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A Comprehensive Review: Herbal Phytoconstituents as Anti-Fertility Agents

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ABSTRACT
Population is increasing day by day but now, it reaches to an alarming position. Various approaches have been applied in the control population. Many studies have been done on the basis of traditional system of herbal medicine. Most of the studies until are mainly based on the plant with anti-fertility activity. Now, this article is further approach in fertility control in both male and female by giving main attention on active phytoconstituent present in anti-fertility plants. In this article active constituents are discussed based on their abortifacient, anti-estrogenic, anti-spermatogenic and their anti-fertility activity based on their mechanism of action in various animal models. In this article we discussed 37 active constituents having anti-fertility activity. Recent study on anti-fertility constituent is published with basic aim to control the population.

Keywords: Anti-fertility, abortifacient, Herbal medicine, Plant, Phytoconstituents

I. INTRODUCTION

The global population is now approaches to 7 billion and projected continuously to rise substantially leads to impact on the availability of essential food and clean water supplies. The prospect of global warming has signaled that unless the human population is controlled within few decades, demand for resources will result in serious irreversible harm to the planet. [1]

The development of anti-fertility drugs from medicinal plants is an innovative proposition, because from times human have relied on plants and their products as sources of drug because of their therapeutic activity. Population control has been promoted through several methods of contraception, but due to serious adverse effects of synthetic steroidal contraceptives. Therefor indigenous plants has now been focused for possible contraceptive effect. Estrogen and progesterone are responsible for the contraceptive action of but the risks associated to the drugs have influenced the need to develop newer molecules from medicinal plants. Hence, there is a need for the isolation of suitable active constituents from indigenous medicinal plants. [2]

Females fertility regulated through rapid expulsion of the fertilized ova from the fallopian tube, inhibition of implantation due to a disturbance in estrogen - progesterone balance, fetal abortion, perhaps due to lack of supply of nutrients to the uterus and the embryo, and through affecting sperm count, motility and viability in males. [3]

II. DESCRIPTION OF CONSTITUENTS HAVING ANTI-FERTILITY ACTIVITY:-

Phytoconstituents having potential anti-fertility activity in both male and female, [4-5] have been devised and summarized below:

Abrin

It is a steroidal compound obtained from seeds of plant *Abrus precatorius* Linn. (Family: Paplionacae). It has shown post-coital anti-fertility action. [6] Abrin, cause the alteration in tesisis by influencin the pituitary level which leads to decrease in production and release of testosterone. Abrin also inactive the rRNA thus resulting in inhibition of protein synthesis in sertoli and leydig cells.[7] It has shown teratogenic action due to DNA damage or genotoxicity in spermatozoa.[8] Recently, it has been reported to have sperm anti-motty activity producing 100% sterility in male mice.[9]

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Acacetine and Luteoline

Both of these flavonoids, Acacetine and Luteoline, obtained from the plant *Striga lutea* Linn. (Family: Sacrophulariaceae) are responsible for the anti-fertility effect. These compounds have significant anti-fertility activity in the pre-implantation stages. These compounds possessed 40-50% estrogenic potency. Anti-implantation effect of these flavonoids was due to their estrogenic activity which in turn might be: (a) due to expulsion of ova from the tube (b) disturb the equilibrium between estrogen and progestron. [10]

Andrographolide

Andrograholide isolated from plant *Andrograhis paniculata* Wall. (Acanteaceae) is a diterpenoid. It has shown anti-spermatogenic effect when administered at a dose of 20 mg powder/day/rat for 60 days with positive results. [11, 12] It has no toxic effect (50 mg/kg) treatment for up to 8 weeks on number and motility of sperm was observed. [13]

Anethole

It is an aromatic compound isolated from the fruits of *Foeniculum vulgare* Linn. (Family: Umbelliferae). *Trans*-anethole reported 100% anti-implantation activity at 80 mg/kg *p. o.* in female rats and along with significant estrogenic effect, no anti-estrogenic, progestational, anti-progestational, androgenic or anti-androgenic activity. [14] It also produced anti-implantation effect on female rats and reduced the secretory activity and weight of sex glands. [9]

Artemether

Artemether (methyl ether of dihydroartemisinin), is obtained from the herb *Artemisia annua* L. (Asteraceae). It caused the extensive degeneration of leydig cells lead to reduced transport of cholesterol into the cell and subsequently reduction of synthesis of testosterone. It caused significant decrease in sperm count in mice testes at a dose of 4.8 mg/kg for 5 days.[15]

Coumaric acid

P-Coumaric acid, obtained from the roots of *Aristolochia indica* Linn. (Family: Aristolochiaceae) showed 91.7% and 100% anti-implantation activity in mice at a single oral dose of 100 mg/kg and 50 mg/kg body weight. [16, 17]

Aristolic acid

Aristolic acid isolated from the roots of *Aristolochia indica* Linn. (Family: Aristolochiaceae), showed 100% abortifacient activity at a single oral dose of 60 mg/kg body weight when administered on 6^{th} or 7^{th} day of pregnancy.[17]

Azadirachtine

Azadirachtin isolated from the leaves of plant *Melia azadirachta* Linn. (Meliaceae). Azadirachtine cause androgen depletion in cauda epididymis leads to reduction in the sperm count, motility and sperm speed. [18]

Chalepensin

Chalepensin is isolated from the aerial part of the plant *Ruta graveolens* Linn.(Family: Rutaceae). Suspension of aerial parts in pre-, peri-, and postimplantation periods showed significant anti-fertility activity in rat when administerd intragastically on 1-10 post coitus act at early stage of pregnancy. [19, 20]

Colchicine

Colchicine is an alkaloid isolated from the root of the plant *Gloriosa superba* Mill. (Family: Liliaceae) [28], its early abortifacient activity appears to suggest that its activity is oxytocic. [21]

D-pinitol (3-o-methyl-chiroinositol)

It is an active constituent isolated from the leaves of plant *bougainvillea spectabilies* Willd. (Family: Nyctaginaceae). oral administration of aq. Extract of plant prolonged metaestrus and decrease the estrogen level whereas in male there is decrease in sperm count and testrosterone. [22]

Embelin

It is a bioactive molecule isolated from the fruit of plant *Embelia ribs* Burm. f. (Family: Myrsinaceae). It showed 83% anti-fertility activity at a dose of 120 mg/kg post coital from (Day1 - 15 of pregnancy). [23] It also exhibit the Oral doses of Embelin (embolic acid) of 15, 30, 60 and 120 mg/kg on proven fertile females administered on Day (1 -5 of pregnancy) exhibited 55.55-83.33% anti-implantation activity at a dose 15, 30, 60 mg/kg. [24]

Ergosterol peroxide, β-sitosterol and 5-stigmastene-3β,7α-diol

These are the major constituents isolated from leaves of plant *Ananas comosus* Linn. (Family:

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Bromeliaceae) claimed to have abortifacient property in Indian medician. (1) Compound ergosterol peroxide has maximum abortifacient activity (2) β-sitosterol has delayed action but same side effect and devoid of activity when given on 6-7day of pregnancy. (3) Most consistent action is because of 5-stigmastene-3β,7α-diol before and after implantation and without side effect .[25]

Ferujol

It is an active constituent isolated from the aerial parts of plant *Ferula jaesochkeana* Linn. (Family: Apicaceae). It has contraceptive activity when administered from (1-5) post-coitus. [9]

Fraxinellone

It is an active constituent isolated from the root bark of plant *Dictamnus albus* Linn. (Family:- Rutaceae). It shows its anti-fertility effect due to inhibition of implantation. It exerted its action after tubal exit of ova to prevent implantation. It is toxic at the dose of about 1.46 g /kg through p.o route. [26]

Gamma-sitosterol

It is isolated from the plant *Ricinus Communis* L. (Euphorbiaceae). Four phytosterols which were ergost-5-en-3-ol (6.10%), stigmasterol (35.80%), gamma-sitosterol (44.77%), and fucosterol (8.40%). [27] It causes alteration in the motility, mode of movement and morphology of the sperms. [28]

Gossypol

It is a phenolic compound isolated from seed of *Gossypium herbaceum* Linn. (Family: Malvacae). It used as male contraceptive because it reduce the level serum testosterone and leutinizing hormone (LH). [29] It acts directly on testes and induce azospermia or oligospermia.[30-31]The high dose of gossypol (10 mg/kg body wt) caused signs of tubular degeneration, retarded body growth, markedly reduced testosterone concentrations, involutions of the ventral prostate and seminal vesicles and gastrointestinal disturbances. [32]

N-hexacosanol, sitosterol, stigmasterol, campesterol

These are the steroid isolated from the plant *Heliotropium indicum* Linn. (Family: boraginaceae) used as folkloric anti-fertility drug .[54] It ethnolic extract has 50% and 60% abortifacient activity whereas n-hexane fraction shown 50% and 60% and benzene fractions have shown 30%and 60% abortion.[33]

Isothankuniside and thankuniside

It is a chief constituent isolated from the leaf of plant *Centella asitica* Linn. (Family: Apiaceae). It is a oral antifertility agent causes consistent reduction of fertility in female rats. [9] Crude extract that contains isothankuniside and thankuniside showed anti-fertility action in mice. [34]

Kampferol, β- sitosterol, ferulic acid, myritic acid, prostaglandine

These are the constituents isolated from the bulb of the plant *Allium cepa* Linn. (Family: Liliaceae).[35] These constituents are responsible for the anti-implantation activity which is due to anti-zygotic and blastotoxic activity. [36]

Lapachol

Is an active phytoconstituent isolated from the genus *Tabebuiea* (Bignoneaceae). It causes significant reduction sperm count due to action on seminal vesicle. [37]

Lupeol

Lupeol is obtained from *Alstonia scholaris* Linn. (Apocynaceae). The treatment with lupeol acetate at the dose level of 10 mg/rat/day cause significant reduction in the weight of reproductive organs, i.e. testes, epididymides, seminal vesicle and ventral prostate, was observed. Testicular sperm count, epididymal sperm count and motility were found significantly declined when compared with controls, which resulted in reduction of male fertility by 100%. [38]

Marsdenikoside A and B

Marsdenikoside A and B are isolated from the plant *Marsdenia koi* (Family: Ascelepediacae). These steroidal glycoside showed anti- fertility activity. [39]

Oleanolic acid

It is a terpene isolated from the flowers of *Eugenia jambolana* Lam. Myrtaceae. It cause decrease in fertilizing capacity on administration for 60 days. The compound produced arrest of spermatogenesis but did not cause any abnormality to spermatogenic cells, Leydig interstitial cells and Sertoli cellst. [40]

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Piperine

It is an important constituent isolated from the fruit of plant *Piper longum* Linn. (Family: Piperaceae). [41] It has antifertility efficiency ranging from 100-86%. [54] Piperine increased the period of the diestrous phase. [42] It inhibits the implantation and produce abortion. It also inhibit the uterine contraction but does not possess any action like anti-estrogenic and anti-progestational activity thus piperine has anti-fertility activity without any hormonal imbalance and uterotonic action. [43]

PLUMBAGIN

It is a active constituent isolated from the leaves of plant *Plumbago rosea*_Linn. (Family: Plumbaginaceae). [44]The antifertility action of plumbagin seemed to be related to its antiovulatory action. [58] Plumbagin administered by intubation to albino female rats at 10 mg/kg for 15 days significantly inhibited mating and prolonged duration of estrus cycle and diestrus phase. [45]

Polysterol and polyphenol

These are isolated from the bark of the plant *Amaranthus spinosus* (Family: Amarantheacae). It causes anti-implanation and abortifacient action due to its anti-zygotic and anti-blastocytic activity. [46] These are responsible for the antifertility activity and these compound exert inhibitory effect on sperm motility. [47, 48]

Pseudolaric acid b

It is a diterpenoid isolated from the root of plant *Pseudolarix kaempferi* Lamb. (Pinaceae). At the concentration of 5 micrograms/ml the capacity of fertilization of the cumulus-free ova was inhibited and at 20 mg/kg for 4 d before mating, partial antifertility effect was observed. [49]

Quassin

Quassin is isolated from the stem wood of plant *Quassia amara* Linn. (Simaroubaceae). It caused the reduction in the weight of the testis, epididymis and seminal vesicle. It decreases the Epididymal sperm counts, serum levels of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Eight weeks after the withdrawal from extract treatments changes seemed to be restored. [50]

Rohitukine

It is an alkaloid isolated from the stem bark of the plant *Dysoxylum binectariferum* Hook.f. (Meliaceae). It prevents pregnancy at the 10-mg/kg dose administered on Days 1-7. [51]

Solasodine

It is an active isolated from the plant *Solanam xanthocarpum* Schradt. & wendl. (Family: solanaceae). It is an alkaloid possesses anti-spermatogenic activity. At dose 20 mg/kg alternately for 30 caused the testicular lesion leading to impairment of spermatogenic element. Solasodine administration cause low Acid phosphates enzyme activity of testes, low level of which causes the reduction in the size of epididymis which lead to epididymal degeneration leads to anti-fertility in males.[52]

Tinctoramine and Tinctoralactone

There are the active steroidal alkaloid isolated from plant *Marsdenia tinctoria* R. Br (Family: Asclepiadaceae) both have significant Anti-implantation and abortifacient activities in mice and rats. Both of these isolated compounds produce their action by interruption on normal estrus cycle of rats and mice. Antifertility activity of compound is due to presence of steroidal moiety. [53]

Triptolide

It is an impotant glycoside isolated from the plant *T. wilfordii* Hook f. (Celastraceae). It causes the reduction in sperm motility in male rats. [54]Its action is mainly on epididymal sperm with minimal affect on testis. [55] Its spermatogenic action is due to inhibitory action on calcium channel of spermatogenic cells. [56]

Vicolide B and vicolide D

These active constituents are isolated from the plant *Vicoa indica* Linn. (Family: Asteraceae). Both of these sesquiterpenoid lactone are reported to have anti-fertility activity. [57]It possesses the antifertility activity which is dose dependent and does not produce any side effect. Vicolide B cause the resorption of implant whereas Vicolide D prevents implantation. [58]

Vinblastine, vincristine

These are the indole-indoline demeric alkaloid isolated from the leaves of plant *Catharanthus roseus* Linn. (Family: Apocynaceae). It effect the spermetogenic cell line other than spermatogonia. [59, 60]. It causes the regression of whole reproductive system. [61]

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Yuanhuacine
It is a diterpenoid isolated from the flowers of plant *Daphne genkwa* sieb, et zucc. (Family: Thymalaeaceae). It is responsible for the abortifacient activity of this plant. It produce its action by decreasing the level of progesterone which lead to inflammation, degeneration and necrosis of decidua (mucous membrane formed when conception occur and envelops the impregnated ovum). It shows its action in second trimester not in early stage. [62]

Yuehchukene
It is an active constituent isolated from the root of plant *Murraya paniculata* Linn. (Family: Rutaceae). At a dose 3 mg/kg, It has potent anti- implantation activity in rats by effecting implantation, terminating early pregnancy and mid-pregnancy of mice. [63]

III. DISCUSSION AND CONCLUSION

Medicinal plants are traditionally used in the treatment of many diseases. Drastic increase in population is the major problem in now days. Modern system of medicine is mainly concern on the allopathic medicine to inhibit the conception. Traditional medicine is adopted by most of the country to inhibit conception and for anti-fertility activity due to ill effect of allopathic medicine. This article is mainly concern with active constituents in the plants reported to have anti-fertility activity both in male and female. These constituents inhibit the pregnancy by their different mechanisms. Abridine has significant contraceptive action but it cause DNA damage of spermatozoa and produce spermatodenic action. Ergosterol peroxide, is a compound has maxium abortifacient activity as compare to other two constituent isolated from the same plant but has side effect like it cause loss of weight, lethargy and anemia in rat. Vicolide B and Vicolide D, both isolated from the same plant but anti-fertility activity of Vicolide B is 100% as compare to Vicolide D. Aristolic acid has 100 % abortifacient activity. Gossypol produce the anti-fertility activity by decreasing the level of testosterone and lutenizing hormone at low dose but when it is taken at high dose it cause tubular degeneration, markedly reduced testosterone concentrations, involutions of the ventral prostate and seminal vesicles and gastrointestinal disturbances. Thus the constituent isolated from plant for their anti-fertility activity also has side effect when these are taken at higher dose so choice for contraceptive constituent should be only to those not cause ill effect on other organs. There are various plants with anti-fertility have been reported but the isolation of constituents responsible for this activity is not an easy task. May this article may helpful in the research of other isolated constituent beneficial in the development of suitable herbal formulation free from side effect and has reversibility of action.

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