IOSR Journal Of Pharmacy www.iosrphr.org
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 8, Issue 7 Version. I (July 2018), PP. 46-62

Arabian Medicinal Plants Affected Female Fertility- Plant Based Review (Part 1)

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Abstract: Medicinal plants have been widely used to enhance or regulate fertility in females. Several medicinal plants stimulated normal pituitary reponse of gonadotropin-releasing hormone, improved normal pulsatile secretion of FSH and LH, induced ovulation, enhanced secretion of steroid hormones, possessed estrogenic and progesteronic effects, and directly regulate ovarian function, at least in part by inducing the secretion of cytokine. Also many herbal therapeutics controlled birth. The current review will highlight the medicinal plants used to enhance fertility and to control birth in females, which confirmed experimentally and clinically.

Keywords: Medicinal plants, Fertility, Control birth, Contraceptive, females.

Date of Submission: 22-06-2018 Date of acceptance: 05-07-2018

I. Introduction

Medicinal plants have been widely used to enhance or regulate fertility in females. The bneficial effects of medicinal plants on female fertility were included: stimulation of normal pituitary reponse of gonadotropin-releasing hormone (GnRH), improved normal pulsatile secretion of FSH and LH, induction of ovulation, enhanced secretion of steroid hormones in ovarian cell, possessed estrogenic and progesteronic effects, and directly regulate ovarian function, at least in part by inducing the secretion of cytokine[1-3]. On the other hand, plants were also used as contraceptive in females, the sites of action of antifertility effects of medicinal plants in females were included: the hypothalamus, the anterior pituitary, the ovary, the oviduct, the uterus and the vagina. Medicinal plants possessed antifertility effects by various mechanism of actions included: modulation of luteinzing hormone (LH) and follicle stimulating hormone (FSH), decreasing their secretions and inhibiting follicles maturation and ovulation, inhibit process of development of ovum and endometrium, inhibit implantation and abortifacient effects[4-7].

Ailanthus altissima

Ailanthus altissima was evaluated for progestogenic and anti-progestogenic properties. Extracts of the plant were analysed for progestogenic and antiprogestogenic activities by using progesterone response element-driven luciferase reporter gene bioassay. *Ailanthus altissima* was recognized to have anti-progestogenic like activities. It inhibited the 314.46 ng/ml progesterone activity in a dose-response manner [8-9].

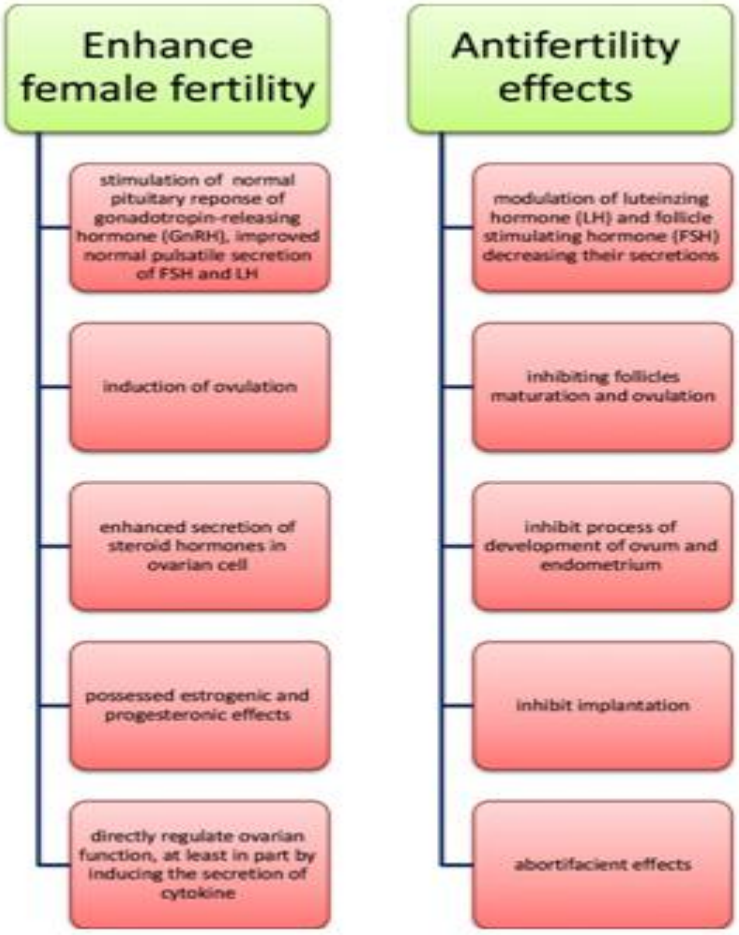

Fig 1: the mechanisms of enhancing fertility and antifertility effects of medicinal plants in females

Plants affected female reproductive system:

Alhagi maurorum

Adding of histamine in doses of 3 µg/ml bathing fluid to the isolated guinea-pig ureter induced continuous contractions. Adding of the ethanolic extract (EE) of *Alhagi maurorum* powdered roots in doses of 5 mg/ml bathing fluid completely suppressed histamine induced contractions. Addition of another dose of histamine did not reverse the inhibition. Glyceryl-n-tetracosan-17-ol- 1-oate (a new aliphatic ester isolated from the root of the plant) induced relaxations to the guinea – pig ureter and suppressed histamine – induced spasms. It seemed to possess an anticolic action and a ureter relaxing action that can enhance getting rid of renal stones and relieve of the accompanying pain (contraction of the ureter). Treatment of the ureter with two doses of 20 and 40 micrograms/ ml of solution surrounding the ureter for 5 min, reduced the ability of histamine to contract the ureter through 100 s by a percentage equal to 75% and 100%, respectively [10-11].

Allium cepa

Allium cepa showed significant antifertility activity, female rats treated with ethanolic extract showed significant inhibition of number of implant sites at a dose of 300 mg/kg. There was no change in ovulation, hence the antifertility activity observed for *Allium cepa* was attributed largely to its antiimplantation activity [12]. Fresh bulb juice was enhanced uterine contraction in rats. The treatment was equivalent to 0.003 IU of oxytocin. Water extract of the bulb was also produced strong activity on pregnant mice and rats[13]. *Allium cepa was investigated* in renal failure in male rats which experimentally infected by *Toxoplasma gondii*. The study showed that *T. gondii* exerted significant effect on serum creatinine, albumin, blood urea nitrogen (BUN), malondialdehyde (MDA) and total antioxidant capacity (TAC), and fresh onion juice returned and treated these harmful effects [14-15].

Ammannia baccifera

Ethanol (90%) extract of *Ammannia baccifera* (whole plant) was evaluated for antisteroidogenic activity in mature female mice ovaries. The ethanol extract at the doses of 100, 200 and 400 mg/kg body weight

(ip) arrested the normal estrus cycle at dioestrus phase and significantly decreased weight of ovaries. The cholesterol and ascorbic acid content in ovaries were significantly elevated in treated mice. The extract also significantly inhibited the activity of Δ5-3β-hydroxy steroid dehydrogenase and Glucose-6-phosphate dehydrogenase, the two key enzymes involved in ovarian steroidogenesis. These results showed that the ethanol extract of whole plant of *Ammannia baccifera* induced antisteroidogenic activity [16-18].The ethanol extract of *A. baccifera* whole plant induced antifertility effects in rat males. It was significantly reduced the weight of the testis , epididymis, sperm density and motility, content of fructose in the seminal vesicles, Δ5-3β -hydroxy steroid dehydrogenase (Δ5-3β-HSD) and glucose-6-phosphate dehydrogenase (G-6-PD [19].

Anthemis nobilis

The effectiveness of *Anthemis nobilis* aqueous-alcoholic extract was studied in polycystic ovary syndrome induced in rats by a single dose of estradiol valerate. Histological investigations revealed that the animal administered with dose of 50 mg/day showed small cysts and less inflammation, with decreasing of serum estrogen hormone($P<0.029$) [20-21].

Anethum graveolens

The effects of *Anethum graveolens L***.** (dill) extracts on female reproductive system were studied female rats. The experimental groups were fed 0.045 g/kg and 0.45 g/kg of aqueous extract and 0.5 g/kg and 5 g/kg of ethanol extract for 10 days. Treatment with high dose of the extract resulted in a significant increase in duration of the estrous cycle and diestrus phase. Smooth endoplasmic reticulum (SER), rough endoplasmic reticulum (RER) and mitochondria were increased in granulosa lutein cells in high dose groups. There were no significant statistical differences in amount of serum estradiole between experimental, control and sham groups but the serum progesterone concentration increased significantly in high dose treatment group compared with control and sham groups[22-23]. Dill seed possessed contractive effects on myometer, enhanced releasing of oxytocin which is an effective hormone in uterus contractions. A dose of 6-7 gm of dill seed extract after delivery decreases postpartum hemorrhage due to its contractive characteristic. Limonene and anethole showed contractive effect on uterine myometrium[24-27]. Zagamil *et al.* carried out a clinical study to evaluate the effect of Dill seed on uterus contractions in active phase of labor. 40 women used *Dill* seed infusion (one tablespoon of whole dill seed seeped in a half or whole cup boiling water for 3-4 min before going to the hospital at the beginning of uterus contractions), and 60 women used nothing in the control group. Interpretable electronic fetal monitoring was obtained for half an hour at the beginning of the active phase. The Fall: Rise ratio was calculated by measuring the duration of time for a contraction to return to its baseline from its peak (fall) divided to the duration of its rise time to its peak (rise).The number of contractions in the treated group was significantly more than the control group. The ratio of contraction's fall time to its rise time in the treated group was shorter than the control group. The study showed thatdill seed shortens duration of the first stage of labor[28].

Arachis hypogaea

Introduction of refined peanut oil to form 10% of the food ration of immature mice increases uterine weight [29-30]. Phytoestrogens are plant-derived compounds that structurally or functionally mimic mammalian estrogens and therefore are considered to play an important role in the prevention of cancers, heart disease, menopausal symptoms and osteoporosis .*Arachis hypogaea* showed high levels of phytoestrogens including isoflavones (formononetin and biochanin A , 729 ug/g dry weight) [31-34].

Arctium lappa

In Traditional Chinese Medicine, *Arctium lappa* L. root is recommended as an aphrodisiac agent, and used for the treatment of impotence and sterility, while Native Americans included the root in herbal preparations for women in labor [35]**.** *In vivo A. lappa* induced uterine stimulant activity [36-37].

Asplenium trichomanes

Investigate the in vitro estrogenic activity of *Asplenium trichomanes* extracts ability to activate ERalpha and ERbeta, MCF7/EREluc cell line which expresses endogenous ERalpha, and SK-NBE cells transiently transfected with the estrogen receptors (ER alpha and ER beta) were used for the estrogenic activity assays. Leaves infusion and methanolic extract were active in MCF7 model; selectivity for the ERbeta receptor was observed in the SK-NBE test [38].

Avena sativa

In an experimental study, oat straw stimulated the release of luteinizing hormone from the adenohypophysis of rats. *Avena sativa* contained oestrone which been shown to induce ovulation [39-42].

Bryophyllum calycinum

The plant exerted relaxant effect *in vitro* on the contractility of human myometrium on oxytocin-stimulated contraction at a minimum concentration almost 100-fold lower than in the case of spontaneous contraction[102].A prospective double-blind trial with orally applied Bryophyllum versus placebo was carried out. Thirty-two patients divided into two groups , 15 patients received Bryophyllum and 17 received the placebo. The time of delivery did not differ between the groups. In both groups the mean time of birth was in the 35 week of gestation. The mean birth weight was slightly higher in the placebo group (2192 g) compared to the Bryophyllum group (1948 g). A transition to the intensive care unit was slightly higher in the placebo group (13) compared to the Bryophyllum group (11)[43-45].

Caesalpinia crista

Caesalpinia crista alcoholic seed extract caused histological follicular degeneration in ovary, vacuolation and mild disorganization of uterus in rats treated with graded doses of alcohol seed extract of *Caesalpinia crista*. There was a significant decrease ($p \leq 0.05$) in duration of estrous cycle and mean ovarian weight. However, there were no uniform variations in mean uterine weight, serum estradiol and progesterone level. The authors suggest that antiestrogenic effects of alcohol seed extract of *Caesalpinia crista* could be resulted from an inhibition of estrogen secretion [46].

The effect of oral administration of the ethanolic seed extract of *Caesalpinia bonducella* (100, 200 and 300 mg/kg) was studied on the reproductive system in Wistar female albino rat. The treatment prolonged the length of estrous cycle with significant increase in the duration of diestrus stage. The analysis of the principal hormones viz. LH, FSH, estradiol and progesterone showed significantly decreased levels in dose-dependent manner. Ovarian and uterine weight was significantly reduced as compared to that of the control group. Histoarchitectural observations revealed follicular atresia and degeneration of corpora lutea in ovary. Oviduct showed degeneration of mucosal folds and epithelium cells. Uterus showed evidence of degeneration of endometrial epithelium and endometrial glands. Lamina propria and muscularis layer of vagina were found slightly disorganized [43, 47].

Calendula officinalis

Calendula officinalis flowers extracts exerted estrogenic activity in ovariectomized animals [48-51].

Calotropis procera

The effects of ethanolic and aqueous extracts of *Calotropis procera* roots were studied on the oestrouscycle regularity. Both extracts were found to interrupt the normal oestrous cycle in 60 % and 80 % of female rats respectively. The extracts had no oestrogenic activity when tested in immature female bilaterally ovariectomized rats[16]. The antifertility effect of the ethanolic extract of roots of *Calotropis procera* was investigated in female rats. A strong antiimplantation (inhibition 100%) and uterotropic activity was observed at the dose level of 250 mg/kg (1/4 of LD50) [94]. *Calotropis procera* was uterotonic drug, its aqueous extracts induced significant sustained increases in human myometrial smooth muscle cell contractility, with varying efficiencies, depending upon time of exposure and dose [52].

Carum carvi

The effects of aqueous and ethanolic extract of the seeds of *Carum carvi* were investigated on hormone and reproductive parameter of female rat. Aqueous and ethanolic extracts of the seeds of the plant were administered orally to female rat for 30 consecutive days. Estrous cycle, reproductive hormones (LH, FSH and estrogen) and weight of reproductive organ were studied. After oral administration of different doses of aqueous and ethanolic extracts of *Carum carvi*, a significant antifertility activity was recorded. FSH and LH levels were significantly decreased, while amount of estrogen in ethanolic extract was found to be increased. The estrus phase was blocked by treatment with aqueous and ethanolic extract. It also increase the weight of ovary, uterus and body weights, while uterine weight in immature rats increased in extract treated group. Accordingly, the study showed that *Carumcarvi* exerted a significant antifertility activity [53]. Caraway oil was effective in inhibiting tonic and phasic rhythmic contractions of isolated uterine preparations [54-55].

Capsella bursa-pastoris

Capsella bursa-pastoris, dried and ground, was added at rates of 20 and 40% to the stock diet of male and female mice, found that at the 40% level, both materials impeded ovulation and produced temporary infertility in males and females [56-57].

Carthamus tinctorius

In order to evaluate the safety of the flowers of *Carthamus tinctorius*, the teratogenic effects of carthamiflos on the central nervous system development in mice was investigated. Furthermore, its cytotoxic effect on the rat nervous cell culture was studied. The pregnant mice were treated with different dosage regimens of aqueous carthamiflos extract during 0-8 days of gestation. Embryos were then isolated at the 13th gestation day and evaluated for macroscopic, microscopic and morphometric characteristics. The results showed that in higher doses (1.6 and 2 mg/kg/day) the embryos were absorbed, whereas with lower dose (1.2 mg/kg/day) changes in external, internal and longitudinal diameters, open neuropore, changes in cellular orientation and cellular degeneration were observed [58]. The lignan glycoside, tracheloside, was tested as an anti-estrogenic principle against cultured Ishikawa cells. Tracheloside significantly decreased the activity of alkaline phosphatase (AP), an estrogen-inducible marker enzyme, with an IC50 value of 0.31 microg/ml, a level of inhibition comparable to that of tamoxifen (IC50=0.43 microg/ml) [59]. The decoction of *Carthamus tinctorius* exerted stimulating action on the uterus of mouse *in vitro*. The stimulating action of *Carthamus tinctorius* has been found related to the stimulating effects on H1-receptor and alpha-adrenergic receptor of uterus [60]. On the other hand, intraperitoneal administration of a hot aqueous extract of the *Carthamus tinctorius* flowers increased uterine contractions in pregnant female rats [61].

Cicer airetinum

Aqueous, alcoholic and chloroform extract of *Cicer arietinum* were tested for abortifacient activity in female albino rat, it was given from day 11 to 15 of pregnancy at the dose level of 100, 200 and 400 mg/kg body weight. The aqueous extract at a dose of 400mg/kg was found to be most effective abortifacient. Similarly it was also found to increase the reproductive organ weight and possess estrogenic activity when tested in immature ovariectomised female albino rats [62]. Isoflavones, the important chemical components of the seeds and sprouts of chickpea, have drawn attention due to their potential therapeutic use. The estrogenic activity of isoflavones extracted from chickpea *Cicer arietinum* L sprouts (ICS) was observed recently. MTT assay showed that ICS at the low concentration ranges (10^{-3} /mg/l) promoted MCF-7 cell growth, while at high concentrations, (>1 mg/l) inhibited cell proliferation, indicating that ICS worked at a diphasic mechanism. Flow cytometric analysis further calculated the proliferation rate of ICS at low concentration (1 mg/l). ERα/Luc trans-activation assay and then semi-quantitative RT-PCR analysis indicated that ICS at low concentrations induced ERα-mediated luciferase activity in MCF-7 cells and promoted the ER downstream target gene pS2 and PR trans-activation. These effects were inhibited by ICI 182,780, a special antagonist of ER, indicating that an ER-mediating pathway was involved. Alkaline phosphatase (AP) expression in Ishikawa cells showed that ICS at low concentrations stimulated AP expression. Accordingly, ICS has significant estrogenic activity *in vitro*. ICS may be useful as a supplement to hormone replacement therapy and in dietary supplements [63].

Isoflavones extracted from chickpea sprouts (ICS) stimulated estrogen responsive element (ERE)-promoter activity in cells, and concurrent treatment with the nonselective estrogen receptor antagonist ICI 182,780 abolished the estrogenic activity induced by ICS [64].

The estrogenic activities of the isoflavones extracted from chickpea sprouts (ICS) was studied in ovariectomized rats (OVX). The rats were administered via intragastric gavage 3 different doses of ICS (20, 50, or 100 mg/kg/day) for 5 weeks. Their uterine weight and serum levels of 17β-estradiol (E2), follicle stimulating hormone (FSH) and luteinizing hormone (LH) were measured. The epithelial height, number of glands in the uterus, and number of osteoclasts in the femur were histologically quantified, and the expression of proliferating cell nuclear antigen (PCNA) was assessed immunohistochemically. Bone structural parameters, including bone mineral density (BMD), bone volume/tissue volume (BV/TV), trabecular thickness (Tb.Th) and trabecular separation (Tb.Sp) were measured using Micro-CT scanning. Treatments of OVX rats with ICS (50 or 100 mg/kg/day) produced significant estrogenic effects on the uteruses, including the increases in uterine weight, epithelial height and gland number, as well as in the expression of the cell proliferation marker PCNA. The treatments changed the secretory profile of ovarian hormones and pituitary gonadotropins: (serum E2 level was significantly increased, while serum LH and FSH levels were decreased) compared with the vehicle-treated OVX rats. Furthermore, the treatments significantly attenuated the bone loss, increased BMD, BV/TV and Tb.Th and decreased Tb.Sp and the number of osteoclasts. Treatment of OVX rats with the positive estrogen control drug E2 (0.25 mg/kg/day) produced similar, but more prominent effects [65-66].

Citrullus colocynthis

The toxic effects of *Citrullus colocynthis* was studied on the female reproductive system. After administration of 400 mg/kg/body weight to female rats for two time periods 4 and 12 weeks, females were allowed mating with males after 10 days prior to the last administration dose. Then females were autopsied under light anesthesia and several parameters were determined including: number of pregnant rats, body and reproductive organ weight, number of implantation sites, viable fetuses and resorption sites. Exposure

to *Citrullus colocynthis* for 4 weeks did not have much effect on fertility. Significant decrease in the relative ovarian weights and embryo weights in female rats exposed to *Citrullus colocynthis* were observed. Exposure to *Citrullus colocynthis* for a 12 weeks resulted in a reduction in the percentage of pregnancies and in the number of implantation sites when compared with controls in both treatment periods. Rats receiving 12 weeks treatment showed a decrease in ovarian weights and a decrease in viable fetus's number. These results indicate that long-term exposure of female rats to *Citrullus colocynthis* causes adverse effects on the reproductive system and fertility [67-68].

Citrus species

The petroleum ether, alcoholic and aqueous extracts of *Citrus limonum* seeds were investigated for anti-fertility effect in female albino mice. The extracts were administered orally for 7 days after insemination (i.e. post-ovulatory test). The control group received 4% gum acacia. The animals were examined for implantation sites on 10^{th} day of pregnancy. The number of pups delivered at term was recorded for each group. The alcoholic extract showed significant anti-fertility effect as compared to petroleum ether and aqueous extracts. The alcoholic extract was subjected for fractionation and the fractions were again tested for their anti-fertility effect. The fraction of ethyl-acetate showed most encouraging anti-fertility activity. In second part of the study, the alcoholic extract and its ethyl-acetate fraction were subjected to evaluation of their mechanism of action and it was found that their principal mode of action is as an anti-zygotic agent. Withdrawal of the treatment, resulted in complete restoration of fertility [69].

Estrogenic /anti-estrogenic activities of alcoholic extract of *Citrus limonum* seeds was studied in Albino rats. The standard drug estrogen was given sub-cutaneiously and test drug, alcholic extract of lemon seeds was given orally for 7 days from 8^{th} to 14^{th} days of ovariectimised rats. The extract treated rats exhibited estrogenic effect, which include vaginal epithelium cell cornification and increased in uterine weight. For further supporting the estrogenic activity of the extract, isolated rats uterus preparation was mounted, and it showed that alcoholic extract of lemon seeds produced the contraction as pretreatment with stelbistrol [70].

Three extracts of the peels of *Citrus medica* including oil, ethanolic and chloroform extract were investigated for antifertility activity. The alcoholic extract at the dose of 2.5gm/kg and the chloroform extract at dose of 1.0 gm/kg on female wistar rats on days 1-7 post-coital, exhibited significant anti-implantation activity. While, the oil extract at the dose of 100mg/kg on days 1-7 didn't exhibit significant anti-implantation activity [71].

Petroleum ether extract of *Citrus medica* seeds, was administered orally (400 mg/kg body weight) for 30 days to study its effect on fertility in Wistar strain Albino rats. Animal were divided into 3 groups: Group I, received 400mg petroleum ether extract/kg in 0.2ml Tween-80 (1%) orally for 30 days. Group-II, received only 0.2ml Tween-80 (1%)/kg for 30 days and left untreated for another 30 days to served as control. Group-III: received 400mg petroleum ether extract/kg in 0.2ml Tween-80 (1%) for 30 days and left untreated for next 30 days to see the withdrawal effects. The results were analysed depending on gravimetric, histological, histometric and biochemical parameters. Histologically, ovary and uterus in extract treated rats showed reduced number of healthy follicles, regressing follicles and also elevation in corpora lutea in the Group I and II. For the study of withdrawal effects of this extract in Group III, the results indicated that the animals returned to normal and regained gonadotrophin secretion similar to that of control rats [72].

Petroleum ether, benzene and ethanol extracts of the seeds of Citrus *medica* were administered orally at the dose level of 200 and 400 mg/kg to adult female albino rats for 30 days. The estrous cycle of these rats was irregular with prolonged proestrus and estrous, reduced metestrus and diestrus phase during the experimental period. At autopsy on day 31^{st}, petroleum ether extract treated rats showed reduced ovarian weight, benzene extract treated rats showed increased ovarian weight and ethanol extract treated rats showed non-significant change in the weight of ovary. Histological changes of the ovary indicated increases in the number of atretic follicles but decreases in the number of healthy developing follicles, Graafian follicles and corpora lutea. The total cholesterol, activity of acid and alkaline phosphatase and ascorbic acid content of the ovary were increased, whereas, protein and glycogen content were decreased. The uterine weight and its micrometric measurements in the treated rats were increased significantly. However, petroleum ether extract of Citrus *medica* seeds was more effective in causing these changes comparing to other extracts [73].

Estrogenic/anti-oestrogenic activities of petroleum ether extract of *Citrus medica* seeds were studied in albino rats. The extract at the dose level of 200 and 400 mg/kg body weight was administered for seven days to immature ovariectomised rats, along with or without 1 μg ethinyl estradiol. The extract-treated rats exhibited estrogenic effects, which included increase in uterine weight and vaginal epithelial cell cornification. The micrometric measurements of the uterus and its components were increased and glands showed high secretory activity. When the extract was tested in 30-day-old immature rats, they exhibited opening of vagina on the fifth day and cornification of vaginal epithelial cells, which was about 10 days earlier compared to controls, which

further supporting the estrogenic activity of the extract. Hence, these results strongly indicate the potent estrogenic nature of petroleum ether extract of *Citrus medica* seeds [74].

The estrogenic activity of petroleum ether extract of *Citrus medica* leaves was studied in immature female rats. The petroleum ether extract proved to retain high estrogenic activity in immature female rats. Oral administration of petroleum ether extract of Citrus *medica* in ovariectomized immature female Wistar rats for 7 days in a dose of 400 mg/kg resulted in significant increase in the uterine weight (g) (1.7±0.11) when compared with ovariectomized control rats (1.3±0.07) [75-76].

II. Coriandrum sativum

Effect of the aqueous extract of fresh coriander (*Coriandrum sativum*) seeds has been studied on female fertility in rats including the effects on oestrus cycle, implantation, foetal loss, abortion, teratogenicity and serum progesterone levels on days 5, 12 and 20 of the pregnancy. The extract at doses of 250 and 500 mg/kg orally produced a dose-dependent significant anti-implantation effect, but did not produce complete infertility. Treatment of animals during day-8 to day-12 and day-12 to day-20 of the pregnancy did not produce any significant abortifacient activity. There was no significant change in the weight and length of the foetuses delivered by rats treated with the extract and no abnormalities were seen in the organs of the offsprings. The extracts produced a significant decrease in serum progesterone levels on day-5 of pregnancy which may be responsible for its anti-implantation effect [77-78].

Crocus sativus

The effects of different concentrations of saffron (*Crocus sativus*) aqueous extract (SAE), was evaluated in *in vitro* maturation (IVM) of immature mouse oocytes. Cumulus-oocyte complexes (COCs) were collected from 6-8 weeks old female mice ovaries. COCs were cultured in IVM medium supplemented with 0 (control), 5, 10, 20 and 40 µg/ml of (*Crocus sativus*) aqueous extract (SAE) in 5% CO2 at 37℃. The rates of maturation, fertilization and development were recorded. The maturation rate was significantly higher in all groups treated with different concentrations of SAE compared with the control group ($p<0.05$). However, the lower concentrations of SAE (10 and 5 µg/ml in maturation medium) increased the fertilization rate of oocytes and *in vitro* developmental competence when compared with the control group ($p<0.05$). The authors conclude that addition of appropriate amounts of SAE to maturation medium improved oocyte maturation and embryo development [79].

The effects of different concentrations of saffron (*Crocus sativus*) aqueous extract (SAE) and its ingredient, crocin, were evaluated on the improvement of *in vitro* maturation (IVM) and subsequent *in vitro* fertilization (IVF) and embryo development of mouse oocytes. Cumulus oocyte complexes were collected from ovaries, and germinal vesicle oocytes were cultured in the presence of SAE and crocin. SAE was added at dosages of 5, 10, and 40 µg/m and crocin 50, 100, and 400 µg/ml. All dosages were added to maturation medium and a group without SAE or crocin was considered as the control group. Both SAE and crocin improved the rate of IVM, IVF, and *in vitro* culture. Addition of 40 µg/ml SAE to maturation medium significantly increased the rate of IVM, IVF, and *in vitro* culture ($p < 0.05$). Furthermore 100 µg/ml crocin significantly increased the IVM rate compared to the control group ($p < 0.05$) [80].

A double-blind and placebo-controlled trial was designed to investigate the effect of saffron (stigma of *Crocus sativus*) on the symptoms of premenstrual syndrome. The study was carried out on women aged 20–45 years with regular menstrual cycles and experience of PMS symptoms for at least 6 months. Women were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice a day; morning and evening) or capsule placebo (twice a day) for two menstrual cycles. The primary outcome measure was the daily symptom report, and secondary outcome measure was the Hamilton depression rating scale. The trial showed that saffron was effective in relieving symptoms of PMS. A significant difference was observed in efficacy of saffron in the total premenstrual daily symptoms and Hamilton depression rating scale [81-82].

Crotalaria juncea

Petroleum ether, benzene and alcohol extracts of seeds of *Crotalaria juncea* administered orally at the dose level of 25mg/100g bw to adult female mice for 30 days, resulted in irregular estrous cycle with prolonged estrus and metaestrus and reduced diestrus and proestrus during the experimental period. Histological studies of the ovary indicated increases in the number of atretic follicles but decreases in the number of developing follicles, Graafian follicles and corpora lutea. The total cholesterol content of the ovary was increased, whereas ascorbic acid content is decreased. The weight of the uterus and its micrometric measurement in all experimental mice were increased significantly. The alcoholic extracts showed estrogenic activity in immature mice by early opening of the vagina, premature cornification of the vaginal epithilium and increases in uterine weight. However, alcohol extract of seeds of *Crotalaria juncea* was more effective in causing these changes compared to other extracts [83].

The ethanol extract of *Crotalaria juncea* seeds which showed promising antiovulatory activity in female albino rats was examined for the isolation of its active fractions. Two fractions were obtained using thin layer chromatography (TLC). Both fractions were subjected for testing their anti-ovulation activity and the effect on estrous cycle in rats. After preliminary trials, the fraction I (200mg/kg body weights) showed maximum antiovulatory activity when administered orally to the rats for 30 days. Decreased number of healthy follicles (Class I – ClassVI) and corpora lutea and increased number of regressing follicles (Stage IA, Stage IB, Stage IIA, Stage IIB) were observed in the ovary after 30 days treatment. The treatment caused an increase in the cholesterol level and acid/alkaline phosphatase activity and a decrease in protein and glycogen contents of the ovary. Estrous cycle was affected as a significant increase in estrus and metaestrus phases with a decrease in diestrus and proestrus phases in the treated groups during experimental period of 30 days [84].
Petroleum ether, benzene and alcohol extracts of the seeds of *Crotalaria juncea* were tested for antiimplantation and pregnancy interruption activities in female albino rats. Of these three extracts, the alcohol extract was found to be the most effective in causing antiimplantation and pregnancy interruption activities. These adverse effects on fertility were reversible upon withdrawal of the extract treatments. The alcohol extract was found to possess estrogenic activity [85-86].

Cynodon dactylon

The effect of administration of aqueous extract of entire plant of *Cynodon dactylon* for thirty days on reproductive hormones and reproductive organ weight of female, was studied in Wistar rats. Administration of the extract produced significant increase ($p<0.001$) in the serum estradiol concentration whereas, follicle stimulating and luteinizing hormones were significantly ($p<0.001$) reduced. Furthermore, a significant increase ($p<0.001$) in the weight of the uterus and significant decrease in the weight of the ovaries ($p<0.001$) was observed in the treated group when compared to the control group. In addition, the estrous cycle was found to be irregular and disturbed [87-89].

Cyperus rotuntdus

The anti-dysmenorrhea effect of the essential oil of the rhizome of *Cyperus rotundus* (EOC) was investigated in mice. Mice were divided into four groups: Group 1 served as control and group 2, group 3, group 4 were given low, middle and high dosage (0.01g/kg, 0.02g/kg, 0.1g/kg) of EOC respectively. The animals were first given diethylstilbestrol for 12 consecutive days (2mg/kg/day) by intragastric administration to create dysmenorrhea animal model. Different dosage of EOC and equivalent saline were given to animals in each group during the last three days. 30 mins after the last drug administration, the mice were injected intraperioneally with 0.1ml oxytocin injection and distortions were observed and recorded in 15 mins and 30 mins. EOC obtained from rhizome of *Cyperus rotundus* was subjected to column chromatography for fractionation, six fractions were obtained, namely F1-F6. EOC and its fractions F2 - F6 significantly reduced distortion times in 15 mins, 30mins after ip oxytocin injection; F4 performing the best among the fractions, it was contained spathulenol as well as β-caryophyllene oxide and isoaromadendrene oxide according to GC-MS analysis. Accordingly, EOC and its fractions F2 - F6 showed significant anti-dysmenorrhea. More than one components were attributed to anti-dysmenorrhea effect according to the GC-MS analysis of EOC and its fractions F2 - F6 [90-91].

***Datura* species**

The antifertility activity of the acetone extracts of *Datura metal* was evaluated in female albino mouse. The crude acetone extract of *Datura metel* seeds were administered orally to the female mouse (25 gm of bodyweight) in the concentration of 0.5%, 1% and 2% respectively. After 15^{h} day of treatment the female mouse was mated with the normal male mouse. After 10 days of mating they were dissected and observed the number of implantation sites in the uterine horns. The results revealed that the females treated with 2% seed extracts caused 100% anti-implantation activity followed by 1% and 0.5% seed extracts which caused 40% and 80% anti implantation activity respectively. The authors study concluded that the seed extracts of Datura metel L may be recommended as a good source of antifertility compounds with minimal side effects after testing in the other human models[92-93].

Daucus carota

The petroleum ether extract and fraction 5 (fatty acids) of carrot seeds arrested the normal estrus cycle of adult mouse and reduced the weight of ovaries significantly. The cholesterol and ascorbic acid content in ovaries were significantly elevated by the extract and fraction 5 of carrot seeds. The significant inhibition of delta 5,3-beta-hydroxy steroid dehydrogenase and glucose-6-phosphate dehydrogenase, the two key enzymes involved in ovarian steroidogenesis, were also recorded in mouse ovaries after 15 days of treatment[94].

The petroleum ether, alcoholic, and aqueous extracts of Daucus carota were evaluated for their possible antiovulatory activity in rabbits with copper-induced ovulation. All extracts inhibited ovulation in 40%, or less, of the animals[95].

The alcoholic extract of *Daucus carota* seed was administered at different doses ranging from 50 to 250 mg/kg bw after coitus showed a significant dose dependent antifertility effect. The administration of the extract at a lower dose showed anti-implantational activity, whereas higher doses caused fetus resorption. The main effect of the extract appears to be an abortifacient activity. At higher dose levels, the extract demonstrated an estrogenic nature with a prolonged estrous phase, whereas lower doses showed an antiestrogenic nature and an increase in the percentage duration of the diestrous phase of the estrous cycle. This extract is neither progestational nor antiprogestational[96-97].

Dodonaea viscose

The methanolic extract of the leaves of *Dodonea viscose* was investigated for its anti-fertility activity in female rats. It was found that the extract reduced significantly ($p< 0.01$) the number of liters when administered through oral route. It also produced anti- fertility effect in a dose dependent manner and the contraceptive effect was manifested for a definite period of time. Furthermore, the extract significantly the showed anti-implantation and early abortifacient activity[98-99].

Foeniculim vulgare

The compound anol or anethole, which is the major active compound of fennel oil, is considered to be an active estrogenic agent due to its structural resemblance to diethylstilbesterol, a synthetic estrogen. The effect of acetone extracts of *Foeniculum vulgare* seeds at different dose levels (50, 150 and 250ug/100gm bw) was investigated on mammary glands and oviducts of castrated rats. The extract was found to increase nucleic acids and protein concentration as well as the organ weights in both tissues. The medium and high doses were very effective. The results confirm the estrogenic nature of the seed extract[100].

The essential oil of fennel seeds (500, 750, 1000 mg/kg for 30 days) was investigated for its and anti-osteoporotic activities in ovariectomized rat osteoporosis model. The findings assessed on the basis of bone mineral density and uterine weight showed that the fennel essential oil has a preventive effect on development of osteoporosis in ovariectomized rats. This protective effect on early post-ovariectomy bone loss was dose dependent and at the dose of 1000 mg/kg, it was even more than estradiol (BMD of 0.082±0.008 g cm-2, $p<0.05$)[101].

The clinically efficacy of fennel extract was compared with echinophora-platyloba in the primary dysmenorrhea. The clinical trial was carried out in sixty unmarried students with mild and moderate dysmenorrhea in Shahrekord University of medical sciences. The severity of pain was detected by the visual analogue scale during two cycles before and two cycles after the intervention. There was no significant difference in the mean of dysmenorrhea severity during the two cycles before the intervention between the two groups, but during the two cycles after the intervention, both drugs could reduce the severity of dysmenorrheal but fennel extract showed more significantly ($P<0.001$) reduction[102-103].

Fumaria parviflora

The ethanolic extract of the plant as well as the isolated alkaloid protopine exhibited a stimulatory effect on rat's uterus at various stages of sex cycle *in vitro*. The extract shows *in vivo* oestrogen-like effects as evidenced by vaginal smear and uterine weight tests. In contrast, it failed to produce progesterone or testosterone-like activities [104-105].

Glycyrrhiza glabra

Glycyrrhiza glabra (25 mg alcoholic extract) showed high estrogenic activity reflected by uterine response and vaginal opening. Based upon the mouse uterine weight method, three doses of 25 mg of the alcoholic extract showed an estrogenic activity 1:4716980 of estradiol monobenzoate[106].

Six *Glycyrrhiza* phenols showed binding affinities for the bovine uterine estrogen receptor. The affinity of a dihydrostilbene with two 3-methyl-2-butenyl (prenyl) groups, gancaonin R, was higher than those of isoflavone phytoestrogens (genistein and daidzein) in dietary foods. The affinities of the other five phenols, a flavanone (liquiritigenin), two prenylflavanones (isobavachin and sigmoidin B), a prenylated coumestan (glycyrol), and a pyranoisoflav-3-ene (glabrene), were similar to that of the dietary isoflavone, genistein or daidzein[107-108].

***Gossypium* species**

Gossypol also affected female fertility, (5mg/kg bw/day) caused longer diestrus in female rats, (25mg/kg bw/day) decreased the levels of estradiol-17β in female rats, (20mg/kg bw/day) caused irregular and longer estrous cycles, prolonged time for mating, decreased pregnancy rate, and reduced number of viable embryos in rats, (5 g of free gossypol/animal/day) reduced number of ovarian follicles >5mm in heifers [109-112].

Using of 20 mg/day of racemic gossypol for 2-3 months followed by a maintenance dose of 40 mg/week for 4-5 months in women with endometriosis, uterine myomas and functional uterine bleeding, resulted in amenomania and atrophy of the endometrium. Examination of uterine biopsies showed a local cytotoxic effect on the uterus together with a systemic effect on the ovarian function[113-114].
Furthermore, gossypol affected male and female gametogenesis and caused embryo toxicities[115-116].

Helianthus annuus

he effects of ethanol extract of leaves (0.5 g/kg of orally for 2 weeks) of *Helianthus annus* on the fecundity was studied in rats. The results showed that coital frequency was unaffected by the extract treatment but pregnancy rate and number of pups per rat and per group were reduced significantly. The histo-degenerative in the gonads induced by the ethanol extract may be responsible for the reduced fecundity observed in treated adult rats[118-119].

Hibiscus rosa-sinensis

The effect of *Hibiscus* rosa sinensis on the estrous cycle and reproductive organs was studied in female albino rats. The benzene extract of the flowers disrupted the estrous cycle. Treatment for 30 days resulted in a significant ($P < 0.05$) reduction in the weight of the ovaries, uterus, and pituitary gland. Histologically, ovarian follicular atresia and uterine atrophy were observed. Treatment resulted in degranulated gonadotrophs in the pituitary, the effect was dose-dependent[120].

The benzene extract of *Hibiscus* rosa sinensis flowers administered intraperitoneally at the dose levels of 125 and 250 mg/kg body weight to adult female mice, resulted in an irregular estrous cycle with prolonged estrus and metestrus. An increase in the atretic follicles and the absence of corpora lutea indicated the antiovulatory effect of the extract. The extract also showed estrogenic activity in immature mice by early opening of the vagina, premature cornification of the vaginal epithelium and an increase in uterine weight[121].

Ethanolic extracts (50%), as well the benzene extracts, of *H.* rosa-sinensis reduced significantly the glycogen contents in the uterus of adult rat dose dependently. Benzene extract seemed more potent. These effects were due to antiestrogenic nature of the extracts[122].

The postcoital antifertility properties of benzene hot extracts of Hibiscus rosa sinensis flowers, leaves, and stem barks, were investigated in female rats. Only extracts from the flowers of the plant were 100% prevented pregnancy. The flowers collected during the winter showed the greatest potency, followed by those collected in the spring, rainy season, and summer, in decreasing order[123].

Benzene extract of *Hibiscus* rosa-sinensis flowers, administered during day 1-4 of gestation, exerted anti-implantation effect without affecting the tubal transport of zygote. On day 4, normal number of blastocyst was present in the uterus but they did not implant. However, hyper-permeability of the endometrial capillaries which is the earliest known response of a receptive endometrium to any kind of deciduogenic stimulus was inhibited by the extract. Ovarian structure exhibited signs of luteolysis. Inadequate progestational development of the endometrium due to interference with the conditioning of the uterus with progesterone during prenidatory phase of pregnancy was suggested as the plausible cause of the extract-induced implantation failure[124].

The antifertility and estrogenic activity of ethanolic extract of the roots of Hibiscus rosa-sinensis was investigated. A strong anti-implantation (inhibition 100%) and uterotropic activity was observed at the dose level of 400 mg/kg body weight. Histological findings gave further documentation to the results[125].

The benzene extract of *Hibiscus* rosa-*senensis* flowers was administered at four different dose levels (250-1000 mg/kg body weight/day) from day 1-4 postcoitus in mice. Anti-implantation response and associated changes in the uterine chemical composition were studied. With an increase in the dosage of the extract, the percentage of implantation failure increased. At the dose level of 1 gm/kg body weight, the extract led to failure of implantation in 93% of the mice. The effect was accompanied by adversely altered uterine weight, its protein content and alkaline and acid phosphatase activity. The effect of the extract on uterine uptake of progesterone was studied in bilaterally ovariectomized mice treated with or without estrogen. The extract exerted neither inhibitory nor stimulatory influence on uterine progesterone uptake in untreated castrated mice but the estrogen-induced increase in the uptake level was significantly inhibited by the extract[126].

The antiimplantation activity of water extract of leaves of H. rosa-sinensis was investigated in mice. Pregnant female mice were dosed with extract (100 mg/kg bw) from days 1 to 6 of pregnancy. No implantation sites were observed in day 15 of pregnancy. Biochemical and biophysical alterations were observed in the

endometrium in treated animals, especially on day 5, at 4:40 a.m., the day of implantation. A sharp increase in superoxide anion radical and a sharp fall in superoxide dismutase (SOD) activity, the extract also exhibited antiestrogenic activity, as judged by increase in uterine weight[127].

Oral administration of the benzene extract of *Hibiscus* rosa-sinensis flowers at a dose level of 1 gm/kg body weight/day from day 5-8 of gestation caused termination of pregnancy in about 92% of female mice. The effect was associated with a significant fall in peripheral level of progesterone and increase in uterine acid phosphatase activity, as measured on day 10. The ovary exhibited signs of luteolysis, and the corpus luteal delta 5-3 beta -hydroxysteroid dehydrogenase activity decreased markedly. The interceptive effect of the extract was prevented completely by exogenous progesterone (1 mg/mouse/day) or chorionic gonadotropin (1 I.U./mouse/day) and partially (62.5%) by exogenous prolactin (500 micrograms/mouse/day). The extract caused resorption of the fetuses accompanied by reduction in weight of the ovaries[128].

The effect of aqueous extract of *H. rosa-sinensis* flowers was investigated in maternal-fetal outcome in pregnant rats with diabetes. The non-diabetic treated group showed decreased high density lipoprotein cholesterol, increased atherogenic index (AI) and coronary artery risk index (CRI), and increased preimplantation loss rate compared to the non-diabetic group. Although treatment with *H. rosa-sinensis* showed deleterious effects on cardiac and reproductive functions, the diabetic treated group showed increased maternal and fetal weights, reduced AI and CRI, and reduced preimplantation loss rate compared to the untreated diabetic group[129].

The effect of aqueous extract of *Hibiscus rosa sinensis* flowers (100 mg/kg from day 0 to 7 of pregnancy, 200 mg/kg from day 8 to 14 and 400 mg/kg from day 15 to 20) was investigated on biochemical parameters and oxidative stress in diabetic and non-diabetic pregnant rats. After treatment with Hibiscus rosa sinensis extract, non-diabetic and diabetic rats showed no glycemic changes. The treatment with H. rosa sinensis in diabetic group was able to decrease the triglycerides and ALT levels compared to diabetic non-treated animals[130].

Hibiscus sabdariffa

The effects of H. sabdariffa (HS) on the development of the male reproductive tract following in utero exposure were investigated in rats. Pregnant rats received 250 or 500 mg/kg of HS extract from gestational day 12 until day 21 of lactation. Both doses of HS increased the body weight of male offspring at weaning, without compromising the puberty onset parameters. At puberty, there was a significant increase in the vas deferens absolute weight and a significant reduction in the relative weight of kidney at higher dose. These animals also presented a significant reduction in the sperm number in the caput/corpus of epididymis after exposure to both doses and a reduction in the sperm number in the cauda epididymis for the lower dose. At adulthood, the highest dose significantly reduced the sperm production in relation to controls and both doses provoked a reduction in the relative sperm number in the epididymis without affecting the sperm morphology[131].

The effects of different concentrations of aqueous extracts of *H. sabdariffa* calyces (10%, 15% and 20%) in drinking water for 10 consecutive weeks, and its anthocyanins (50, 100, 200 mg/kg for 5 days, orally) were investigated in male and female rats, on the weight and histology of the testis, and on some biochemical constituents in testicular homogenates, as well as on plasma concentrations of testosterone, luteinizing hormone and estradiol. The possible presence of an estrogenic effect of the extract and anthocyanins on the uteri of immature female rats was also tested. Neither the *H. sabdariffa* extract nor the anthocyanins significantly altered either testicular weight and histology, or uterus weight. Plasma concentrations of the three hormones, the testicular concentrations of protein, reduced glutathione and total cholesterol, and superoxide dismutase activity were all insignificantly affected by either the extract or the anthocyanins[132].
Hibiscus sabdariffa consumption caused delayed puberty of the offspring either the mothers consumed it during pregnancy or during lactation periods[133-135].

Furthermore, consumption of aqueous extract of HS during the juvenile-pubertal period decreased fluid and food consumption, increased weight gain and delayed puberty onset in rats[136].

Juniperus communis

The antifertility mode of action of *Juniperus communis* various extracts were investigated for estrogenic, antiestrogenic, progestagenic and antiprogestagenic properties in laboratory animals. Investigations reveal that the extract possessed only antiprogestational activity which accounts for its antifertility effect[137].
Extract of *juniperus communis* fruits in 50 % ethanol was screened for antifertility activity in female rats. 300 mg and 500 mg per kg bw of the extract was administered orally from day 1 to 7 of pregnancy. The extract possessed dose dependent antiimplantation activity, it also showed abortifacient activity at both dose levels when administered on days 14, 15 and 16 of pregnancy. No evidence of teratogenicity was observed[138-139].

Jussiaea repens

The crude aqueous extract of *J. repens* (except root) was investigate on uterine contraction in *in-vitro* condition. The results showed that the crude aqueous extract of *Jussiaea repens* at a dose of 40mg dry extract / 30 ml physiological fluid in a bath, on isolated non pregnant uterus of adult female rats *in-vitro* causes significant increase of force and frequency of contraction than normal. The results (as percentage) were compared with the effect of oxytocin in presence of atropine. The results showed that the extract may act as oxytocin which was antagonized by atropine[140-141].

III. CONCLUSIO

Several hormonal therapeutics to compensate the hypothalamic and pituitary deficiencies and ovarian stimulants were used to enhance fertility, and synthetic contraceptive to control birth, but they caused a wide range of side effects. The great proportion of medicinal plants which used traditionally to solve female reproductive disorders and infertility and to control birth have not yet been scientifically evaluated. The aim of this review was to provide a comprehensive summary of medicinal plants used to enhance fertility and to control birth in females, which confirmed experimentally and clinically.

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IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 5012

Prof Dr Ali Esmail Al-Snafi "Arabian Medicinal Plants Affected Female Fertility- Plant Based Review (Part 1)." IOSR Journal of Pharmacy (IOSRPHR), vol. 8, no. 07, 2018, pp. 46-62.