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Examining the Effect of the Aqueous Extract of *Anchusa italica* on abortion and Fetal-placental parameters in Wistar Female Mice

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ABSTRACT
The borage plant with scientific name of Anchusa italica belongs to the Boraginaceaae family. These plants contain fatty acids, seed oils, and chemical compounds. Any uterine bleeding associated with closed uterine cervix and bloody discharge in the first half of pregnancy is called a threatened to miscarriage, and in 50% of cases results in abortion. The placenta is the main organ for maintaining healthy pregnancy and has an important role in transferring the foodstuffs from mother to fetus. Fetus weight gaining during pregnancy is a response to placenta growing that is considered as an independent factor in predicting the neonatal weight.The aim of this study is to evaluate the effect of aqueous extract of Anchusa italica on miscarriage and related parameters and Fetal-placental parameters. In this experimental study, after mating and observation of vaginal plug, 30 Wistar female mice were randomly divided into five groups including one group receiving physiological saline intraperitoneally, and four treatment groups receiving aqueous extract of Anchusa italica at concentrations of 100, 200, 300, and 400 mg/kg. Injection was daily conducted for 5 days after the 7th day of pregnancy, and cesarean operation was performed on 16th day of pregnancy. The number of absorbed fetus were counted and considered as abortion also Fetal-placental parameters were evaluated and the results were analyzed using SPSS software. The results of this study suggest that Injecting Anchusa italica extract affected the number of fetus absorbed(p=0.016), The number of fetus formed(p=0.000), The number of fetus observed(p=0.000), Fetus weight(p=0.000), placental weight(p=0.016), Placental size(p=0.002), The number of placental(p=0.000)._Has been effective because the standard deviation is less than 0.05. Therefore, the differences shown in the figure were statistically significant. The results suggest that the aqueous extract of Anchusa italica affected the number of fetus absorbed, the number of fetus formed, and the number of healthy fetus observed and Fetal-placental parameters.
Keywords: Anchusa italica, fetus weight, Placental size

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INTRODUCTION

The new studies show that herbal plants can influence on all body organs and systems including the productive system [1]. Extracts of several plants can manifest its effect during the pregnancy or during delivery which indicates the importance of mothers' diet during pregnancy [2].The borage plant with scientific name of *Anchusa italica* belongs to the Boraginaceaae family. This plant has contain fatty acids (Linoleic, oleic, α- Linoleic, ɣ- Linoleic, Palmitic, Stearic, Eicosnoic, Erucic and Steroosonic) and seed oils [3]. Raw polysaccharides of *Anchusa italica* roots include poly (oxy-1-carboxy-2-3,4-dihydroxy-phenyl ethylene) [4]. The plant petals also contain flavonoids, saponin and phenolic compounds [5]. Endulatocid, Tri-terpenes glycoside and Flavonoid glycoside were first separated from the Anchusa plant.(6). Phytosterols are found in large quantities in plant oils such as Anchusa italic. In addition, beta-Sitosterol and Campesterol were identified as the major sterols [7]. After fertilization, the womb becomes a place for keeping cell mass which will be transferred to the fetus. If no disorder occurs in it, it leads to childbirth after passing the pregnancy dumouseion with the uterine contractions, while if there occurs inconsistency in this part of body due to disordering effects, it will be influenced by these factors regarding the pregnancy step, there occur adverse effects on fetus that sometimes lead to abortion [9] The underlying mechanisms of miscarriage include fetus - maternal and environmental [10]. Numerous studies conducted in different countries have obtained different results. Mental problems (depression, anxiety, suicide) are likely to occur in women who experience miscarriage increase (11).The placenta is the main organ for maintaining a healthy pregnancy and has an important role in transferring the foodstuffs from mother to fetus [11].As the fetus grows in the womb, main changes occur in shape and

function of the placenta to be a proper solution and good response to fetus needs during growth stages. Reaching such consistency requires unique metabolic, immunologic and endocrine changes in placenta trophoblasts [11, 12]. Fetus weight gaining during pregnancy is a response to placenta growing that is considered as an independent factor in predicting the neonatal weight [13]. Infant underweight is due to reducing the receiving function of placenta such that it reduces by placenta of exchanging area between mother and fetus means the velocity placental level and capillary level of fetus reduce therefore the ability of transferring oxygen and food from mother to fetus reduces (11).As it is expected, the capacity of weight growth is mostly determined by fetus and fetus growth belongs to placental weight [14].Meanwhile, placenta as an important auxiliary and additive source contributes the estrogen production and if pregnancy is natural, its production will be increased since 10th pregnancy week by its end especially in 5 last weeks [15].Such hyper-estrogen is one of the progressive criteria of pregnancy which is removed immediately after placenta and fetus removal [16].During delivery, the plasma level of progesterone increases from 1-2 ng/m to above 100 ng/m. During the week 6-36th weeks of pregnancy the level of 17-alpha-hydroxy of plasma progesterone increases from 0.5 ng/m to 50-60 ng/m, and in the 32nd week of pregnancy, its plasma levels gradually increases from 0.5 ng/m to 140-120 ng/m. [17].The metabolic clearance of progesterone in pregnant women is similar to that of non-pregnant women and men. During pregnancy, a disproportionate increase occurs in the plasma concentration of α-5 d-hydroxy-progesterone, and the concentration of this metabolite to progesterone concentration reduces in pregnant women. The mechanism is still unknown; perhaps it is in relation to the development of resistance against shrinkage factors that occur during a normal pregnancy. In pregnant women and the fetus, the progesterone converts into the strong mineral corticosteroid dexa corticosterone (DOC) [18].Termination of pregnancy, whether spontaneous or induced, before the fetus is developed enough to evolve is called abortion [19].A genetic factors influencing in miscarriage is the progesterone receptor modulator UPA as a contraceptives factor in women [20]. [21] concluded that Runx3 (Runt3) plays an important role during implantation and decidualization. Press35 gene is also involved in capital letter development, ovulation, implantation, and decidualization [22]. IGFBP7 inhibition through specific immunization of DNA significantly reduces the pregnancy rate and implantation of fetus [23]. [24] study that RU-486 is an anti-progesterone factor that can cause premature labor.Fatty acid amide hydrolase (FAAH) is effective in the development and implantation of the embryo [25]. Wnt7a has an important role in the formation and function of the uterus gland required for implantation of the blastocyst and reproductivity in adult uterine [26].The results of studies by [27]. showed that the lack of N and O sets of Glycon in growing oocytes damages the primary stages of fetus growth and leads to delaying in implantation and a small infant. During the pre-implantation stage, the uterine growth influences on the process of implantation and fetus growth. Uterine unnatural growth causes many productive diseases in human. Among adjusting factors of uterine growth, vascular remodeling promoters are important for uterine function and fertilization. Meanwhile VEGF vascular endothelial growth factor is important in endothelial cell growth and development of blood vessels and nonendothelial cells [28]. IGFBP7 is mainly in Granular epithelium and platform and has more exposition after fetus implantation. IGFBP7-t, PCR3/1 is made by exposing IGFBP7. IGFBP7 inhibition via special DNA immunization considerably reduces the pregnancy and implanting fetuses [29].The methanol extract of Iranian *Anchusa italica* is effective in seizure induced by picrotoxin (30).*Anchusa italica* is harmful for pregnant women due to alkaloid compounds [31]. *Anchusa italica* liver toxicity effects is generally accepted for its alkaloid compounds [32]. *Anchusa italica* and fish oil causes inflammation and bone repair [33]. *Anchusa italica* extract has higher liver toxic effects compared to valerian extract [34]. *Anchusa italica* has obvious effect of increasing blood pressure, especially in high blood pressures, and using dried limes brewed mixed with *Anchusa italica* is recommended to reduce heart beat rate [35]. Aqueous extract of *Anchusa italica* is an effective and safe drug for the treatment of patients with obsessive-compulsive disorder [36]. Methanolic extract of *Anchusa italica* shows anti-inflammatory effects [37]. Anti-oxidizing, anesthetic, immune modulating and anxiolytic anxioletic of (Iranian) *Anchusa italica* show that this plant has a beneficial effect in acute pancreatitis, and has anti-inflammatory, antioxidant and immune modulating effects [38]. Indian *Anchusa italica* essence oil is a natural resource to control African malaria-carrying mosquito [39]. The antiviral activity of flu was evaluated in aqueous and alcoholic extracts of the *Anchusa italica* plant. These findings suggest that the antiviral activity of the plant is likely due to interference with the replication and transcription of the virus [40]. The *Anchusa italica* effects on pregnancy outcome in this study was to evaluate the effects of the extract on abortion, placenta and fetus.

MATERIALS AND PROCEDURE

Preparing *Anchusa italica*:

Anchusa italica was prepared from semirom and them systematic diagnosis was done in herbarium plant, and their flower and shoot were dried and then the dried plant was grinded and for preparing the extract, the powder was soaked in distilled water in vitro for 24 hours and then having used shaker for 48 hours, the pure extract was obtained, this extract was prepared in concentmouseion of 100, 200, 300 and 400 mg/lit and then extracts were ready for injection.


Fig1 : Experimental Plant and Extraction

Treatment animals:

In this research, 30 wistar female mice and 20 wistar male mice in mean weight of 25 gram to 30 gram were bought from Islamic Azad University, Shiraz branch. Then the female and males mice were put sepamouseely in special cages and they were kept for 7 days for compatibility with labomouseory conditions in 27^{o}C and natural light. Food and water were available for animals unlimitedly. Meanwhile the mice were pathologically studied daily. After 7 days, the male and female mice were put next to each other randomly for intercrossing and having controlled the vaginal plaque in female mice, the mice whose vaginal plaque were observed were sepamou seed from the remaining mice in sepamousee cages. G0 at 1st day of pregnancy was written for them, then pregnant female mouses were randomly divided into 5 groups, these groups included control group, group receiving 100 concentmouseion, 200 concentmouseion, 300 concentmouseion and 400 concentmouseion. After 7st pregnancy day, *Anchusa italica* was Intraperitoneally injected to the mice in treatment group for 5 pregnancy days and physiology serum was intraperitoneally injected to mice in control group and the caesarean was done on 16th day of pregnancy. For doing this opemouseion, at first the animal was anesthetized by chloroform and having establishing transverse cleft on abdomen and removing Retroperitoneal, the uterine horns containing fetus are observed. Having used narrow edge of surgical scissors, the wall of uterine horn was opened precisely and fetus was got out of it. Thus, healthy fetus were counted. Then, in order to determine the number of fetuses aborted, by examining the lining of the uterine horn was examined and the number of placenta without fetus and the number of born prematurely babies were added were considered as the number of aborted fetuses. its pill-shape and easily get out if wall of uterine horn. For measuring placental weight, they were put on digital scale after getting out the placenta in an animal and weight was registered in each animal and finally mean of placental weight is obtained in a treatment group. For measuring placental size, its diameter is determined by caliper and/or ruler and then total mean was determined in each treatment and finally the results were analyzed by SPSS18.

RESULTS

Effect of *Anchusa italica* on The number of fetus absorbed, The number of fetus formed, The number of fetus observed:

Injecting *Anchusa italica* extract affected the number of fetus absorbed, since the standard deviation is less than 0.05 (p =0.016). Therefore, the differences shown in the figure are statistically significant. Injecting *Anchusa italica* extract affected the number of fetus formed, since the standard deviation is less than 0.05 (p =0.000). Therefore, the differences shown in the figure are statistically significant. Injecting *Anchusa italica* extract affected the number of healthy fetus observed, since the standard deviation is less than 0.05 (p =0.000). Therefore, the differences shown in the figure are statistically significant (Table 1).

Variable	Changes	Sum of squares	Degree of freedom	Mean square	Fischer Z	p_value
The number of fetus absorbed	Between Groups	36.795	4	9.199	3.889	0.016*
The number of fetus formed	Between Groups	136.449	4	34.112	8.125	0/000*
The number of fetus observed	Between Groups	224.705	4	56.176	12.440	0/000*

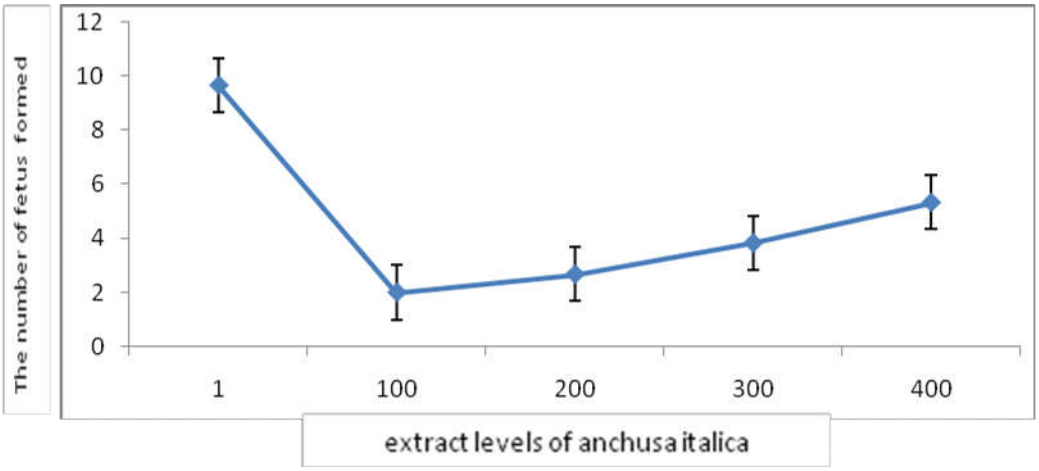


Diagram 1. Comparison of the average number of fetus formed in different treatments of plant

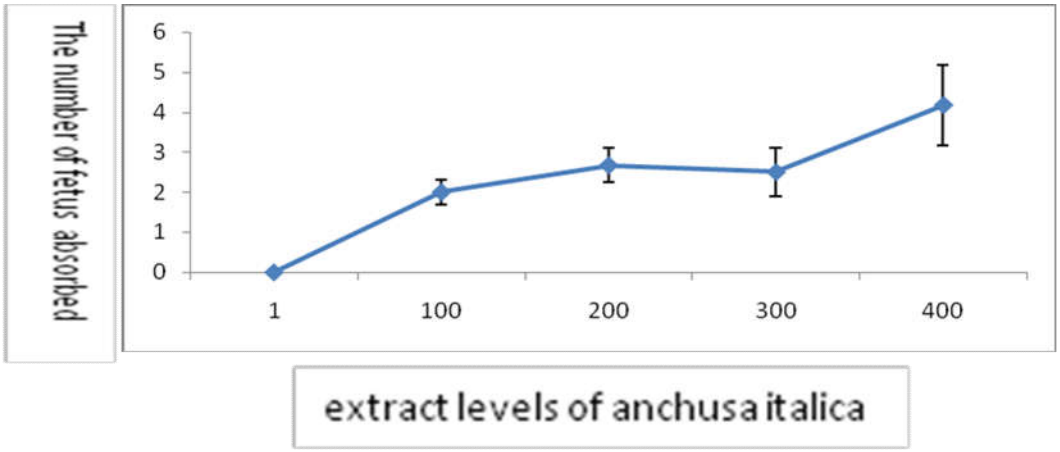


Diagram2. The correlation between the number of fetus absorbed in different treatments of plant

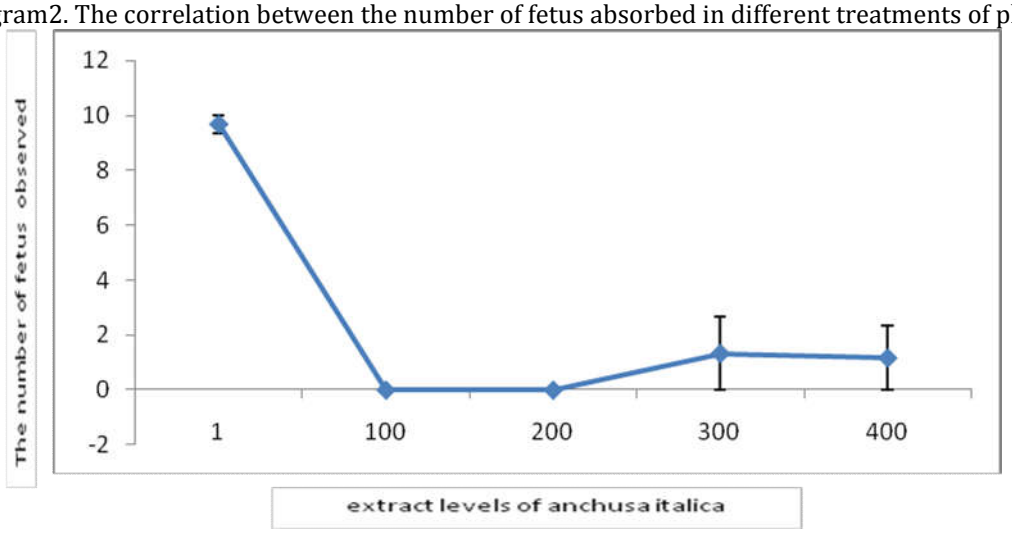
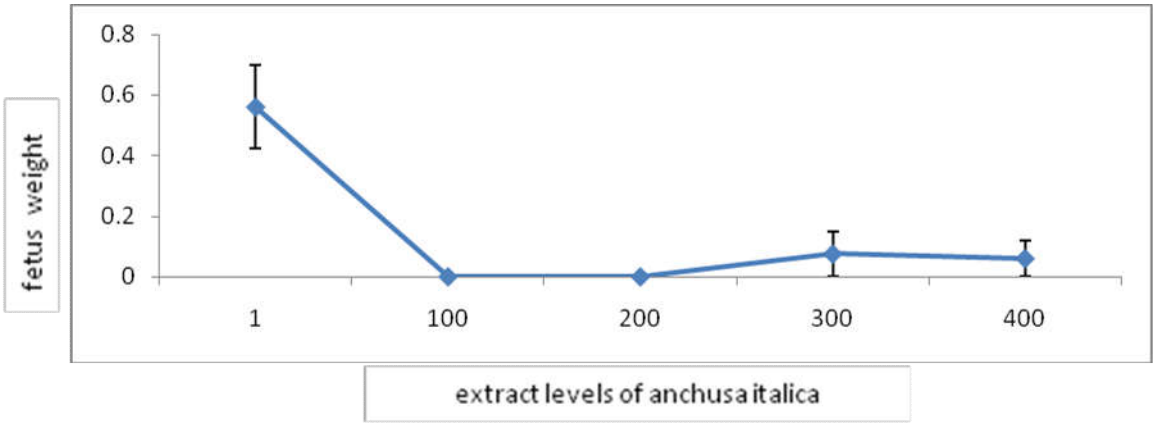


Diagram 3. Comparison of the average number of fetus absorbed in different treatments of plant

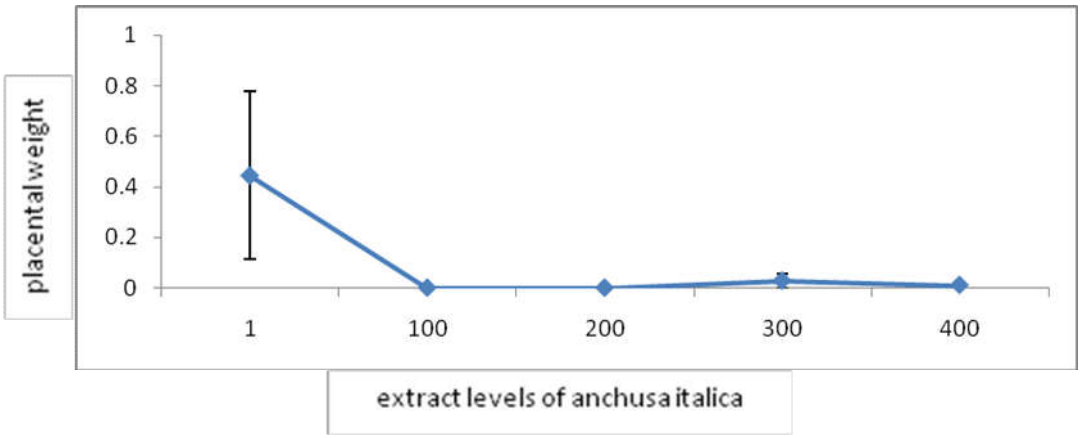
Effect of *Anchusa italica* on, Fetus weight, placental weight, Placental size, The number of placental:
The injection of *Anchusa italica* is effective on fetus weight since standard deviation is less than 0.05 (P= 0.000) and the differences in graph are statistically significant. The injection of *Anchusa italica* is effective on placental weight since standard deviation is less than 0.05 (P= 0.016) and the differences in graph are statistically significant. The injection of *Anchusa italica* is effective on placental size since standard deviation is less than 0.05 (P= 0.002) and the differences in graph are statistically significant. The

injection of *Anchusa italica* is effective on number of placenta since standard deviation is less than 0.05 (P= 0.000) and the differences in graph are statistically significant. (Table 2).

Variable	Changes	Sum of squares	Degree of freedom	Mean square	Fischer Z	p_value
Fetus weight	Between Groups	0.757	4	-1.189	10.298	0/000*
placental weight	Between Groups	0.506	4	0.126	3.899	0.016*
Placental size	Between Groups	121.643	4	30.411	6.243	0.002*
The number of placental	Between Groups	136.449	4	34.112	8.125	0/000*

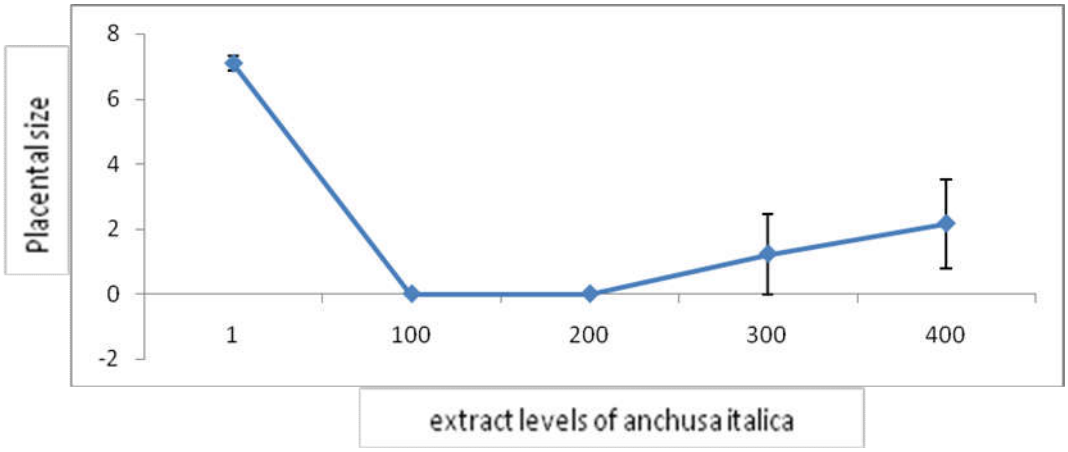


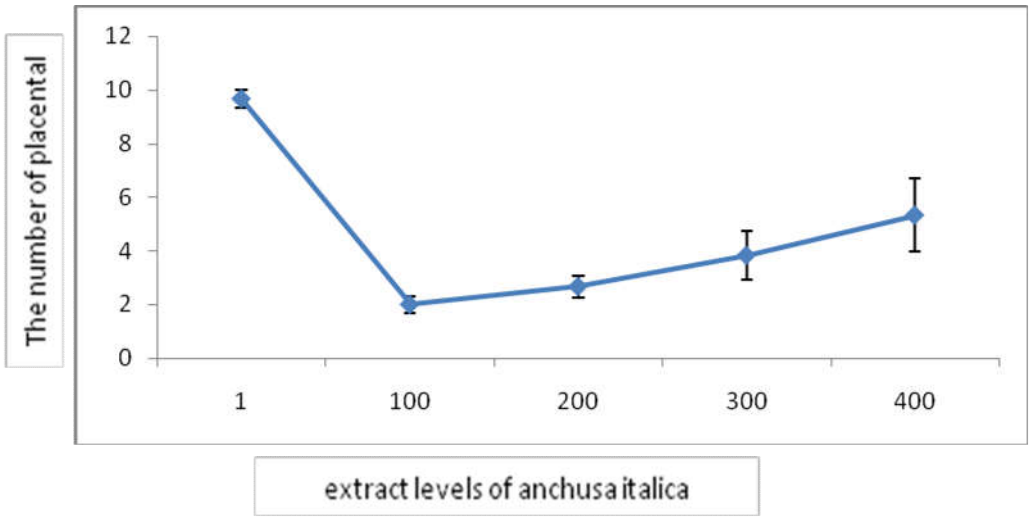
Graph 1: comparing mean of fetus weight in different treatments of plant



Graph 2: comparing mean of placental weight in different treatments of plant

Graph 3: comparing mean of placental size in different treatments of plant





Graph 4: comparing mean of number of placenta in different treatments of plant

RESULTS AND DISCUSSION

Effect of *Anchusa italica* on The number of fetus absorbed:

The results of the study showed that the number of embryos absorbed in the 100 and 200 control is a significant difference. In contrast, the number of embryos absorbed in level control significant difference was observed in the control group (Table 1).

[41] introduced Anethum graveolens as a contraceptive and a factor to regulate the menstrual cycle .Studies by (42) showed that *Stachys lavandulifolia* perforatum extract has properties that cause miscarriage and it should be used cautiously during pregnancy .In a study on the aqueous extract of pjyllanthus amarus (AEPA), results showed that the AEPA resulted in miscarriage in pregnant mice [43]. MSX homeobox genes regulate embryonic implantation through paracrine signaling between the substrate and epithelium type 1 and type 2, which encodes the transcription factors and control organogenesis and tissue interactions during the growth of fetus. Lack of these genes increases Wnt signaling in substrate cells and enables β-catenin that causes production of fibroblast growth factors (FGFs) in these cells. The secreted FGFs act in paracrine method through FGF receptors in epithelium to increase proliferation of epithelial cells. These findings indicate a unique signaling network, which includes Msx 1/2, Wnts, and FGFs, and at the time of implantation, work to control the mesenchyme - epithelial relationship [44]. [45] showed that exposure Using genistein leads to major changes in gene expression of fallopian tubes, Other changes in gene expression of fallopian tubes were observed only in early pregnancy. After the FRT is exposed to inflammatory or antigenic stimuli resulted from ovulation and mating, changes in fallopian tubes affect the growth of developing fetus through increased branching and a reduced the cell ratio of trophectoderm cellular mass in blastocyst stage.The effects of Bisphenol A (BPA) on uterus and embryo factors in implantation shows negative effects of high doses of BPA on the processes that are critical for embryo implantation. These processes include fetus transportation, fetus development before implantation, and stabilization of the uterus receptivity [46]. [47] Yellow Daphne consumption in early pregnancy showed that it can cause destruction and necrosis in decidual tissues and release prostaglandins, while increasing the levels of alpha 2PGF and 2PGE and decreasing progesterone level. On the other hand, the plasma levels of alpha PGF2 and PGE2 remained unchanged, and estrogen and progesterone levels dropped. In general, the contraceptive mechanism of Yellow Daphne mainly intervenes in intrauterine environment to maintain pregnancy, which in turn lead to abortion [1].In contrast, studies by [48] suggest that using ethanolic extract of eremomastax speciosa leaves has toxic effects on the endocrine system of female mice, and it is not dangerous as a drug in the management of infertility in female mice.

Flavonoids are polyphenolic compounds. Flavonoids have strong antioxidant effects and inhibit free radicals and reduce the risk of some chronic diseases [49, 50]. Luteolin, and kaempferol phytophenols apply anti-inflammatory properties in the pregnancy tissues. Anti-inflammatory properties in the pregnancy tissues are shown by inhibiting activity of binding to DNA NF-Kb, the AP1 path, and its target genes. In addition to anti-inflammatory activity, phytophenols have a wide range of biological activities. Kaempferol increases the length of pregnancy. Luteolin and kaempferol does not affect secretion of cytokines on the pregnant myometrial cells. In myometrium cells, luteolin, and kaempferol have substantially reduced incidence of COX-2, prostaglandin release, and MMP-9 activity resulted from the

B1-L1. The two substances perform their activity through AP-1 and NF-Kb paths, and prevent binding of DNA 65 NF-kBp and c-jun in myometrial cells [51].TNF-α and B1-L1 apply inflammatory activity, such as elevating prostaglandin and ECM destructive enzymes. This results in the beginning of three important stages in human delivery: fetus membranes rupture, cervix maturation, and uterine contractions [52]. The COX2 produces prostaglandins that are important in the initiation and maintenance of labor through increased uterine contractions and cervical maturation and activation of fetus-decidual membrane (52, 53).Linoleic acid is an essential fatty acid for the formation of cholesterol sterols through ACAT enzyme in the membrane of the yolk sac. This acid has a negative impact on the absorption of lipids in chicken fetus at the last embryonic stage that leads to increased fetus mortality [54]. Studies have shown that saponins have a contraceptive effect with a negative feedback mechanism. The effects of this extract occur before and after implantation. The anti-implantation activity is probably due to estrogenic activity that excretes the ovule from the fallopian tube and disrupts the luteotrophic activity of blastocyst [55]. Recent studies have shown that long-term use of phytosterols can increase reproductive success in short-tailed mice [56], and stimulate egg production in hermaphrodite marshy snails. However, despite the increased quantity, the quality of eggs will be reduced [57].

Effect of *Anchusa italica* on, Fetus weight, placental weight, Placental size, The number of placental:

The results of this study indicate that 100 with 200 pairs showed a significant difference in weight (p=0.000). In contrast, the control group showed no significant difference with other levels.

The results of this study suggest that placental size is a significant difference in the level of control with the 100 and 200 levels (p=0.11). As well as the 300 there is a significant difference(p=0.45). The size of the pair in the 100 to 200 showed a significant difference (p=0.000). In contrast, other levels did not show significant difference.

The results indicate that the number of pairs in the control group with a significant difference in the levels of 100 and 200(p=0.000). As well as the 300 there is a significant difference (p=0.009). In contrast, the number of pairs in other levels did not show significant differences.

Zingiber officinale causes wide disorders and anomalies in fetus maybe due to its effect of smooth muscles and also due to its effect on synthesis of leukotriene and prostaglandins [58]. Tmouseogenic effects of *Stachys lavandulifolia* on skeleton system and fetus growth of mouse showed that *Stachys ivandulifolia* at different doses causes disorder in fetus growth (height and weight) and such disorder upon increasing the dose increases. Meanwhile this extract has tmouseogenic characteristics and reduces growth and reduces interparital ossification belonged to dose [59].The findings of a research showed that both *Anchusa italica* and matricarica chamomile causes disorder in natural process of pregnant mousee weight gaining and it reduces the length of rumps-seats and their fetus weight [60].The consumption of pigeon pea extract as edible increases the infant size of mouse while the infants' weight reduces. Meanwhile, this extract reduces the mother's weight gaining [61].[62] showed that *Peganum hermla* influences of skeleton system and fetus growth of mouse and reduces the fetus height and weight.The consumption of Zataria multiflora in second week of pregnancy causes partial changes like tail size and placental diameter [63].The studies about the effect of Physalis alkekengion anomalies showed that this extract reduces the diameter, weight and size of placenta, meanwhile, Physalis alkekengi may have negative effect on quantitative growth of fetus and distinction of some cells through preventing the cellular division and distinction and reducing the function of several enzymes and hormones (64).On the other hand, the results of studies of [65] showed that Green tea catechins (GTC-H) has no effect on mean of uterine weight of the uterus growth or living. Palmitic acid is a satumouseed fatty acid and this acid has distinctive effects on fetus trofektrom and internal cell mass and influence on placenta growth (66). Palmitic contact in fetus after implantation will include changing R1IGF and increasing GPT2 activity. Such metabolic changes with cellular nucleon are in fetuses which influenced by palmitic acid which is probably the result of increasing epoptosis and reducing cellular prolifemouseion in fetus and TS cells are exposed to increasing the palmitic concentmouseion. Meanwhile, metabolic changes can influence on long-term consequences merely via influencing on cellular prolifemouseion before implantation and epoptosis via changing the availability of energy. The other probability is that these metabolic changes indicates changes in genetic immune adjustment of metabolism or abnormal planning of Mitochondrial function organisms. The fetus shows the change of growth and metabolic patterns connected to extra palmitic acid before implantation and these fetus shows growth limitation in uterine (67, 68). Several long fatty acid supplements of Omega 3 chains increases the pregnancy dumouseion in humans and animals [69].Deco Hexanoic acid (DHA) with CLA causes delay in delivery time in induced lambing by beta-methasone and fish oil in human can increase the pregnancy dumouseion by 4 days (70, 69). Increasing pregnancy dumouseion maybe related to the inhibitory effect of CLA on Prostaglandins production. the recent researches knows the inhibitory effect of CLA in prostaglandin as decisive and related to PPAR activation since PPAR inhibits the activity of nuclear polygraph factor (NFκB) after

activation [71]. Several researchers believe that the fatty acids in diets influence on homeostasis adjusting hormone of body weight and energy balance (liptin) (72, 73).
Therefore regarding the results obtaining, *Anchusa italica* shall be used with caution.

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