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Herbal options for Contraception: A Review

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ABSTRACT - Due to existing and overwhelming growth rate of world population, oral contraceptive have become need of the time. But steroids have various side effects. This forced us to review the existing options of plants having anti-fertility activity. Plant plethora is rich source of plants having anti-fertility activity. In this review we have also covered the plants having anti-fertility activity by different mechanism in both male and female.

KEY WORDS: Anti-fertility, abortifacient, anti-implantation, spermicidal, estrogen.

INTRODUCTION

The extraordinary growth of the world population stands as one of the significant events of the modern era to think over. The current world population is around 6.46 billion and that of India in particlualar is around 1.1 billion (1). One of the critical problems of the developing countries like India is its geometrical increase in human population.

Today we understand that our sheer numbers have increased so much that they are straining Earth's capacity to supply food, energy and raw materials. Advances in medicine and public health have led to a significant decrease in mortality and an increased life expectancy. This population explosion will have negative impact on our economic policies and would simultaneously misbalance our socio-economic infrastructure. Thus the control of human fertility in the sense of its limitation is the most important and urgent of all-biosocial and medical problem confronting mankind today.

Contraception is literally the prevention of conception, but generally is taken to mean the prevention of pregnancy (2). The development of new fertility regulating drug from medicinal plants is an attractive proposition, because from times immemorial humans have relied on plants and their products as sources of drugs and therapeutic agents, although in recent times, synthetic drugs are used extensively in modern medicine. However many modern medicines are developed through the clues obtained from phytochemicals. More over the phytochemicals even today are important resources for medicine. The plant products are becoming more popular than the synthetic drugs. In recent times it is mainly attributed to their low toxicity and long standing experience of exposure of these drugs in ethnic medicine system like Ayurveda.

Family planning has been promoted through several methods of contraception, but due to serious adverse effects produced by synthetic steroidal contraceptives, attention has now been focused on indigenous plants for possible contraceptive effect. Although contraceptives containing estrogen and progesterone are effective and popular, the risks associated to the drugs have triggered the need to develop newer molecules from medicinal plants. Hence, there is a need for searching suitable product from indigenous medicinal plants that could be effectively used in the place of pills.

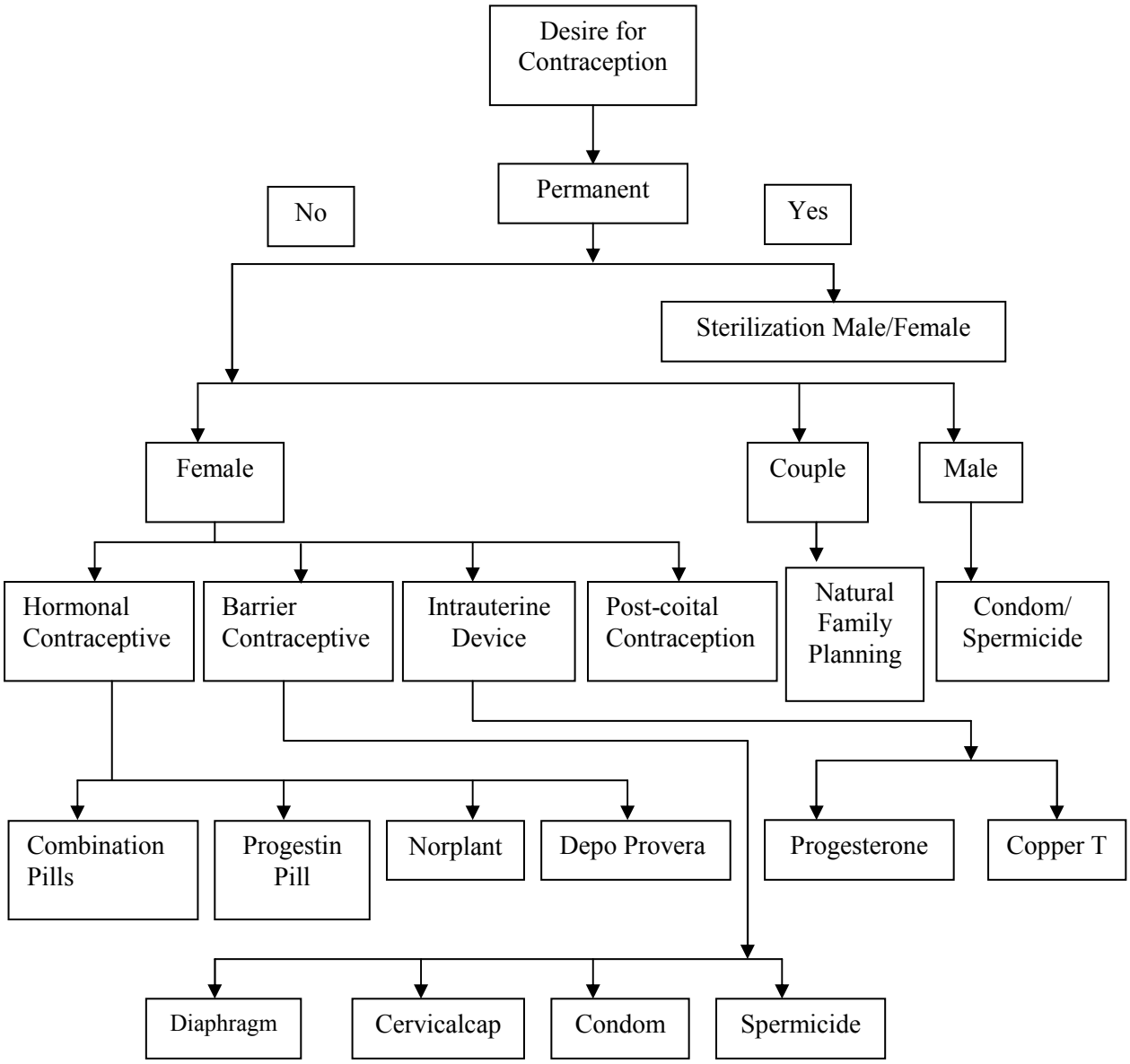
All combination oral contraceptives (COCs) contain both an estrogenic compound and a progestin. Over the years, the amounts and types of these components have changed in attempts to lower side effects and improve efficacy.

Mechanism of steroid hormone action

Estradiol, like other steroids, is thought to exert its action directly on the nucleus of the cell. As a consequence, an estrogen-response tissue must have estrogen receptor and nuclear acceptor sites to which activated receptor can bind. Upon entry into the cytosol of the cell (by diffusion), estradiol is bound to a specific receptor (ERc). In the cytoplasm, the estrogen receptor complex is activated (ERn) and translocated to the nucleus. This complex binds to acceptor sites in chromatin and enhances processes associated with differentiated functions of the responsive tissue, which include the production and utilization of messenger and other classes of RNA needed for the synthesis of constituent enzymic and secretory proteins, as well as the receptor itself. In some cells replication of DNA is also stimulated, followed by cell division. The concentration of estrogen receptors in most tissues is constitutive, but in some instances it is increased by estradiol. The

concentration of progesterone receptors in the uterus and other progesterone response tissues is markedly increased by estrogen. In fact, one of the recognized actions of estradiol is to stimulate synthesis of progesterone receptors. The induction of progesterone receptors with estrogen can explain the synergistic action of these two hormones on the uterus.

Methods of contraception



Hormonal control of fertility

The most effective method of contraception, the birth control pill, is based on oral administration of steroids. Estrogens and progestins are used either combined or, as with the "minipill", progestins are used alone. In addition, various combinations of steroids can also be administered as long-acting injectable preparations or via intrauterine systems.

The pills to be effective via the oral route, estradiol and progesterone cannot be used since they are metabolized in the gastrointestional tract and liver. As a consequence, synthetic estrogens such as mestranol (50-100 μg/day) or ethinyl estradiol (20-50 μg/day) are

used in combination with various synthetic progestins, such as norethindrone, norethindrone acetate, norgestrel, ethinodiol diacetate or norethynodrel (0.3 – 100 mg/day). The hormones are given in a cyclic fashion for 21 days, beginning on day 5 of the menstrual cycle, followed by 7 days of placebo treatment or no pills.

The elevated estrogen and progestin levels inhibit the midcycle LH surge and ovulation by exerting negative feedback effects on the hypothalamus. Irregular LH peaks are sometimes observed, while FSH levels are usually suppressed. Ovarian progesterone production is diminished, but estrogens continue to be secreted. The effects on the endometrium are variable and depend on the type and dosage of the contraceptive. Rapid progression from proliferation to early secretory changes can be observed within a few days from the start of daily intake, followed by regressive changes. Secretory activity is either minimal or absent. The pregnancy rate for combined pills is approximately 2%.

Risks

The reason why some women may be reluctant to take combination oral contraceptives (COCs) consistently and correctly is a fear of possible adverse effects.

Cardiovascular disease

Historically, combination oral contraceptives have been associated with increased risks for myocardial infarction and stroke. Overall, oral contraceptives were found to multiply the effects of age and other risk factors for MI and stroke, rather than just add to them. Because cigarette smoking is far more prevalent among women of reproductive age than any of these other risk factors, it becomes by far the most important factor.

Whereas early epidemiological studies of high-dose oral contraceptives found significantly increased risks of developing cardiovascular disease among users of combination oral contraceptives.

Use of oral contraceptives by healthy women who do not smoke does not appear to be associated with an increased risk of either myocardial infarction or stroke.

Hypertension

As with the increased risks for MI and stroke, older formulations of combination oral contraceptives have been associated with significant elevations of blood pressure as well. The risk of hypertension appears to be much lower when estrogen and progestin doses are lowered.

The mechanism for contraceptive-induced changes in blood pressure is still unclear, with alterations in plasma angiotensinogen and increases in sodium and water retention being noted. Although these are primarily estrogenic effects, progestins may have a synergistic effect, as significant elevations in blood pressure have only been apparent in the combination products and not with either hormone alone.

Thrombosis

As doses of estrogenic were lowered to less than 50 μg, a marked drop in the incidence of fatal and nonfatal pulmonary embolism was noted, thus implying an estrogen dose-related effect.

As with the other concerns for myocardial infarction, stroke, and hypertension, patient selection remains the most important method of reducing the incidence of these adverse effects. Women who are already at high risk for cardiovascular problems (hypertension, smoking and older than 35 years, or diabetes with vascular complications) or have already had a cardiovascular or thromboembolic event should not use combination oral contraceptives.

Hepatomas

It may occur in women taking oral contraceptive, the most common of which are focal nodular hyperplasias and liver cell adenomas. Hepatocellular cancer was also felt to be associated with combination oral contraceptives use (3).

Here it is clear that estrogen and progesterone play a crucial role in anti-fertility activity but not without the serious side effects. So in this background we have reviewed some of the plants having anti-fertility activity in both male and female.

Following is the list of plants available for anti-fertility activity with their parts used and somewhere mechanism of action to understand this activity.

Alangium salviifolium

The family Alangiaceae consists of twenty-two species out of which *A. salviifolium* (Linn.f) Wang is mainly used as medicine in India, China and Phillipines (4). Different parts of this plant are reported to possess acrid, astringent, emollient, anthelmintic, diuretic and purgative properties. It is also used externally in acute case of rheumatism, leprosy and inflammation. Applied externally and internally in case of rabid dog bite. Root bark is an antidote for several poisons. Fruits are sweet, cooling and purgative and used as a poultice for treating burning sensation and heamorrhage period (5). Daily administration of petroleum ether, ethyl acetate, chloroform, methanol or aqueous extracts of *A. salvifolium* at a dose of 100mg/kg body weight for eight days starting from the first day of pregnancy showed significant abortifacient activity in comparison to vehicle treated group. Interestingly, except petroleum ether and ethyl acetate extracts, all the extracts showed no anti-implantation activity. Eight

days of drug treatment lead to resorption of fertilized ovum as noticed by red spots in the horns of uterus. Among the extracts, chloroform extract was found to be least effective followed by petroleum ether extract. Methanol extract showed total resorption sites in two animals. Aqueous and ethyl acetate extracts have also shown good activity. These results indicate that *A. salviifolium* (Linn.f) Wang produced mainly abortifacient activity and less antiimplantation activity. It indicates that the herbal drugs may have anti-progesterone effect (6).

Aloe vera

Twenty samples of fresh ejaculate donated by healthy volunteers ranging in age from 20-30 years were obtained. Lyophilized *A. barbadensis* at concentrations of 7.5% and 10% proved to be spermicidal due to the multiple microelements (boron, barium, calcium, chromium, copper, iron, potassium, magnesium, manganese, phosphorus and zinc) which were toxic to the tail causing instant immobilization. These results suggest the possibility of using lyophilized *A. barbadensis* as a new, effective and safe vaginal contraceptive (7).

Aristolochia tagala

Aristolochia, a large genus of shrubs, rhizomatous perennial herbs often twining, is distributed in tropical and termerate regions of the world. *A. tagala* is a perennial herb highly prevalent in Himalayas, Bihar, Assam and southwards in forest cleanings. The root of the plant is reported to contain aristalochic acid, which possesses tumor-inhibiting activity and has been used in the treatment of cancer, snakebite and helmenthiasis (8).

Preliminary phytochemical studies revealed that the ethanol extract showed the presence of alkaloids, saponins, flavonoid glycoside, steroids and phenolic compound. The ethanol extract of *A. tagala* showed significant reduction in the number of corpora lutea and increase in the number of resorptions in comparison to the control. The extract showed 72% antifertility activity on oral administration of 100mg/kg whereas a remarkable 100% antifertility activity resulted on the administration of 200mg/kg as compared to the untreated control group (9).

Azadirachta indica

Male albino rats were administered orally 100 mg/kg *A. indica* leaf powder with or without testoesterone. Suitable controls were maintained. Damaged semineferous tubules and abundance of vacuoles of varying size were observed in *A. indica* treated rats. The germ cells showed overall decrease in cytoplasmic ground substance. Leydig cells exhibited characteristics of degeneration with condensed nuclei. Total count of spermatocytes, spermatids and Leydig cells were reduced. The cell and nuclear diameter of spermatogonia, spermatocytes, spermatids and Leydig cells were also reduced. From the result obtained, it can be observed that effects of *Azadirachta indica* on the testis are possibly due to gonadotrophic hormone deficiency, caused directly or indirectly (10).

Neem oil proved spermicidal against rhesus monkey and human spermatozoa *in vitro* (11). *In vivo* studies showed that intravaginal application of neem oil prior to coitus can prevent pregnancy (11). Antifertility effect of neem oil has also been studied and suggested to be a novel method of contraception (12-14). Oral administration of aqueous extract of neem leaf also shows antifertility effect in mice (15). Purified neem seed extract has also been demonstrated to abrogate pregnancy in both baboons and bonnet monkeys, when administered orally (16). From the hexane extract of neem seed, an active fraction containing six components has been found to completely abrogate pregnancy in rodents when given orally up to a concentration of 10%, with no apparent side effect (17).

Biophytum sanctivum

Different extracts of *B. sanctivum* were tested for their antifertility activity. Ethyl acetate and n-butanol extracts significantly inhibited pregnancy in 4/6 rats with mean number of implants 3.0 ± 1.92 ($P \leq 0.05$). It is also understood that the chloroform and the ethanol extracts significantly inhibited pregnancy in 5/6 rats with a mean number of implants of 2.0 ± 1.23 ($P \leq 0.05$) and 6/6 rats with mean number of implants of 0.00 ± 0.00 ($P \leq 0.05$), respectively (18).

Calotropis procera

90% ethanolic and aqueous extracts of roots of *C. procera* produced on female Wister rats temporary and reversible modification on oestrous cycle characterized by absence of oestrous and metaoestrous phases and dioestrus stage prolonged. Therefore, extracts provoked inhibition of ovulation with consequent reduction of cyclicity (19). Ethanolic extract of roots shows 100% anti-implantation activity at the dose of 250mg/kg (20).

Cardiospermum helicacabum

Ethanolic extract of whole plant at a dose of 250mg and 500mg/kg body weight /day orally for day 1 to 7 of pregnancy showed significant decrease in the implantation sites. Animals treated with 500mg/kg body weight showed 60% inhibiton of implantation sites.

Table 1: Plants with anti-fertility activity.

Sl. No	Common Name	Botanical Name	Family	Parts used	Action
1	Ankota	*Alangium salvifolium*	Alangiaceae	Stem bark	Abortifacient, anti-implantation
2	Kumari	*Aloe vera*	Liliaceae	Latex	Spermicidal
3	**Nallayiswari**	*Aristolochia tagala*	Aristolochiaceae	Whole plant	Anti-implantation
4	Neem	*Azadirachta indica*	Maliaceae	Seed, oil	Spermicidal, abortifacient
5	Lajalu	*Biophytum sanctivum*	Oxalidaceae	Leaves	Anti-implantation
6	Akada	*Calotropis procera*	Ascrophluariaceae	Roots	Anti-implantation
7	Kanphuti	*Cardiospermum helicacabum*	Spindaceae	Whole plant	Anti-implantation, increase uterus weight, inhibit sperm motility and decrease sperm count
8	Papai	*Carica papaya*	Cariaceae	Seeds	Inhibit sperm motility and decrease sperm count
9	Amaltas	*Cassia fistula*	Caesalpiniaceae	Seeds	Anti-fertility
10	Haldi	*Curcuma longa*	Zingiberaceae	Rhizomes	Anti-implantation, inhibit sperm motility
11	Akasbel	*Cuscuta reflexa*	Convolvulaceae	Stem	
12	Parvel	*Cyclea burmanni*	Menispermaceae	Roots	Resorption, estrogen effect
13	Jamun	*Eugenia jambolana*	Myrtaceae	Flowers	Decrease sperm count
14	Chobehyat (Pookwood)	*Guaiacum officinale*	Zygophyllaceae	Aerial parts	Abortifacient
15	Jangli-arandi	*Jatropha curcus*	Euphorbiaceae	Fruits	Abortifacient
16	Tulsi	*Ocimum sanctum*	Labiatae	Leaves	Decrease sperm count and sperm motility, Abortifacient
17	Utranajutuka	*Pergularia daemia*	Asclepiadaceae	Twig	Anti-implantation, late abortifacient
18	----	*Stevia rebaudiana*	Compositae	Whole Plant	Decrease sperm count

After confirming the antiimplantation activity of ethanol extract, the extract was subjected for its estrogenic/antiestrogenic studies in immature overiectomised albino rats. The dose increase in uterine weight was observed (21).

Carica papaya

Manivannan et.al reported the structural changes in the testis and epididymis of rats followed by the treatment with the benzene chromatographic fraction of the chloroform extract of the seeds of *C. papaya*. Administration of benzene chromatographic fraction of the chloroform extract of the seeds of *C. papaya* at a dose of 10mg/rat/day for 150days showed a total inhibition of sperm motility, reduced sperm count and infertility. It is concluded that the inhibition of sperm motility by the drug could be due to other epididymal factors rather than the subcellular characteristics of the testis and epididymis (22). Udoh et.al has reported the activity of the alkaloid extract of *C. papaya* seeds on male reproductive physiology in rats. Each male rat was treated with *C. papaya* seed extract (10, 50 and 150mg/kg/day) daily for three days for fecundity study, semen analysis and testis histopathology respectively. Twenty male rats treated with *C. papaya* seed extract (10, 50 and 150mg/kg/day), abstained from sex for 7 days and divided into 4 groups were mated with fertile female rats. Another set of 30 male rats, divided into 4 groups, treated with the seed extract (10, 50 and 150mg/kg day-1), respectively, was used for semen analysis and testis histopathology. The results showed that the oral administration of *C. papaya* seed extract prevented ovum degeneration, and induced testicular cell lesion. These observations led to the conclusion that the *C. papaya* seed extract oral administration could induce reversible male infertility (23).

Cassia fistula

Oral administration of aqueous extract of seeds of *C. fistula* to mated female rats from day 1-5 of pregnancy, at the doses of 100 and 200 mg/kg body weight resulted in 57.14% and 71.43% prevention of pregnancy, respectively, whereas 100% pregnancy inhibition was noted at 500mg/kg body weight (24).

Curcuma longa

Petroleum ether and aqueous extracts of turmeric rhizomes show 100% antifertility effect in rats when fed orally (25). Implantation is completely inhibited by these extracts (26). Curcumin inhibits 5*a*-reductase, which converts testosterone to 5*a*-dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster (27). Curcumin also inhibits human sperm motility and has the potential for the development of a novel intravaginal contraceptive (28).

Cuscuta reflexa

Methanolic extract of *C. reflexa* stem has significantly increased the carbonic anhydrase activity in the uterus of mice. This is associated with elevated level of prosgesterone, which is supporting the antifertility effect of the plant (29).

Cyclea burmanni

The petroleum ether and chloroform extracts of the roots of *C. burmanni* have been found to possess significant antifertility effect in rats. Both these extracts exhibited partial and complete resorption of implants at 200 and 400 mg/kg body weight dose levels. In estrogenic activity study, both the extracts increased uterine weight and caused opening and cornification of vagina in immature rats. The present work justifies its effectiveness in preventing pregnancy in all rats when administered at 400 mg/kg p.o. (30).

Eugenia jambolana

Flowers of *E. jambolana* significantly decreased the fertilizing capacity of the male albino rats without any significant change in body or reproductive organ weight. It causes significant reduction in conversion of spermatogenesis at the early stages of meiosis leading to decrease in sperm count without any abnormality to spermatogenic cells, leydig interstitial cells and sertoli cells (31).

Guaiacum officinale

The hot aqueous extract of aerial parts caused abortion in the second and third trimesters only. At a dose of 480.75 mg/kg, the extract did not reduce the litter size in mice when given during the first trimester of pregnancy (32).

Jatropha curcus

Fruits when fed to the female rats at a dose of 3.3% of the diet exhibited 100% effect. Seeds, when fed to female rats at a dose of 3.3% of the diet exhibited 100% effect (33). Foetal resorption was observed with methanol, petroleum ether and dichloromethane extracts of fruits of *J. curcus* indicating the abortifacient property (34).

Ocimum sanctum

Treatment of albino rats with a benzene extract of *O. sanctum* leaves (250mg/kg body weight) for 48 days decreased total sperm count, sperm motility, and forward velocity. The percentage of abnormal sperm increased in caudal epididymal fluid and the fructose content decreased in the caudal plasma of the edpididymis and the seminal vesicles (35). Histological and biochemical studies on mice fed with leaves

showed evidence of mild impairment of spermatogenesis with significant reduction of seminal pH. There was also a decrease in the reducing substance, acid and alkaline phosphatases and mucoproteins. Treated male mice failed to fertilize females of proven fertility (36). The benzene extract of the leaves (100mg/kg) showed antifertility effect in 80% rats whereas the petroleum ether extract showed the effect in only 60% animals. The extract did not reveal an abortifacient activity (37). *O. sanctum* leaves have been reported to show abortifacient and antifertility activity. The aqueous extract at a dose of 100mg/kg showed antiimplantation action (38).

Pergularia daemia

Golam Sadik et.al. revealed that oral administration of the ethanol extract of *P. daemia* at a dose of 600, 400 and 200 mg/kg body weight daily was found to terminate pregnancy in the pre-implantation stage in mice. But when the dose was reduced to 100mg/kg-body weight, pregnancy occurred in 20% of the mice. and demonstrated that the extract was able to prevent implantation or cause resorption depending upon the dose. To identify the bioactive fractions, the steroidal fraction was separated from the ethanol extract and was tested for antifertility activity in mice. The fraction at a dose of 200mg/kg-body weight exhibited antifertility activity in mice at preimplantation stage. The possible cause of termination of pregnancy upon oral administration of the ethanol extract and its steroidal fraction from day 1 to day 9 of pregnancy might be due to antizygotic, antiblastocytic as well as antioestrogenic property. The ethanol extract also showed late abortifacient activity in the mice. In this case pregnant mice was treated with the extract at a dose of 600 and 800 mg/kg body weight daily for any two consecutive days from 12 to 13 of pregnancy, respectively. The former dose produced 50% abortifacient activity with 50% mortality as two of the mice died after oral administration of the extract. The extract at a dose of 600 mg/kg body weight exhibited 100% abortifacient activity without any mortality. The mice aborted all the fetuses within 48 hours of drug treatment. The present investigation clearly demonstrates that the ethanol extract and its steroidal fraction are able to prevent fertilization in the female mice (39).

Stevia rebaudiana

Aqueous extract of *S. rebaudiana* (Compositae) was fed orally to 3 groups of adult male Wistar albino rats for a period of 65 days at the doses of 100, 1000 and 5000 mg/kg body weight. A control group was also maintained. The results revealed decrease in the epididymal sperm count, plasma testosterone concentration and decrease in organ body weight ratio of testis and cauda epididymis in the group fed with 5000 mg/kg body weight as compared to saline fed control group. This study revealed the anti-fertility effect of *S. rebaudiana* in adult male Wistar albino rats (40).

DISCUSSION

It is well known fact that estrogenic substances inhibit pregnancy by suppressing the level of both follicular stimulating hormone (FSH) and luteinizing hormone (LH) which in turn prevent the implantation. Estrogen and progesterone are the hormones responsible for histological and functional modifications of female genital tract. The exogenous administration of physiological doses of estrogen, in sexual immature rats, stimulated histoarchitecture of uterus (41). According to Laurence (42) any compound possessing estrogenic activity may exhibit antifertility activity, they act by suppressing gonadotrophin secretion, with consequent inhibition of ovulation. In immature female rats, hence the antiimplantation activity of these plants may be due to an imbalance in endogenous estrogen and progesterone levels. The loss of implantation caused by the extracts may be due to their anti-zygotic, blastocytotoxic or antiimplantation activity as described by Hafez (43). Isoflavones along with coumarins (also flavonoids) and lignans belong to a class of substances known as non-steroidal phytoestrogens, they produce infertility in animals (44). According to Miksicek (45) several commonly occurring flavonoids mimic the biological effects of 17 β-estradiol by virtue of their ability to bind to and activate the nuclear estrogen receptor.

The primary way in which a woman can prevent microbial infection and pregnancy through intercourse is with effective vaginal contraceptives. However, formulations generally available are not as effective as some other birth control methods. So that spermicidal activity was also included in the present study to check that whether the plants can be used in the formulation of vaginal contraceptives. The results of the spermicidal activity tend to suggest that many plants showed spermicidal effect at lower concentration. It is interesting to note that use of herbal contraceptives generally did not lead to permanent sterility in rats, since discontinuation of the treatment allowed a prompt return to normal fertility.

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