of the present study showed that the consumption of alcoholic extract of *Verbena officinalis* significantly reduced the levels of LH, FSH, the number of abnormal follicles, the number of graph follicles, and the number of corpus luteum in the experimental group compared to the control group ($p \leq 0.05$), the number of primary follicles, the number of growing follicles, the number of ethereal follicles, and the number of blood vessels in the experimental group compared to the control group ($p \leq 0.05$). The weight, ovarian weight, ovarian diameter, secondary follicle diameter, and primary follicle diameter decreased in experimental groups compared to control group and sham group; however, this decrease was not significant and abnormal follicle diameter in experimental groups compared to control group and group. Sham increased but this increase was not significant ($p > 0.05$). The results of the present study show that consumption of *Verbena officinalis* medicinal plant can be effective in abortion.

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Introduction

In traditional medicine, the special attention has been paid to the use of medicinal herbs and the useful and valuable effects of some herbs have been identified [1]. Medicinal plants have natural antioxidant compounds, since the consumption of some synthetic antioxidants is limited due to their toxicity, so the medical, food and pharmaceutical industries are focused to the use of natural antioxidants especially those in medicinal plants [2].

Verbena officinalis with its scientific name belongs to the Verbenaceae family. It is found along roadsides and sunny meadows as well as near rivers and grows wildly [3]. *Verbena officinalis* is a perennial plant with several straight stems (30 to 60 cm) found in West Asia, North Africa, and throughout Europe [4]. The important compositions of *Verbena officinalis* herbaceous species include Flavonoids, Alkaloids, Glycosides, and Steroids compounds [5]. Moreover, it has antidepressant and anticonvulsant properties [6]. It has further been proved to be useful in the treatment of liver, gall bladder diseases, and neurological disorders [7]. The species of this plant has been used for the treatment of hormonal diseases of women and hormonal regulation [8]. *Verbena officinalis* reduces serum levels of testosterone, LH, and FSH in the male rats [9]. The unsaturated fatty acids in this plant species by decreasing the number of LH receptors present on the surface of Leydig cells, reduces testosterone secretion, which has a negative effect on male fertility [10]. The extract compounds of this plant with effect on dopamine receptor in hypothalamus and anterior hypophysis, inhibits prolactin secretion, increases progesterone secretion, and induces normal formation of the corpus luteum [11]. It has been determined that this plant with estrogenic and progesterone function, stimulates uterine activity and prevent abortion [12]. It has also been revealed that it has various effects on

different stages of rat development, including improvement of fetal growth on days 8 and 9 of pregnancy, and the appearance of abnormalities in the rat skeletal axis [13].

The aim of this study is to investigate the effects of the medicinal *Verbena officinalis* herb on the level of the sex hormones of female rats during pregnancy.

The use of herbs to treat diseases in traditional medicine has always been considered, today for abortion are used chemical drugs which have side effects. In the present study, the extract of *Verbena officinalis* medicinal plant was used in abortion along with microscopic images which can provide new information on the subject of abortion.

Material and Methods

This was a laboratory study in which all experiments were performed in the cellular and molecular research department of Yasuj University of Medical Sciences. First, the adult female NMRI rats were weighed with 25 to 30 g from the Pasteur Institute of Tehran and transferred to the Animal Care Room of medical faculty of Yasuj University of Medical Sciences. In order to adapt the animals to the new environment, the experiments were resumed following a one-week gap. The animals were housed in specified, standard-size plastic cages where food and water were accessible, and wood chips were used as their cage bed. The feeding of these animals was done by special and prepared plates (Iranian Medical Industries Production) and the water used was the tap water of Yasuj City, which was provided with special glass to the animals. The temperature of the animal breeding room was 23 ± 2 °C, which was maintained by the cooler during the warm seasons and by the heater in the cold seasons. The rat cage was cleaned twice a week. The *Verbena officinalis* was prepared at concentrations of 5, 10, and 15 mM. Rats were divided into 5 groups as follow:

- 1- Control group (without injection of *Verbena officinalis* alcoholic extract)
- 2- Sham group (0.5 mL injection of deionized distilled water as a solvent of *Verbena officinalis* alcoholic extract)
- 3- Experimental group 1 (5 mM injection of *Verbena officinalis* alcoholic extract)
- 4- Experimental group 2 (10 mM injection of *Verbena officinalis* alcoholic extract)
- 5- Experimental group 3 (15 mM injection of *Verbena officinalis* alcoholic extract) [3].

The injection was done intraperitoneally. The control group received no injections. For sham group, the distilled water and for experimental groups, the desired concentration of alcoholic extract of *Verbena officinalis* was injected for 14 consecutive days [14]. One day after the last injection, all groups were anesthetized by ether (Iran production Medical Industries). Blood was drawn directly from the left ventricle. The blood samples were kept in the fixed laboratory for 15 to 20 minutes and then centrifuged (RPM) for 5 minutes at 3600 rpm. The serum levels of FSH and LH were measured by ELISA (Biotech). After blood sampling, the ovaries were removed for histological examination, and then they were transferred to a Bowen-containing container. After 4 hours, they were immersed in 70% alcohol. After the dewatering and molding steps of each group, 12 slides were prepared with serial slices from 5 to 7 μm and stained with hematoxylin eosin (Merck) [15].

The cell count and thickness measurement of different ovarian cells, primitive follicles, primary follicles, growing follicles, graph follicles, Corpus luteum, blood vessel, atherosclerotic follicles, and abnormal follicles (presence of 2 or 3 oocytes in one follicle) at 6 cross sections of tissue sections from different groups were examined microscopically. The analysis and comparison of the means were performed by SPSS 23 software considering one-way ANOVA and Tukey's test. Then, the histograms were plotted using Excel software.

Results

The results revealed that by using alcoholic extract of *Verbena officinalis* in experimental group 2 and 3, the level of blood Serum LH decreased significantly in comparison to both control and sham groups, in a way in the control group it decreased from 21.23 mIU/mL to 26.33 mIU/mL in experimental group 2 and 24.16 mIU/mL in experimental group 3 ($p \leq 0.05$) (Figure 1).

By consuming the alcoholic extract of *Verbena officinalis*, the FSH levels in experimental group 1, 2, and 3 were significantly decreased compared to control and sham groups, in a way that it decreased from 62.69 mIU/mL to 56.45 mIU/mL in experimental group 1, 46.18 mIU/mL in experimental group 2, and 43.86 mIU/mL in experimental group 3 ($p \leq 0.01$) (Figure 2).

Results revealed that in experimental groups 1, 2, and 3 the number of primary follicles and abnormal follicles increased compared to control and sham groups, but this increase was not significant ($p > 0.05$). The number of the primitive follicles and the number of growing follicles in experimental group 2 and 3 were significantly higher than control and sham groups ($p < 0.05$). The number of graph follicles in experimental group 2 and 3 was significantly decreased ($p < 0.05$) compared to control and sham groups. Atretic follicles were significantly increased in experimental group 1, 2, and 3 ($p < 0.05$).

Table 1 presents the effect of alcoholic extract of *Verbena officinalis* on the number of follicles, the number of corpus luteum, and the number of blood vessels. The results revealed that the atretic follicle counts in experimental group 1, 2, and 3 was significantly higher than control and sham groups ($p < 0.05$). The number of corpus luteum in experimental group 1, 2, and 3 was significantly decreased ($p < 0.05$) compared to control and sham groups. The number of blood vessels in the experimental group 3 was significantly higher than the control and sham groups ($p < 0.05$). (Table 1).

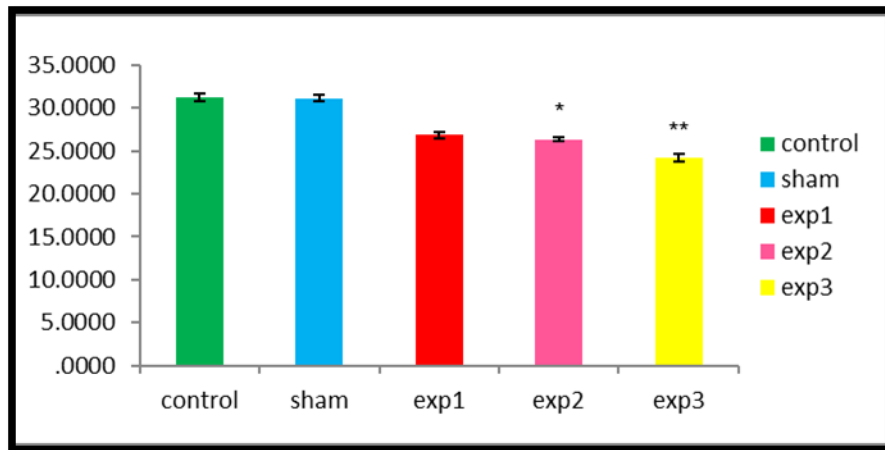


Figure 1. Results of the comparative analysis of LH hormone level in experimental control, sham groups 1, 2, and 3 (* $p \leq 0.05$, ** $p \leq 0.01$)

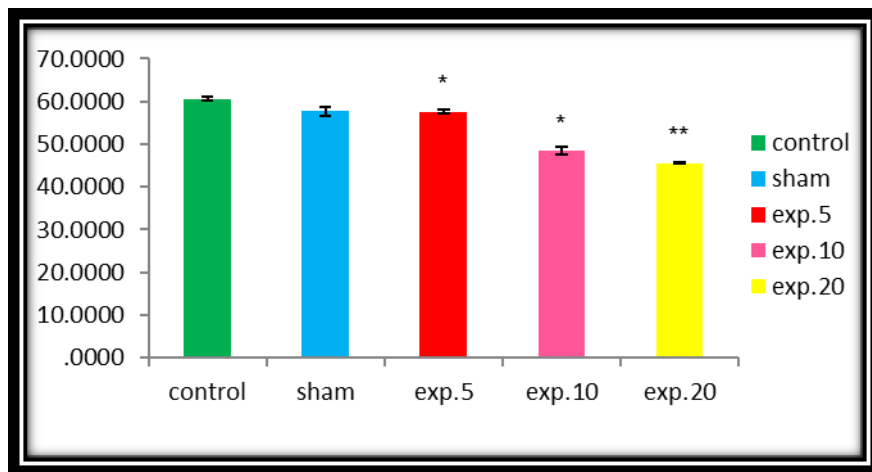


Figure 2. Results of the comparative analysis of FSH hormone levels in experimental control, sham groups 2, 1, and 3 (* $p \leq 0.05$, ** $p \leq 0.01$)

The results illustrated that rats weight, ovarian weight, ovarian diameter, the secondary follicle diameter, and the primary follicle diameter decreased in experimental groups compared to control and sham groups. However, this decrease was not significant and abnormal follicle diameter increased in experimental groups compared to control and sham groups but this increase is not significant ($p > 0.05$) (Table 2). Primary follicle diameter increased significantly ($p < 0.05$) in experimental group 3 compared to control and sham groups. The diameter of

growing follicles in experimental group 3 was significantly decreased ($p < 0.05$) compared to control and sham groups. The follicle diameter of the graph and the diameter of the corpus luteum in experimental groups 2 and 3 were significantly decreased at the level of $p < 0.05$ and $p < 0.01$, respectively, compared to the control and sham groups. Ertic follicle diameter in experimental groups 2 and 3 increased significantly at $p < 0.05$ and $p < 0.01$ levels, respectively compared to control and sham groups (Table 2).

Table 1. Results of statistical analysis of the effect of alcoholic extract of *Verbena officinalis* on follicle count, corpus luteum, and blood vessel count in sham and experimental control groups 1, 2, and 3

Observation /Treatment	Control	Sham	Experimental group 1	Experimental group 2	Experimental group 3
number of primary follicles	3.16±0.16	3.33±0.32	4.52±0.21	5.32±0.21	4.43±0.24
number of primitive follicles	4.5±0.22	4.66±0.21	7±0.25	**8.66±0.41	**10.33±0.33
number of growing follicles	2.33±0.42	3±0.36	2.83±0.5	**4±0.25	**4.4±0.35
number of graph follicles	5.5±0.22	4.5±0.22	2±0.36	**1.33±0.51	**1.11±0.21
number of Atretic follicles	0.28±0.11	0.33±0.21	**2.66±0.21	**4±0.36	**5.33±0.45
number of corpus luteum	3.66±0.35	3.5±0.42	*2.16±0.35	*1.96±0.16	**1.32±0.47
number of blood vessels	8.83±0.16	12.66±1.05	11.16±0.87	**13.5±0.67	**13.66±0.45
number of abnormal follicles	0	0	1±0	1.25±0.25	1.5±0.28

Table 2. Results of statistical analysis of the effect of alcoholic *Verbena officinalis* extract on different parts of ovarian tissue diameter and animal weight

Observation. treatment	Control	Sham	Experimental group 1	Experimental group 2	Experimental group 3
Animal weight	34.04±0.99	33.50±0.50	32.21±0.57	29.51±0.80	26.02±0.57
Ovarian weight	13.40±0.53	12.31±0.25	11.30±0.25	9.91±0.29	8.91±0.30
Ovary diameter	131.66±3	134.58±3.25	110.41±3.84	104.16±2.63	101.25±1.25
Diameter of the primitive follicle	4.50±0.22	4.03±0	3.66±0.33	3.33±0.21	3.88±0.36
Primary follicle diameter	7.83±0.16	8.66±0.33	10.33±0.33	9.66 ±0.21	*10.33±0.55
growing follicles	22.50±1.11	20.83±0.54	15.83±0.83	15.01±0	**12.50±1.70
secondary follicle diameter	19.16±0.83	18.50±0.34	14.50±0.84	13.50±0.22	12.01±0.81
Grapefruit CrossFit	39.16±0.83	37.50±1.11	30.50±1.7	*26.83±1.35	**25.03±1.09
Etertic follicle diameter	5.83±3.74	13.33±1.66	15.04±1.12	*16.83±1.53	*18.50±0.76
Yellow body diameter	36.66±1.66	32.50±1.11	29.66±1.11	*24.16±0.83	**24.83±1.60
Abnormal follicle diameter	0	0	12.21±0.70	13.75±1.25	13.75±2.39

Photomicrographs were prepared from ovarian specimens of experimental, control, and testator/witness groups that by increasing the dose of the consumed material, in ovarian tissue,

of the decreased diameter of the corpus luteum (Figure 3), increased atretic follicles as well as the presence of abnormal follicle (the presence of two oocytes in one follicle) (Figure 4), decrease

in graph follicle diameter, the presence of abnormal follicle (three oocytes in one follicle), single layer disruption and ovarian stromal disruption compared to control, sham, and witness groups (Figure 5), increased primitive

follicles (Figure 6) increased growth follicles, and decreased diameter of growing follicles, decreased luteinization, and irregularities of luteal cells were observed in the experimental group compared to controls (Figure 7).



Figure 3. Ovarian tissue of the second experimental group by injection of 10 mg of *Verbena officinalis* alcoholic extract per kg of rat weight. Attention should be paid to 100X hematoxylin-eosin staining and increase in atretic follicles as well as follicle destruction. A: Primitive follicles, B primary follicles, C atretic follicles, D: growing follicles, E: Graph follicles, F: blood vessel, G: corpus luteum, and H: blood vessel

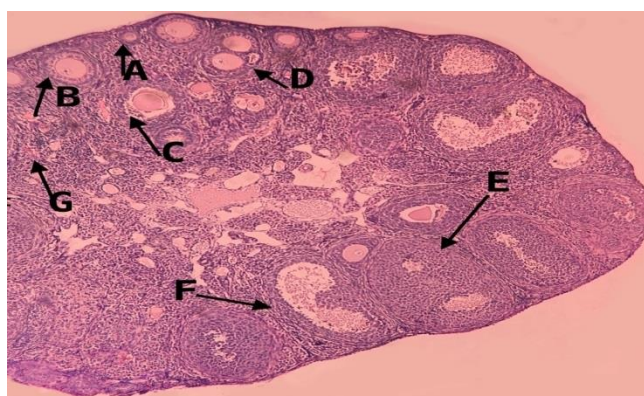


Figure 4. Ovarian tissue of the second experimental group by injection of 10 mg of *Verbena officinalis* alcoholic extract per kg of rat weight, Hematoxylin-Eosin 400X staining, the reduction of the corpus luteum, and the increase in atretic follicles as well as the absorbance of oocyte follicles graphs.

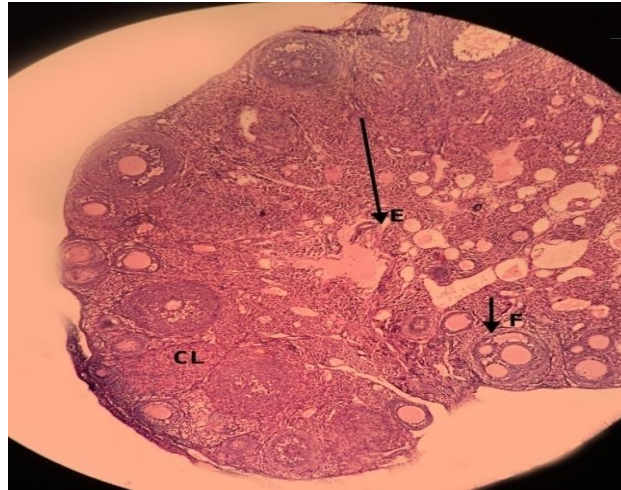


Figure 5. Ovarian tissue of experimental group 3 to (E) Irregular stroma (the presence of three oocytes in follicle (F) Reduction of the number and size of the corpus luteum and Hematoxylin-Eosin 400 X staining should be taken into consideration.

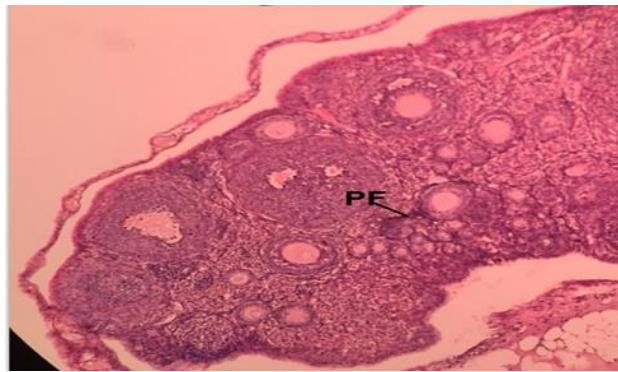


Figure 6. Part of ovarian tissue, increasing number of primitive PF follicles and Hematoxylin-Eosin 400 X staining

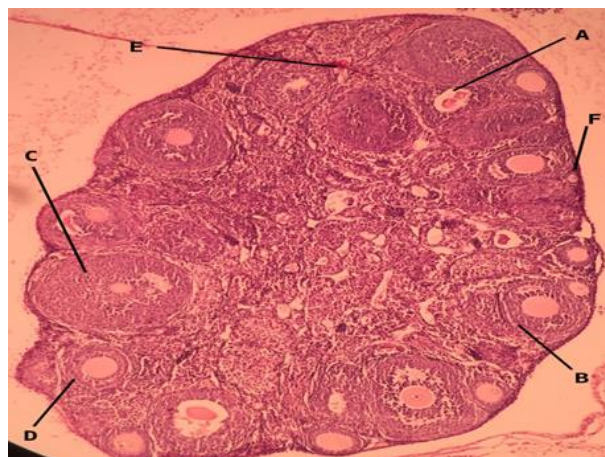


Figure 7. Ovarian tissue of the experimental group, paying attention to the decrease in the number of the corpus luteum and the increase in the growing follicle. A- atretic follicles, B-growing, C- secondary follicle, D-Primary follicle, E-blood vessel, F-primitive follicle, and Hematoxylin-Eosin 400X primitive staining

Discussion and conclusion

The purpose of this study was to investigate the effects of medicinal plant of *Verbena officinalis* flower on the sex hormones of NMRI rats during pregnancy. The results of this study were significant. Fertility and its control in the public health system are important issues, so a number of researches have been conducted to find an effective, low-cost, and low-conditional drug in infertility treatment or fertility control. In the meantime, medicinal plants have proved to be effective in experimental research and are regarded as the first stage of care in many parts of the world [17]. Various experimental studies have investigated the effect of medicinal plants on infertility, birth rate and sex ratio of neonates [18]. On the other hand, in previous studies, histomorphological changes of the other species of this plant (*V. negundo*) have been demonstrated and proved in rats [19]. According to the results of this study, the prescription of alcoholic extract of *Verbena officinalis* flower caused significant changes in placental structure and survival rate of neonatal rats. In the present study, the consumption of *Verbena officinalis* alcoholic extract in experimental group 2 and 3 significantly decreased LH and FSH hormones level in blood serum as compared with control and sham groups, the results of this study revealed that in experimental group 1, 2, and 3, the number of primary follicles increased compared to control and sham groups, but this increase was not significant.

The present results indicated that the number of primitive follicles in experimental group 2 and 3 was significantly increased compared to control and sham groups. The number of growing follicles in experimental group 2 and 3 increased significantly compared to the control and sham groups. The number of graph follicles in experimental group 2 and 3 was significantly decreased compared to the control and sham groups.

Concerning abnormal follicles, the results showed that despite the increase of follicle numbers in the experimental groups compared to the control and sham groups, this difference was not significant.

The findings of this study demonstrated that the number of lutein corpus in the experimental group 1 and 2 and in the experimental group 3 decreased significantly. The results illustrated that the number of blood vessels in the experimental group 3 was significantly increased compared to the control and sham groups. The results of this study implied that rats weight, ovarian weight, ovarian diameter, secondary follicle diameter, and primary follicle diameter decreased in experimental groups compared to control and sham groups. However, this decrease was not significant and abnormal follicle diameter increased in experimental groups compared to control and sham groups, but this increase was not significant.

Photomicrographs were prepared from the ovaries samples section of experimental, witness, and control groups that by increasing the dose of consumed material, in ovarian tissues decreasing the diameter of the corpus luteum, increasing atretic follicles as well as abnormal follicles (two oocytes in one follicle), decreasing Graf follicle diameter abnormal follicles (three oocytes in one follicle), single layer disruption and ovarian stromal disruption compared to control and sham groups and witnessing an increase in primitive follicles, an increase in growing follicles, and a decrease in diameter of growing follicles, decreased corpus luteum, and irregularities of corpus luteal cells in the experimental group compared to controls.

Azernia et al. (2007) showed that the *Verbena officinalis* flower produces important ethers during pregnancy in different stages of rat embryo development (weight gain and growth), which is not in line with the results of the present study. On the other hand, the researchers indicated that the *Verbena officinalis* herb

resulted in an increase in fetal body length on day 8–9 of pregnancy and caused abnormalities in the skeletal axis, in fact, the plant has the dual effect of enhancing fetal growth and, on the other hand, adverse effects on the development of vital organs including the eye and liver [13]. In another study, Dogua et al. (2008) revealed that during pregnancy, there was little theoretical and laboratory evidence of uterine stimulation, abortion, or increased or decreased milk production from this plant [20]. Ohiyama et al. (2003) reported that *Verbena officinalis* herb adverse effects may be related to cellular changes or disruption of cell division cycle stages [21]. Based on the results of the previous studies, the extracts of this plant with effect on dopamine receptor in hypothalamus and anterior hyper phase inhibits prolactin secretion, increases progesterone secretion, and induces normal formation of the corpus luteum [22]. It has also been shown to affect different stages of mouse development, including improvement of fetal growth on days 8 and 9 of pregnancy and the appearance of abnormalities in the rat skeletal axis [13].

According to the results of this study, the prescription of alcoholic extract of *Verbena officinalis* flower caused significant changes in placental structure and survival rate of neonatal rats. According to the results of the present study, the prescription of this plant may impair the natural placental structure, decrease the exchange of nutrients to the fetus, thereby reducing fetal growth and reducing neonatal survival after birth. Although the possible mechanisms for the adverse effects of this plant on placenta and neonates are not well understood and require further studies including electron microscopy studies, since previous reports indicate that the plant extract contains various constituents including: flavonoid, alkaloid, glycosidic, and steroids, these compounds can cross the fetal blood barrier and blood-brain barrier and can even accumulate in

tissues such as the fetal brain [23]. Therefore, it may be concluded that the presence of these compounds in the structure of the plant may cause anatomical and histological changes.

Conclusion: According to the findings of this study, *Verbena officinalis* flower has adverse effects on placental structure and later growth rate and neonatal survival. The use of this herb is not recommended during pregnancy as described in some reports.

Research suggestions

Verbena officinalis medicinal plant is used in abortion due to its effective medicinal compounds.

The use of Shahpasand medicinal plant for abortion has fewer side effects than chemical drugs.

The use of Shah-friendly and proximity to this plant is not recommended for pregnant women.

It is suggested that pharmaceutical companies use effective pharmaceutical compounds to produce drugs.

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