



## THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF THEIR EFFECT ON REPRODUCTIVE SYSTEMS (PART 1)

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### ABSTRACT

The previous studies showed that a wide range of medicinal plants exerted many effects on reproductive systems function. These plants included: *Achillea santolina*, *Ailanthus altissima*, *Alhagi maurorum*, *Allium cepa*, *Althaea rosea*, *Ammannia baccifera*, *Anthemis nobelis*, *Anethum graveolens*, *Arachis hypogaea*, *Arctium lappa*, *Asclepias curassavica*, *Asplenium trichomanes*, *Avena sativa*, *Bacopa monniera*, *Bryophyllum calycinum*, *Caesalpinia crista*, *Calendula officinalis*, *Calotropis procera*, *Carum carvi*, *Capsella bursa-pastoris*, *Carthamus tinctorius*, *Chenopodium album* and Date palm. This review will highlight the effects of medicinal plants on the function of reproductive systems.

**Keywords:** Pharmacology, Therapeutic, Pharmacognosy, Medicinal plants, Reproductive systems, Males, Females.

### INTRODUCTION

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives. The previous studies showed that a wide range of medicinal plants exerted endocrine and reproductive effects [1-50]. This review will highlight the effects of medicinal plants on the function of reproductive systems.

#### *Achillea santolina*

The hydroalcoholic extract (300 mg/kg/day intraperitoneally, for 20 days) of *Achillea santolina* caused histological alterations in the seminiferous tubules included disorganized germ epithelium, exfoliation of immature germ cells, germ cell necrosis and increased number of metaphases in germinal epithelium of seminiferous tubules in mice. The authors concluded that *Achilleasantolina* exerted antispermatogenic effect [51].

#### *Ailanthus altissima*

*Ailanthus altissima* was evaluated for progestogenic and anti-progestogenic properties. Extracts of the plant were analysed for progestogenic and anti-progestogenic 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 [52].

#### *Alhagi maurorum*

Addition of histamine in doses of 3 µg/ml bathing fluid to the isolated guinea-pig ureter induced continuous contractions. Addition 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 anticollic 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 [53].

### ***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 [55].

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 [56]. *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 [57].

### ***Althaea rosea***

In traditional folk medicine the *Althaearosea* flowers were regarded as an emmenagogue. Literature data have proved that the infusion and methanolic extract of *Althaea rosea* influence hormonal activity and affected the morphology of the sexual organs of the rats. It exerted estrogenic activity, but exact component of this plant responsible for this activity was not determined. The *in vivo* test proved that *p*-hydroxybenzoic acid was estrogenic. Dudeket *al* proved that this compound present in different parts of *Althaea rosea* and could be responsible for its estrogenic activity [58].

### ***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  $\Delta 5$ -3 $\beta$ -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<sup>(59)</sup>. 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,  $\Delta 5$ -3 $\beta$ -hydroxy steroid dehydrogenase ( $\Delta 5$ -3 $\beta$ -HSD) and glucose-6-phosphate dehydrogenase (G-6-PD) [60].

### ***Anthemis nobelis***

The effectiveness of *Anthemis nobelis* 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 ( $P < 0.029$ ) [61].

### ***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 [62]. 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 [63-66]. 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 that dill seed shortens duration of the first stage of labor [67].

### ***Arachis hypogaea***

Introduction of refined peanut oil to form 10% of the food ration of immature mice increases uterine weight [68, 69]. 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  $\mu\text{g/g}$  dry weight) [70-

72].

#### ***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 [73]. The aqueous extract of *Arctium lappa* L. roots enhanced sexual behavior in male rats. Oral administration of *Arctium lappa* L. roots extract at 600 and 1,200 mg/kg body weight significantly increased the frequencies of mount, intromission, and ejaculation frequency ( $p < 0.05$ ). Administration of the extract also reduced the post-ejaculatory interval [74-76]. *In vivo* *A. lappa* induced uterine stimulant activity [77].

#### ***Asclepias curassavica***

The ethanol extract water and petroleum ether extracts did not show any significant antifertility activity [78].

#### ***Asplenium trichomanes***

Investigate the *in vitro* estrogenic activity of *Asplenium trichomanes* extracts ability to activate ERalpha and ERbeta, MCF7/ERE<sub>luc</sub> 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 [79].

#### ***Avena sativa***

In an experimental study, oat straw stimulated the release of luteinizing hormone from the adenohypophysis of rats [8]. *Avena sativa* contained oestrone which been shown to induce ovulation [80-82].

#### ***Bacopa monniera***

*Bacopa monniera* extracts caused reversible suppression of spermatogenesis and fertility. The treatment caused reduction in motility and viability of the sperms and reduced the number of spermatozoa in caudaepididymidis and testis, and caused alterations in the somniferous tubules in mice [83].

#### ***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 [84]. 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) [85].

#### ***Caesalpinia crista***

When *Caesalpinia crista* meal fed to mice and rats, it caused antifertility effect. This effect could be attributed to its contents of gossypol and cyclopropane fatty acids, which has been implicated as an antifertility compounds [86]. *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 [87]. Electron microscopic examination showed that the graded doses of an alcoholic extract of *Caesalpinia crista* caused morphological changes in the sperm of albino rats including disturbance in the plasma membrane and acrosomal membrane. Considerable changes in the shape and size of the sperm head were observed, with the middle region of the sperm head being slightly constricted dorso-ventrally. Most sperm appeared morphologically abnormal in the head region showing the distortion at the anterior region and bulging of the acrosomal membrane when compared with the control. The authors suggest that such effects might have resulted from general disturbance in proteins and alteration in the caudaepididymal milieu, probably due to an androgen deficiency consequent to the treatment with *Caesalpinia crista* [88].

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 [89].

#### ***Calendula officinalis***

*Calendula officinalis* flowers extracts exerted estrogenic activity in ovariectomized animals [90-92].

#### ***Calotropis procera***

The effects of ethanolic and aqueous extracts of *Calotropis procera* roots were studied on the oestrous cycle 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 [93]. The antifertility effect of the ethanolic extract of roots of *Calotropis procera* was investigated in female rats. A strong antiimplantation (inhibition 100%) and uterotrophic activity was observed at the dose level of 250 mg/kg (1/4 of LD<sub>50</sub>) [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 [95].

#### ***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 *Carum carvi* exerted a significant antifertility activity [96]. Caraway oil was effective in inhibiting tonic and phasic rhythmic contractions of isolated uterine preparations [97].

#### ***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 [98].

#### ***Carthamus tinctorius***

The effects of aqueous extract of *Carthamus tinctorius* was tested on mouse spermatogenesis. Histopathological criteria such as epithelial vacuolization, sloughing of germ and detachment were significantly decreased in *Carthamus tinctorius* L. treated mice ( $p < 0.001$ ). *Carthamus tinctorius* extract induced

formation of multinucleated giant cells in the germinal epithelium. It also caused a significant decrease in seminiferous tubule diameter, seminiferous epithelium height and maturation arrest ( $p < 0.001$ ). Accordingly, *Carthamus tinctorius* extract has toxic effects on mouse testicular tissue, and it was recommended to be use with caution with reproductive problem [99]. 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 13<sup>th</sup> 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 [100]. 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 IC<sub>50</sub> value of 0.31 microg/ml, a level of inhibition comparable to that of tamoxifen (IC<sub>50</sub>=0.43 microg/ml) [101]. 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 [102]. On the other hand, intraperitoneal administration of a hot aqueous extract of the *Carthamus tinctorius* flowers increased uterine contractions in pregnant female rats [103].

#### ***Chenopodium album***

Ethanolic extract of *Chenopodium album* at doses of 100, 250 and 500mg/kg bw orally, in male albino mice showed significant increase in the mount frequency, intromission frequency, intromission latency as well as aggregate of penile reflexes and significant reduction in the post ejaculatory interval. Moreover 500 mg/kg, orally, was found to be the most effective dose [102]. The ethanolic extract of seeds of *Chenopodium album* was evaluated for its effect on anabolic activity, sexual behavior and sperm count in male rats. Administration of ethanolic extract at a concentration of 200 mg/kg bw resulted in pronounced anabolic effect in treated animals as evidenced by an increased body weight as well as the weight of reproductive organs. Sexual behavior and performance were also markedly improved as reflected in reduction of mount, intromission and post ejaculatory latency. Furthermore, the extract also enhance sperm count [105]. However, on the other hand, the effect of *Chenopodium album* seed extract (CAE) induced sperm death, the effect

which is due to (a) lipid peroxidation of the sperm cell membrane, oxidation of some critical cellular proteins and depletion of intracellular reduced glutathione, indicating production of ROS; (b) activation of Mn-SOD and inactivation of catalase favoring endogenous accumulation of H<sub>2</sub>O<sub>2</sub>; (c) generation of O<sup>2-</sup> at an enhanced rate during oxidative stress as evidenced by increased Mn-SOD activity and protein expression; (d) accumulation of ROS in spermatozoa and (e) increased production of O<sup>2-</sup> and H<sub>2</sub>O<sub>2</sub> induced apoptosis-like death in sperm cells as observed by DNA ladder formation. Therefore, the sperm death caused by CAE is due to oxidative damage of cellular macromolecules by in situ generation of ROS [106]. Aqueous decoction of *Chenopodium album* seeds (CAD) was assessed for its sperm-immobilizing and contraceptive efficacy in laboratory mammals. The minimum effective concentration of CAD that induced instantaneous immobilization of rat spermatozoa *in vitro* was 2 mg/ml. The mechanism of CAD action involved disintegration of sperm plasma membrane and dissolution of acrosomal cap causing sperm death. Fertilization of oocytes and establishment of implantation were prevented

in the uterine horn that was administered with CAD. In rabbit, intravaginal application of CAD significantly blocked the establishment of pregnancy. Accordingly, CAD possesses appreciable spermicidal potential, which may be explored as an effector constituent of vaginal contraceptive [107].

#### **Phoenix dactylifera (Date palm)**

Pollen of Date palm (500 mg iq) and a combination of zinc sulphate & pollen of Date palm (500 mg iq) in infertile men significantly increased serum LH, FSH, & testosterone levels. It was also, increased significantly sperm count & motility. Sexual desire was also significantly increased. Wives of treated men got pregnancy during the treatment period [3, 43].

#### **CONCLUSION**

The paper reviewed the effects of the medicinal plants on the functions of reproductive systems, to be utilized in medical applications as a result of effectiveness and safety.

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