

A Systematic Review on Natural Based Anti-Fertility Drugs

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Abstract

The aim of this review is to provide a comprehensive summary of natural based anti-fertility agents in males and females throughout the world by various tribes and ethnic groups. The present study explores the reviews published in this domain from 2006-2018. A comprehensive bibliographic database and abstracting systems such as Journal of Traditional Knowledge, Ayush portal and PubMed were explored for the purpose of the study. The use of natural products with its therapeutic properties as possible anti-fertility drugs is as ancient as human civilization. Now-a-days natural products have made an immense contribution to the development of drugs used in modern medicine. The rise in population in the developing countries is overwhelming and this intensifies the need for effective birth control measures. Thus, this review is much needed to explore the reported findings from various original research work in this domain. The main focus is to have alternative steroidal pills free from side effect. The need has been felt since the sixties as a combination of progesterone-estrogen.

Keywords: Implantation; Anti-Fertility, Contraception; Anti-Ovulatory Drugs; Anti-Implantation; Anti-Spermatogenic Activity; SERM

Introduction

Anti-fertility agents are drugs that control fertility and are also called oral contraceptives. These drugs affect and are involved in the menstrual cycle and ovulation in females. Estrogen and progesterone in combined form are given as birth control pills. The anti-fertility substance is deemed to be active in females when it prevents fertilization, prevents ovulation, implantation and destroys the zygote or causes abortion. In males it prevents spermatogenesis, inhibits testosterone or affects the gonadotropin of the organs or the mortality of sperm [1]. The development of fertilized ovum and the priming of the uterus for implantation there is a clear understanding of the role of estrogen-progesterone balance serve as the basis of developing an agent that would prevent pregnancy by interfering with implantation but without disturbing the hypothalamus-pituitary-ovarian axis.

Progesterone is the most common progestin synthetic substances such as Norethindrone have been developed that the superior to progesterone when taken orally to turn off ovulation.

They induce temporary infertility. Synthetic estrogens have also been developed and they are often used in oral contraceptive in combination with progestins. A very potent synthetic estrogen is the compound called Ethenylestradiol. Mifepristone is a synthetic steroid which blocks the effects of Progesterone and is used as a "morning after pill" in many countries.

Female Hormonal System

- A hypothalamic - releasing hormone, luteinizing hormone (LH) releasing hormone
- The anterior pituitary hormones, follicle-stimulating hormone (FSH), and LH both of which are secreted in response to the releasing hormone from the hypothalamus
- The ovarian hormones, estrogen and progesterone which are secreted by the ovaries in response to the two hormones from the anterior pituitary gland.
- The various hormones are not secreted in constant amounts throughout the female monthly sexual cycle but instead are secreted at drastically different rates during different parts of the cycle [2].

Estrogens

Estrogens are a class of steroid hormones linked principally with the control of female sex organ responsiveness and of reproduction. The important endogenous estrogens are 17 beta estradiol, estrone and estriol. The most potent biogenic form is 17 beta estradiol. Estrogens are biosynthesized in the ovary.

Estrogenic compounds derived from plants are termed phyto-estrogens. The major chemical groups of phyto-estrogens are classified flavonoids, (flavones, flavanones and isoflavanoids) coumestrols, lignans and myoestrogens.

These compounds interacting with the estrogenic receptor exert estrogenic activity, such as uterotropiceffect, sterility or disruption of normal reproductive processes occurs in farm animals grazing in pastures with plants sources high in phyto-estrogens. In human cancer protective properties have been associated with phyto-estrogens [3].

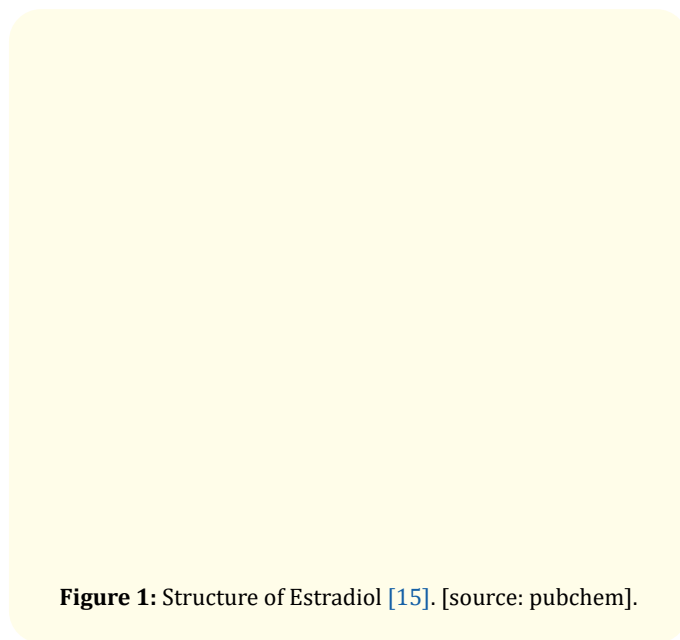


Figure 1: Structure of Estradiol [15]. [source: pubchem].

Physiology of Estrogens [5-8]

Estrogen is required for the normal maturation of the female. They stimulate the development of vagina, uterus and uterine tube as well as the secondary sexual characteristics. They stimulate the development of stroma and ductal growth in the breast. They contribute to the growth of the axillary and pubic hair and later the distribution of body fat. Estrogen also plays an important role in the development of endometrial lining. Estrogens stimulate the synthesis of enzymes and growth factors, leading to uterine growth

and differentiation. In the liver, estrogen alter the circulating levels of proteins such as transcoding (cortisol binding globulin), thyroxin binding globulin, sex hormone-binding globulin, transferrin, rennin substrate and fibrinogen. This leads to increased circulating levels of thyroxin, estrogen, testosterone, iron, copper and other substances. Estrogens enhance the coagulability of blood. Alterations in the composition of the plasma lipids caused by estrogens are characterized by an increase in the high density lipoprotein and a reduction in plasma cholesterol level. Plasma triglycerides levels are increased [4].

Mechanism of action of Estrogen [9-11]

Estrogen may act on the hypothalamic center to inhibit the secretion of gonadotropin releasing factor thereby preventing pituitary gonadotropins and their secretion and the resultant ovulation. The transport of ova through the tubules is either accelerated or inhibited so that the ovum enters the unprepared uterus where it is degenerated or expelled. Administered estrogens also alter the delicate balance of estrogen and progesterone required for implantation of the blastocyst in the endometrium.

Estrogens also induce the formation of hormonal receptors necessary for the interaction of the different hormones. Most of the actions of estrogen are mediated by the activation of intracellular receptors [9].

Progesterone [27]

Progesterone is natural progestin and natural antagonist of testosterone and is derived from cholesterol. It has strong feedback action on hypothalmo- hypophysial axis and reduced plasma luteinizing hormone and testosterone level.

Role of sperms in fertilization [11-13]

Semen is the complete discharge of the male during normal ejaculation. It consists of seminal plasma, spermatozoa and usually some cells cast off from the lining of the reproductive ducts and glands. Seminal plasma consists of the secretion of the prostate, seminal vesicles, bulbo-urethral glands and epididymis, the chief contribution being from the prostate and seminal vesicles. The seminal plasma serves as a food source and vehicle for the spermatozoa.

Testicular or epididymal sperm is inactive but quickly become active in seminal plasma (or saline). The role of the high content of hyaluronidase in sperm is not entirely understood, but histochemical studies indicate that it breaks down the egg coating and aids the sperm in penetrating the egg.

Anti-ovulation Activity [11-14]

Polygonum hydropiper Linn belongs to the family Polygonaceae, which is in part valued for its roots and leaves and includes such active ingredients as formic acid, acetic acid, beldianic acid, tannin, essential oil and oxymethyle-anthraquinones. It is used in cases involving diarrhea, skin problems, hemorrhoids, and dyspepsia. Biologically these ingredients can have antioxidant, antimicrobial, anti-inflammatory, and antifertility effects in humans. In one study there is a report on the antioviulatory activity in this plant. Their study using three types of extract (petroleum, aqueous and alcohol) was conducted to investigate the antifertility activity of this particular plant. Antifertility activity was observed in rabbit with copper-induced ovulation. Petroleum ether extract of the roots of *Polygonum hydropiper* was found effective in inhibiting ovulation in 60% of the animals.

Figure 2: Structure of progesterone [source: pubchem] [27].

Plants	Type	Dose/Body wt	Activity
Cichoriumintybus	50% ethanolic extract	50	Anti-Implantation
Cuscutareflexa	Ethanolic Extract	800	Anti-Implantation
Rubiaccordifolia	Ethanolic Extract	250	Anti-Implantation
Urticadiocia	Ethanolic Extract	250	Anti-Implantation
Abroma Augusta	Petroleum Ether	50	Anti-Implantation
Curcuma longa	Petroleum Ether	200	Anti-Implantation
Plumbagorosea	Acetone Extract	200	Anti-Implantation
Aloe barbadensis	Aqueous Extract	100	Anti-Implantation
Abutilon indicum	50% aqueous extract	500	Anti-Implantation
Strigaorobanchioides	Ethanolic Extract	200	Anti-Implantation
Acalypha indica Linn	Ethanolic Extract	600	Estrogenic Activity
Enicostemma axillare	Ethanolic Extract	375 and 750	Antispermato-genic
Mondia whitei Linn	Ethanolic Extract	400	Antispermato-genic
Moringa oleifera	90% ethanolic extract	175	Abortifacient
Abrus precatorius Linn	70% methanolic extract	20 and 40	Antifertility
Aegle marmelos	50% ethanolic extract	100,200 and 300	Antifertility effect
Albizia lebbek	Methanolic Extract	50,100 and 200	Antifertility effect
Bacopa monnieri	Dry Powder	250	Antispermato-genic
Cannabis sativa	Alcoholic extract	20	Antispermato-genic
Dendrophthoe falcata	70% methanolic Extract	100	Antispermato-genic
Fadogia agrestis	Aqueous Extract	18,50 and 100	Adverse effect on male rat testicular function
Juniperus phoenicea	Ethanolic Extract	400	Antifertility activity
Leptadenia hastata	Aqueous Extract	100,200,400,800	Antispermato-genic
Ocimum sanctum	Benzene Extract	300	Antifertility property
Quassia amara	Chloroform Extract	Single daily IM	Antifertility Effect
Syzygium amara	Hexane Extract	15,30,60	Degenerative changes in seminiferous tubule
Terminalia bellirica	Alcoholic Extract	50 mg/d	Antifertility Effect

Table 1: List of Anti-fertility Medicinal Plants with their reported activity.

Mechanism of action of formic acid [24]

A group of 10 rats and mice were carried out for investigation of sperm morphology and vaginal cytology. The groups of 10 rats and mice were exposed to formic acid concentration of 0,8,32,128 ml/m³. In case of male animals, there was no relevant effect on sperm motility, sperm concentration or on testis or epididymis weights were found. In case of female animals, the oestrus cycle was not affected.

Figure 3: Structure of formic acid [source: pubchem].

Anti-implantation Activity [11-14]

Calotropis gigantean Linn. belongs to the family Asclepiadaceae. Here the plant part primarily used in antifertility treatments is the leaves, which operate within the active principles of glycosides and cardenolides. It is used for cases of colic, flatulence, asthma, cough and whooping cough. The biological activities associated with this plant facilitate wound healing; In addition, they also have anticancer and hypoglycemic effects.

Centchroman [16]

It is an anti-implantation agent as well as first non-steroidal oral contraceptive pill in the world. It is also known as Ormeloxifene. Government of India has included centchroman free of cost to women under the brand name Chhaya in the National Family Planning initiative. It has a unique combination of weak estrogenic

and potent antiestrogenic properties. Due to this mix of estrogenic and antiestrogenic activity (like clomiphene citrate and anastrozole), it inhibits ovum fertilization from nidation and thus prevents pregnancy. It has one good effect that it does not disturb the other estrogen effect.

The use of cent chroman has been evaluated in more than 2000 women who wanted to space their children. Haematology and biochemical tests and laparoscopy and ultrasonographic examinations of ovaries and uterus have shown the drug to be quite safe. Cent chroman does not cause nausea, vomiting, dizziness and break through bleeding and has no adverse effect on lipid profile and platelet function as normally seen with other steroidal contraceptives. The outcome of contraceptive effect is predictable. Cent chroman is advantageous over other steroidal contraceptives because it does not disturb the endocrine system and the normal ovulatory cycle is maintained.

Figure 4: Structure of Cent chroman (Ormeloxifene) [17] [source: pubchem].

Anti-spermatogenic activity

Plumbago zeylanica [18] belongs to the family Plumbaginaceae and its components are roots and leaves. The active principle of Plumbago are plumbagin, isoshinanolone, trans- cinnamic acid, vanillic acid, beta- sitosterol, 4-hydroxybenzaldehyde and plumbagic acid.

Piper nigrum Linn. belongs to the family of Piperaceae, where only fruits are used. The active principles are thujon, piperettine, piperolinA, piperolin B, terpene, volatile oil, starch, piperine, calcium, phosphorus, iron, thiamin, ribovlavin, nicotinic acid, vitamin C.

Figure 5: Structure of piperine [21] [source: pubchem].

Methanol extract of *Morinda lucida* [26]

The study has investigated the effect of *M. lucida* methanol leaf extract on male albino rat reproductive functions. Two groups of rats with 400 mg/kg were treated with extract for 4 and 13 weeks. As a result, it has been shown that there is significant increase in testis weight. After treating for 13 weeks, epididymal sperm counts were significantly reduced due to acetyl cholinesterase inhibition and glucose lowering properties of this plant. Also there is increase of sperm morphological abnormalities and serum testosterone levels. There were also damage of seminiferous tubules.

Aegle marmelos (Linn.) belongs to the family Rutaceae found in tropical and subtropical region of India. Various chemical constituent like alkaloids, coumarins and steroids have been isolated from this tree. Leaves were basically used for fertility control in Bangladesh. The leaf extract of *Aegle marmelos* (Linn.) possesses anti-spermatogenic activity as it resists the process of spermatogenesis and decrease sperm motility in rats [28].

Azadirachta indica (neem) has documented to have anti-spermatogenic activity. The aqueous leaf extract of neem was administered to male mice at a dose of 200 mg/kg for 28 days, as a result it damaged the seminiferous tubules, marginal condensation of chro-

matin in round spermatid and degeneration of germ cells occurs in spermatogenesis [25].

Carica papaya seed extracts have been reported for degeneration of germ cells and germinal epithelium, reduction in number of Leydig cells and presence of vacuoles in the seminiferous tubules when administered orally to male wistar rats at a dose of 100 mg/kg [25].

Role of corals in fertilization [22]

Parmelia perlata belongs to the family of Parmeliaceae, commonly known as stone flower mainly found in Himachal Pradesh and West Bengal. The study of investigation of the petroleum ether extract of the lichen *Parmelia perlata* led to the isolation of compounds (i) Stigma-4,22-diene 3-one (ii) Stigmasterol (iii) 5,4-dihydroxy 3,6,7,3',5' pentamethoxy flavone (iv) Benzyl 2,6 dimethoxy benzoate (v) Benzyl 2,3,5,6 tetramethoxy benzoate. The antifertility activity was studied.

Figure 6: Structure of stigmasterol [20].
[source: pubchem].

Conclusion

This review aims to promote plants and minerals arising from their antifertility activities. Medicinal plants have efficacy as antifertility agents and the detailed mechanism of action of natural products in including antifertility should be elucidated for better and promising drugs in this much neglected area of therapeutics.

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