

**REVIEW ARTICLE**

## **A Review on Birth control: Natural source as Anti-fertility agents**

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**ABSTRACT:**

The population is increasing at a steady rate worldwide and it is now identified as one of the main threats to our planet in the 21st century. Since ancient times herbal medicines have been used for fertility regulation in males and females. Antifertility agents and contraceptive agents are the drugs that hinder the process of fertilization through barrier as well as the anti-fertility effects. Contraception involves the methodology of preventing the normal process of ovulation by affecting the menstrual cycle, fertilization, and ovulation. One example of birth control pills is progesterone and estrogen in combination. Anti-fertility component noticed as an active agent in females for prevention of fertilization and in case of males, prevention of spermatogenesis by inhibiting testosterone or action on the gonadotropin of organs or mortality of sperms. Numerous plants have phytoestrogens as novel agents which have noxious effects by making changes in the normal gestation procedure and lead to impaired fertility in domestic animals. Various experimental models have been developed and evidenced for evaluating the efficacy of antifertility agents. The review provides a comprehensive summary of contraceptive methods used in males and females, various plants, parts of plants and extracts are been used for the facilitation of anti-fertility have used as anti-fertility agents. Moreover highlighted old and presently used experimental models for the evaluating the anti-fertility agents.

**KEYWORDS:** Antifertility agent, Birth control, Contraception, Medicinal plants, Natural source.

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**INTRODUCTION:**

The Entire mankind is enfeebled by a number of problems, but of all, population explosion is the most threatening. Nowadays, the planet earth has already reached a critical point and is just like an ailing planet. Advancement in medical technology and changes in lifestyle have led to a remarkable the decline in mortality rate and an expansion in the future. As per worldometer elaboration of US data the population of India on Thursday, September 24, 2020 is 1,383,122,931. If the preventative measures are not taken immediately to control the population, especially in the developing countries like India, the world is bound to face environmental catastrophe and in a very few years, we will reach a level when the natural life-supporting system might fail to owe to undue burden of the human population on them<sup>1</sup>.

The remedy of various human ailments based upon usage of plants since antiquity worldwide and still they are broadly used in developing countries like India in the form of a traditional/folkloric system of medicine<sup>2</sup>. The task group set up by the WHO (World Health Organization) which is responsible for regulation of fertility-related ailments pinpointed approximately 30 plants with anti-implantation activities but very few of these plants have attained stage of clinical examination<sup>3</sup>. By the introduction of the Family Planning Program, an effective measure was made for restricting birth rate, to provide a good quality family and achieve physical and spiritual well-being.<sup>4</sup> Hormonal constituents consist of oral contraceptive pills, contraceptive patches, implants, injection, intra-vaginal and intrauterine devices. Some products act as a barrier for prevention of pregnancy acts by hindrance to the successful fertilization of an egg by sperm<sup>5</sup>.

**HISTORY:**

The history of prevention of pregnancy has been about a generation back and population believed on number of their imaginations and dexterity for the avoidance of

pregnancy. According to age-old writings back to 1850 BC indicating numerous methods used components containing crocodile dung, fermented dough, gum, honey, and acacia are placed in the vagina providing unfavorable surroundings for sperm. A high acidic nature brew containing fruits, nuts and wool was used for the implantation in the cervix as a kind of barrier for spermicidal effects during the early second century in Rome. Now-a-days diverse preferences are available for contraception with the products differing in the mechanism, competence, and accessibility<sup>6</sup>. Historic evidence shows that females belongs to Egypt were using a pessary, i.e. vaginal suppository built from number of substances that are acidic in nature along with lubrication of honey or oil, that was supposed to be somewhat efficient in spermicidal, oiled paper as a cervical cap have been used by Asian women, as well as beeswax by the Europeans for the same function. Silphium reported abortifacient with less side effects was hoard to annihilation around the 1st century<sup>7</sup>.

#### **CONTRACEPTIVE METHODS:**

##### **Traditional Methods:**

##### **Coitus Interruptus or Withdrawal:**

This is one of the antiquated methods used for contraception that needs male partner assistance. This includes hindrance of semen from entering the women by the withdrawal of the penis from the vagina just before ejaculation. These are not a safe method and have shown failures if semen liberated before ejaculation or leftover external sex organs. Good self-control, including emotionally and physically, is required for the success of this method.

##### **Lactational Amenorrhoea Method:**

Hormones responsible for the prevention of conception are secreted by nursing women for about 6 months. These hormones show prevalence if there is no menstrual bleeding and the baby is on full breastfeeding for the whole day and night. Now –a –days this is considered a myth as irregularity in lactation has been observed and most women start menstruating within three months post-delivery. Moreover, it is unreliable in cases where the newborn sleeps all over the night, or if lactating mother has bruised, broken or inverted nipples and abscessed breast. Innumerable women conceive during this duration before the arrival of menstruation.

##### **Rhythm Method:**

The rhythm method depends on the prediction of ovulation, the period when releasing of an egg from one of a woman's ovaries takes place. Then the released egg travels down the fallopian tube, where fertilization can occur by a sperm cell. The time period for ovulation typically one day and occurs in the medial of a woman's menstrual cycle. This period is considered as the most

fertile period when the chances of getting pregnant are utmost by taking into consideration the menstrual cycle or temperature of a body or cervical mucus changes, or a combination of all these which is also known as a symptom – thermal method. Intimacy is avoided during fertile days. Although a large population has awareness about this method only a few can actually determine the fertile period of the month. The rhythm method cannot be used by women with irregular Periods, or post-pregnancy, or during the menopausal time period. Intimacy is narrowed to few days of the month only with vigilant record-keeping for the calculation of safe period<sup>8</sup>.

#### **MODERN METHODS:**

##### **Oral Contraceptive Pills:**

Here, hormonal pills are advised to be consumed, daily at a same time, and in addition placebo/iron pills have also to be taken in duration when hormonal pills are not be administered. Larger female population uses this method after a medical screening. From 2012 -13, in India, a plan for delivering OCPs near to you by ASHA with affordable charges was started and the brand “MALA-N” was available without any charges at all public healthcare centers.

##### **Condoms:**

Usage of condoms are the procedure acts as a barrier which acts as a physical hindrance for the motility of sperm into the female genital system and provide twin protection from undesirable pregnancies and STI disease. The condoms are available for both males as well as females.

##### **Intrauterine Contraceptive Devices (IUCD):**

IUCDs incorporated with copper are considered as most effectual technique for long duration birth spacing. Usage of these devices should be avoided by women with uterine defects or with Pelvic inflammatory disease or which are at high risk of sexually transmitted infection because of multiple partners.

#### **PERMANENT METHODS:**

##### **Female Sterilization:**

##### **Minilap:**

Minilaparotomy, is generally known as “minilap” is abdominal surgical approach in which fallopian tubes are cut or occluded by making an incision less than 5cm in the abdomen. This method is to be carried out by experienced and skilled MBBS doctor.

##### **Laparoscopy:**

Laparoscopy is a surgical procedure in which a long lean tube having a lens is inserted in the abdomen by making a small incision. With the help of this technique fallopian tubes can be visualized, impeded or cut and can be practiced by trained and skilled gynaecologist /surgeon.

### **Male Sterilization:**

In this method a small cut is made in the scrotum in order to locate the two tubes which carries sperms to the penis and these tubes are docked or occluded and are tied to close or by the application of heat or electricity. Trained and skilled doctors perform this type of sterilization technique. For the duration of post three months of sterilization, alternative contraceptive methods have to be used until there is not perceptible of any sperms.

### **Emergency Contraceptive Pill:**

- This pill is to be taken in case of emergency because of unpremeditated or unsafe intercourse.
- This pill should not be taken as the replacement for a routine contraceptive and to be taken within 72 hours of intimation.

### **Other Commodities:**

#### **Pregnancy Testing Kits:**

These kits are simplest technique to detect pregnancy at a very early stage providing an early possibility for the termination of pregnancy. In this way by using this technique unsafe abortions can be controlled leads to success of family planning program.

#### **Contraceptive Injection:**

Contraceptive injection containing medroxy progesterone acetate that is a progesterone derivative, has its active ingredient shown its usage for preventing pregnancy. Marketed formulation is gettable as a syringe that are filled prior which contains a 150 mg dose applied signally and can be given once after every 3 months by healthcare taker who is trained well and skilled enough. The injection reported adverse reactions such as menstrual irregularities, abdominal pain, weight changes, etc.

#### **Transdermal Patch:**

The norelgestromin and ethinyl estradiol are synthetically prepared hormones gettable as a transdermal patch. The norelgestromin(150 mg) and ethinyl estradiol (35 mg) per day are delivered in the form of a transdermal patch. The application of the patch is done on weekly basis for the first 3 weeks of the menstruation period and in the fourth week no patch is applied. The users are advised to apply the patch on a dry, cleaned, uninjured, followed by a non-irritated part on the midriff, buttocks, dorsum, or upper outer part of the arm where no constriction is observed. The usage of oily substances, skincare products such as powders, lotions are restricted to avoid failure of the patch to adhere in an appropriate way. Regular activities such as bathing, physical workouts, and swimming are allowed until a patch is adhered properly to clean dry skin and the patient should ensure on daily basis regarding the maintenance of the correct position of the patch.

### **Subdermal implant:**

Subdermal Implantation of a rod with the release of etonogestrel can be used as another choice for long-duration contraception as well as proved as the most efficacious method for contraception with a 0.05% yearly rate of failure. The marketed formulation for the subdermal implant with the release of etonogestrel consists of a single rod with the measurement of length (4cm) and diameter (2mm) and having a composition of ethylene-vinyl acetate as the inner core enclosed with crystals of etonogestrel. The inner core is surrounded by ethylene vinyl acetate which controls the rate at which hormone is released. As the implant containing a sum of 68 mg of progestin and in the early period of the implantation release rate of progestin is 60 to 70 mg/d. With the passage of time rate of release is reduced to 35 to 45 mg/d by the last months of initial year and then to 30 to 40 mg/d by the end of 2nd and 3rd year respectively. The device is implanted by trained and skilled health care providers with the requirement of local anesthesia and required only 5 minutes for the completion of insertion. Similarly, the implant can be removed at any time but mostly advised by the end of 3 years of usage with a retrace of ovulation restarting within 3 to 4 weeks<sup>9</sup>.

A single implant named Implanon® was developed by Organon (now merged with Merck, Sharp & Dome), a Dutch-based Pharmaceutical company having a shelf life of three years had been exported to a large number of countries. It showed a large number of advantages over Norplant -2 as it is convenient and quicker to insert. Implanon® containing etonogestrel (68 mg) deliver 60 µg/day of steroid. It blocks ovulation that is why considered a highly effective contraceptive<sup>10</sup>.

### **BIRTH CONTROL MECHANISM:**

Now a day's large number of hormonal contraception methods are available and most of these methods show "variation on a theme". The mechanisms by which these hormonal contraception methods work primarily include suppressing of ovulation<sup>11</sup>.

### **ANTIFERTILITY AGENTS:**

The agents that are used in controlling fertility<sup>12</sup> are known as antifertility agents or oral contraceptives. In Females these drugs show their action by affecting menstruation and ovulation. The combination of Estrogen and progesterone are administered as contraceptive pills. The antifertility agents are considered active in females if these substances are preventing fertilization, obstruct ovulation and destruction of the zygote, or act as an abortifacient. On the other hand in the case of males, these agents prevent spermatogenesis, inhibition of testosterone, or the fatality of sperm<sup>13</sup>. Hormonal method for treatment for

fertility shows effectiveness with failure rates much less than that of condoms<sup>14</sup>. The carcinogenic effects have been reported by hormonal contraceptives<sup>15</sup>. Now a day's herbal plants are the center of attraction for a large number of researchers for the development of herbal contraceptive agents because of their minimum or no adverse effects<sup>16</sup>.

#### **Progesterone:**

Progesterone plays an important role in the method of reproduction. It shows involvement in the menstruation implantation and is crucial for the maintenance of pregnancy. Progestins are the synthetic progestogens that show similar effects as a natural progesterone and are used widely as a single dose or in combination with an estrogen for hormonal contraception. Moreover, progesterone is also very effective when continuation of pregnancy is hampered by immunological factors, luteinic and neuroendocrine deficiencies and myometrial hypercontractility<sup>17</sup>.

#### **FEMALE HORMONAL SYSTEM:**

Reproduction is process in which peripheral organs are coordinated with the nervous system to assure that both internal and external arena are favorable for the productive propagation of the species. This is well established by the hypothalamic-pituitary-gonadal axis that coordinates reproductive behavior with ovulation. The gonadotropin-releasing hormone (GnRH) which is a primary signal from the central nervous system, alters the activity of anterior pituitary gonadotropes which result regulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release. The development of ovarian follicles results in the production of estradiol, which results in negative regulation leading to the release of GnRH and FSH. When estradiol concentration reach extremum result in activation of surge release of GnRH, due to which LH release resulting in the inducement of ovulation. The point at which GnRH is released within the central nervous system helps in alternating behavior and can regulate control over the reproduction process<sup>18,19</sup>.

#### **Estrogens:**

Estrogens or ovarian sex hormones accountable for various reproductive functions such as cellular proliferation and development of tissues. The circulating estrogens are released by ovaries in menstruating women and in case of pregnant women estrogens are secreted in considerable amount by placenta. An estrogen also helps by regulating the skeletal homeostasis, metabolism of lipids, carbohydrates that balances the electrolyte concentration, skin physiology, cardiovascular system and CNS.<sup>20</sup> As estrogen having number of such regulatory functions, so plays a key role for male physiology and also for female sex hormones. After

menopause in women with declining ovary functions and men are widely pendent on the local estrogens production in extragonadal target tissues. Local synthesis of the estrogens gives out an extension of their signaling from endocrine to paracrine, autocrine and intracrine<sup>21</sup>. The various type of estrogen signaling like a well-established direct or indirect genomic signaling, the quick non-genomic actions shown by steroid hormones and ligand-independent signaling<sup>22</sup>

#### **Mechanism of Action:**

The Estrogens have two receptor protein isoforms, ER $\alpha$  and ER $\beta$ , which are responsible for their action with the help of nuclear and cytoplasmic activities. Genomic actions are involved either directly through DNA binding or confined with gene regulation<sup>23</sup>. Their ability to bind and activate the estrogen receptors decides their biological activity. The most active form of estrogen is 17 $\beta$ -Estradiol<sup>24</sup>.

#### **MEDICINAL PLANTS WITH ANTIFERTILITY ACTIVITY:**

##### ***Bougainvillea spectabilis* (Family: Nyctaginaceae):**

Common name for this is Bougainvillea or Paper Flower and this is the tralatitious herbal plant with medicinal value like antifertility action. In addition to antifertility activity, it also possesses anticancer, antidiabetic, antihepatotoxic, anti-inflammatory, antihyperlipidemic, antimicrobial, antioxidant, and antiulcer properties. On the basis of its effective therapeutic properties, it has shown large number of phytoconstituents such as alkaloids, essential oils, flavonoids, glycosides, oxalates, phenolics, saponins, tannins, and terpenoids. The constituents such as bougainvinones, pinitol, quercetagetin, quercetin, and terpinolene have shown their contribution towards remedial properties<sup>25</sup>. After having its dose of *B. spectabilis* leaves by oral route, i.e. 800 mg/kg/day the action on reproductive organs and fertility for male and females was observed in Swiss albino mice for time duration of 30 days. After experimentation, it was reported that the reduction in the sperm count of caudal epididymal from  $.05 \times 10^6$  per ml in the control group to  $0.65 \times 10^6$  per ml for treating group. The reduction in the size of seminiferous tubules along with the thickness of germinal epithelial cells and hypertrophy of interstitial cells of Leydig has been noticed after histological studies of plants. The estrous cycle was disrupted in females, prolongation of metestrus phase from 10.6 h in the control group to 25.0 h in the treated group. The level of hormones, testosterone, and estrogen was declined significantly. From the literature survey, it was concluded that the antifertility activity of this plant is due to numerous phytochemical substances such as saponins<sup>26</sup> and alkaloids<sup>27</sup>.

***Piper betle (Petiole) (Family: Piperaceae):***

Piper betle is the traditional herbal plant and widely used for removing the foul smell of mouth by chewing it. It consists of tannins, chavicol, phenyl, propane, sesquiterpene, cyneole, alkaloid, sugar, and some essential oils and have other medical effects are as digestive, appetizer, aromatic, expectorant, stimulant, antibacterial, euphoria-inducing, antiprotozoal, carminative, anti-fungal, and aphrodisiac, etc.<sup>28</sup> Most of part of this plants have their individual property such as leaves hardens the gums, teeth conserves and helps in digestion, prevention of bronchitis, constipation, congestion<sup>29</sup>. Its extract used as an anti-fertility agent confirms its effects by experimenting on rats and obtained positive result. By experimenting with the alcoholic extract for their anti-fertility action shows the action in % as 51% and 37.2%. The reduction in the implantation caused due to the extracts because of estrogenic or antiestrogenic action<sup>0</sup>.

***Momordica charantia Descourt (Family: Cucurbitaceae):***

*Momordica charantia* Descourt is a tropical and subtropical vine largely cultivated and is known for its most bitter taste among all vegetables. The textual matter of Ayurveda describes that karela or bitter melon have guna – laghu (light) and ruksh (dry), rasa - katu or pungent and tickta or bitter, virya or the potency - ushana or hot and karma - mutsangrehiya. This plant has reported anticancer<sup>31</sup>, antidiabetic<sup>32</sup>, antihypertensive<sup>33</sup>, anti- inflammation<sup>34</sup> and antioxidant<sup>35</sup> activity. According to Ayurveda, this plant is being abundantly used as an abortifacient and for birth control. The seed alcoholic extract of *M.charantia* had reported in vitro antispermatogenic and androgenic activities<sup>36</sup>. *M. charantia* benzene extract showed antiovarian and estrogenic properties<sup>37</sup>. The sperm membrane integrity was significantly mutilated by pulp extract of this plant at 1280 µg/ml concentration and this was proved by the decrease in sperm viability and tail curling. An increase in uterine weight in immature rats was noticed by the giving the dose of pulp extract at 400 mg/kg while on the other hand minimized the uterus weight and inflated the height of the luminal epithelium along with stimulated glands after the co-administration with ethinylestradiol. The estrous cycle and diestrous phase were also prolonged by the pulp extract at dosage of 400 mg/kg<sup>38</sup>.

***Ficus religiosa (L.) (Family –Moraceae):***

The bark show usage as an antibacterial, antiprotozoal, antiviral, astringent, antidiarrhoeal, in the treatment of gonorrhoea, ulcers, and for the treatment of skin diseases, leaves are used. The leaves showed antivenom activity and help in the regulation of the menstrual cycle<sup>39-40</sup>. On treatment with 1% the solution of fruit extract of *Ficus religiosa*, remarkable changes were observed in the

uterus of a goat. The fruit extract induced reduction in the thickness of the surface epithelium, diameters of uterine glands and gland cell, and the thickness of the myometrium layer relying upon the time dependent exposure. As the duration of exposure increased, hypertrophy in uterine glands and distortions of blood vessel were observed in the alcoholic extract of *Ficus religiosa*<sup>41</sup>.

***Leptadenia hastate(Pers) Decne (Family– Apocynaceae):***

It is one of the most main emergent local foods of Africa which is capable to cultivate under harsh environmental situations. Number of studies reported the usage of this plant in hormone-like activities in respond to the administration of extracts of this the plant produces changes in weight of reproductive organs, spermatogenesis, and levels of testosterone<sup>42</sup>. Aqueous extracts of *L.hastata* reduced weight of accessory reproductive glands dependent on androgen, the content of Prostatic and Phosphatase (PAP) levels of fructose in seminal vesicles and prostate. When aqueous extracts of this plant were administered along with Testosterone Propionate (TP) (100,200 and 400 mg kg<sup>-1</sup>) in a dose-dependent manner, a synergetic effect in TP action was observed with the dose of 100mg kg<sup>-1</sup>. This action was evidenced by an increase in weight of androgen-dependent accessory reproductive glands, fructose and PAP levels in seminal vesicles and prostate, and the level of serum testosterone<sup>43</sup>. A decline in the number of sperms was observed on the exposure of male rats to *L. hastata*<sup>44</sup>.

***Artemisia vulgaris (Family – Asteraceae):***

*Artemisia* belongs to a wide and diversified genus of plants having species between 200 to 400. *Artemisia vulgaris* L. (Common Name- mugwort), and contains volatile oil, flavonoids, sesquiterpene lactones, coumarin derivatives, and triterpenes (Kumar and Kumud,2010).A significant reduction in implantation sites in comparison to the control were reported on administrating the methanolic extract of *A.vulgaris* leaves (dose of 600 mg·kg<sup>-1</sup>) by oral route. This was the indication of the anti-implantation activity of the crude extract. Reduction in dose from 600 mg·kg<sup>-1</sup> to 300 mg·kg<sup>-1</sup> lead to only a 50 % reduction in the implantation sites. This evidenced that the effect of the extract on implantation is dose-dependent<sup>45</sup>.

***Butea monosperma (Family –Fabaceae):***

*Butea monosperma* (Common name –Palas)is a plant which is generally found in the drier parts of the India and show numerous biological and pharmacological activities such as anti-hyperglycemic,anti-tumorous,anti-cancerous,anti-oxidant,woundhealingactivity,anti-malarial immunomodulatory and Antiestrogenic and

antifertility. The antiestrogenic and antifertility activities have been reported by methanolic extract of flowers of this plant. Both male<sup>46</sup> and female contraceptive properties have been reported by the active constituent Butin which is isolated from its flower<sup>47</sup>. Moreover, It has also shown effect on uterotrophic and uterine peroxidase activities in ovariectomized rats. Rat uterine peroxidase assay was also used for the determination of estrogenic/antiestrogenic potential of antifertility substances<sup>48</sup>. Reduction in the sperm motility, sperm count and weight of reproductive organs was reported after oral administration of methanolic leaf extract of this plant at the doses (200 and 400 mg/kg body weight) to male albino rats for duration of 21 days.<sup>49</sup>

**Asplenium dalhousiae Hook (Family : Aspleniaceae):**

This is a fern (pteridophyte) which is having a rosette of fronds from a rhizome, leaves are rachies green, scaly beneath, blade pinnatifid, 5-15 cm long, with 6 to 13 pairs of lobes. Width of the lobes is 5-12 mm. This plant is found in moist soil having shady, rocky and ravines<sup>50</sup>. This plant is generally distinguishable from its allied species (*Asplenium exiguum*) on the basis of leaves as *Asplenium dalhousiae* Hook have once pinnatifid leaves and *Asplenium exiguum* have bipinnatifid leaves. This plant is of the genus (*Asplenium*) of about 700 species of ferns found extensively throughout the world<sup>51</sup>. Roots of this plant showed its usage in snake bite<sup>52</sup> and on the other side decoction of the roots is used as Ghutti in infants<sup>53</sup>. Plant extract of this plant was given to the adult male Sprague Dawley rats (40 in numbers and weight about 150 ± 10 g) that were divided into four groups and dose given are 0, 50, 100, 150 mg/kg for a duration of 28 days, 29<sup>th</sup> day the rats were beheading and collection of their trunk blood and reproductive tissues, after this there is separation of blood plasma that was stored for purpose of measuring reproductive hormones. Then assessment of sperms parameters status of oxidative stress and morphometric analysis were done by epididymis and testis. The treatments group received high dose shows decrease in the rate of sperm motility, viability, and production rates of sperm. Disorganization of seminiferous tubule and decrease in spermatocytes number were reported in histological examination of the testis<sup>16</sup>.

**CONCLUSION:**

Numerous plants have been, traditionally used as antifertility agents, and plants parts such as roots, extracts, stems and leaves showed antifertility activity. This review provides a comprehensive summary of contraceptive methods used in males and highlighted old and currently used experimental models for the evaluating the antifertility activity of the agents. However, the need of the hour is to explore more unexploited plants for this activity with proved

contraceptive efficacy and also with the defined mechanism of actions so that it may become of importance for female as well as male fertility regulation.

**CONFLICT OF INTEREST:**

There is no conflict of interest.

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