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A Review on Natural Contraceptive Agents

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ABSTRACT

One of the most critical problems of throughout the world especially in developing and underdeveloped countries is the increase in human population. Fertility control is an issue of global and national public health concern. Sexual and reproductive health is a prerequisite of all goals because it has a direct link to social, economic and human development. Family planning has been prompted through several methods of contraception, but due to adverse effects produced by synthetic steroidal contraceptives attention has now been focused in indigenous plants for possible contraceptive effect. Contraceptive ability of plants has been reported in several animal models. The reversibility of the anti-fertility effects of plants and its active compounds are of potential clinical relevance in the development of contraceptive. This review attempts to focus on the potential of medicinal plants as the source of new contraceptive principles.

Keywords: Contraceptive, medicinal plants, Fertility, adverse effects.

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INTRODUCTION

The population explosion is one of the major problems of present era in the world. The increment of population raises so many sufferings like lack of food, water, energy and raw material supply, decline in mortality etc. Before human beings and it also has increased the life expectancy. In view of the following discussion, scientists have started to tackle this serious problem by developing the effective contraceptives.[1] In women, estrogens and progestins are endogenous hormones that produce numerous physiological actions. These include developmental effects, neuroendocrine actions involved in the control of ovulation, the cyclical preparation of the reproductive tract for fertilization and implantation and major actions on mineral, carbohydrate, protein, and lipid metabolism. Estrogens also have important actions in males, including effects on bone, spermatogenesis and behavior. But in men, testosterone is the principle secreted androgen.[2-4] At puberty, an increased output of the hormones of the hypothalamus and anterior pituitary stimulates secretion of estrogenic sex steroids. These are responsible for the maturation of the reproductive organs development of secondary sexual characteristics, and also, or a phase of accelerated growth followed by closure of the epiphyses of the long bones. Sex steroids are involved in the regulation of the cyclic changes expressed in the menstrual cycle and are important in pregnancy. The menstrual cycle begins with menstruation, which lasts for 3-6 days during which the superficial layer of uterine endometrium is shed. The endometrium regenerates during the follicular phase of the cycle after menstrual flow has stopped. A releasing factor, the gonadotropin-releasing hormone (GnRH), is secreted from peptidergic neurons in the hypothalamus in a pulsatile fashion, the frequency being about 1 burst of discharges per hour, and stimulates the anterior pituitary to release gonadotropic hormones, follicle-stimulating hormone (FSH) and luteininsing hormone (LH). These act on the ovaries to promote development of small groups of follicles, each of which contains an ovum. One follicle develops faster than the others and forms the Graafian follicle, and the rest degenerate. The ripening Graafian follicle consists of thecal and granulose cells surrounding a fluid filled centre within which lies an ovum. Estrogens are produced by the granulosa cells stimulated by FSH, from androgen precursor molecules derived from thecal cells stimulated by LH.[2-4] Gonadotropins and testosterone are secreted in a pulsatile manner. In plasma fluctuate during the course of the day, although integrated daily values are relatively constant. LH and FSH together regulate testicular growth, spermatogenesis, and steroidogenesis. Endogenous hormones: estrogens, progestins and testosterone are regulating the hypothalamic pituitary gonadal axis at both the hypothalamic and pituitary levels through negative feedback mechanism. Thus,

exogenous sexual hormones administration decreases GnRH and then decrease LH, FSH and testosterone level in men. [2-4]

The term contraceptives refers to those chemical substances that inhibit either the sperms production and sperm motility in males or prevent the formation of ovum and produce some changes in the endometrium, rendering it non-receptive to a fertilized ovum in females.[1,5,6]

Mechanism of Action and Adverse Effects

Combination oral contraceptives act by preventing or suppress ovulation (two hormones). Direct measurements of plasma hormone levels indicate that LH and FSH levels are suppressed, a mid-cycle surge of LH is absent, endogenous steroid levels are diminished, and ovulation does not occur. While either component alone can be shown to exert these effects in certain situations, the combination synergistically decreases plasma gonadotropin levels and suppresses ovulation more consistently than either alone. Both types cause a thickening of the cervical mucus and blocking sperm penetration.[3,7,8] Male contraceptives act by one of the following ways: (1) Development of anti-spermatogenic agents to suppress sperm production. (2) Prevention of sperm maturation. (3) Prevention of sperm transport through vas deferens. (4**)** Prevention of sperm deposition.[9]

Shortly after the introduction of oral contraceptives, reports of adverse side effects associated with their use began to appear. Many of the side effects were found to be dose dependent, and this led to the development of current low-dose preparations. Untoward effects of early hormonal contraceptives fell into several major categories: adverse cardiovascular effects, including hypertension, myocardial infarction, hemorrhagic or ischemic stroke, and venous thrombosis and embolism; breast, hepato-cellular, and cervical cancers; and a number of endocrine and metabolic effects. The current consensus is that low-dose preparations pose minimal health risks in women who have no predisposing risk factors, and these drugs also provide many beneficial health.[2,3]

MAIN METHODS OF CONTRACEPTION[10]

A- Mechanical methods

Barrier methods of contraception prevent pregnancy by physically or chemically blocking the entrance of sperm into the uterine cavity. Some, particularly condoms, help to protect against sexually transmitted infections including HIV infection. Barrier methods include cervical caps, condoms, diaphragms, female condoms, spermicides, and sponges.

1- Condoms male and female

The male condom is a sheath made of thin latex that covers the erect penis to prevent semen, vaginal fluid and blood from being passed between sexual partners. Male condoms made of polyurethane or natural membranes are also available for those allergic to latex, though these are

more expensive. The female condom is a sheath made of polyurethane with two flexible rings at either end that is inserted into the woman`s vagina to prevent semen, vaginal fluid and blood from being passed between sexual partners.

2- Diaphragm

A latex rubber dome-shaped device filled with spermicide is placed to cover the cervix. It can be inserted within two hours of sexual intercourse and should be left in for six to eight hours after intercourse. It prevents semen from reaching the egg. Some of the advantages of the diaphragm are that it allows the woman more control over contraception, it can remain in place for multiple acts of intercourse, and it can be washed and reused.

3- Spermicides

Spermicides come in the form of vaginal creams, films, gels, suppositories, sponges, and tablets, working both as a barrier that prevents sperm from entering the external orifice of the uterus, and by reducing the sperm`s motility.

4- IUD (Intrauterine Device)

An IUD is a small plastic and copper device that is put into your womb (uterus). It has one or two soft threads on the end. These thin threads hang through the opening at the entrance of your womb (cervix) into the top of your vagina. There are different types and sizes of IUD to suit different women. An IUD used to be called a 'coil'. The main way an IUD works is to stop sperm reaching an egg. It does this by preventing sperm from surviving in the cervix, womb or fallopian tube. It may also work by stopping a fertilized egg from implanting in the womb.

5- IUD (Intrauterine System)

The IUS works in the same was as an IUD, but it also releases a hormone very slowly in the woman's body, providing additional protection by causing the cervical mucus to become thicker, blocking the sperm's travel to the egg and for some women, stopping ovulation altogether.

B- Hormonal contraceptives

1- Oral contraceptives

A hormonally active pill taken by women on a daily basis which contains either a progestrogen combined with an estrogen or a progestrogen alone (two different female hormones). As discussed previously, combined oral contraceptives (two hormones) suppress ovulation. Progestrogen-only contraceptives also suppress ovulation in about half of women. Both types cause a thickening of the cervical mucus, blocking sperm penetration.

2- Contraceptive patch

A patch is applied to the skin once a week that releases the same hormones as oral contraceptives.

3- Vaginal contraceptive ring

The vaginal ring is inserted by the woman herself into her vagina once a month and removed after three weeks to allow for withdrawal bleeding. The ring releases a steady, low dose of hormones (oestrogen and progestogen), offering continuous protection against pregnancy.

4- Contraceptive injection (Depo-Provera)

Hormones (either progestogen alone or a combination of progestrogen and estrogen) are injected into the muscle of the arm or buttocks. Progestrogen-only injectable contraceptives (POIs) protect against pregnancy for three months at a time, whereas combined injectable contraceptives (CICs) require an injection each month. Contraceptive injections act in the same way as oral contraceptives to prevent pregnancy and have similar potential side effects.

5- Contraceptive implant

Small capsules containing a hormone (progestrogen) are implanted just under the skin on the underside of a woman's upper arm using a minor surgical procedure. The hormone is released in very small daily doses into the woman's bloodstream, preventing pregnancy for three to seven years (depending on the kind of implant used).

C- Surgical intervention-Tubectomy and Vasectomy

D- Natural or behavioral methods to prevent pregnancy

1- Abstinence

No sexual intercourse of any kind. Abstinence prevents sexual contact and exchange of body fluids between partners. Abstinence can be used by individuals or couples who feel they have the ability to refrain from sexual intercourse. It can be an appropriate method, especially for young people, but they need to learn negotiating skills to effectively use abstinence and obtain information about contraceptive methods for the future.

2- Outer course

This can be defined as sex play without vaginal intercourse. It includes body rubbing and mutual masturbation. It requires commitment and self-control from both partners, as well as good communication between partners.

3- Breastfeeding and contraception

Breastfeeding can be a form of contraception in itself. This is usually called the lactation amenorrhea method (LAM). This method is only effective if a woman breastfeeds exclusively or almost exclusively and continues to be amenorrhea (without a monthly menstrual period). Breastfeeding prevents pregnancy by inhibiting ovulation and in cases where ovulation and fertilization do occur, by inhibiting implantation of a fertilized egg.

HERBAL CONTRACEPIVES

For centuries herbal preparations have been connected with the goal of preventing, and or disrupting pregnancy. It is impossible for us to say how effective they were as much of the information remains scarce and fragmented, most recipes are very old and were transmitted orally and information was closely guarded to avoid persecution during the burning times. Some historical information remains unresolved to this day. However, exact recipes are rare, and effectiveness rates are untested in our modern society. Scientific researchers have done some research on botanical anti-fertility agents; some findings have been very interesting and promising. Unfortunately, there is not a lot of money to be made from herbal drugs unless botanical compounds can be extracted, refined, patented and proven safe, so pharmaceutical companies can make a profit from marketing the discovery to the general public. China and India are two countries that have done quite a bit of research on herbal contraceptives. Numerous herbs have been used historically to reduce fertility and modern scientific research has confirmed anti-fertility effects in at least some of the herbs tested. Herbal contraception may never reach the level of contraceptive protection as the pill, but it offers alternatives for women who have difficulty with modern contraceptive options or who just want to try a different way. Very little is known about many of the herbs, or about long term side effects or safety concerns. There's not much information available on using herbs for contraception, but there are historical references with clues to what ancient women did and the scientific community has published some studies, mostly on animals, showing some of the herbs do seem to have contraceptive effects. There have also been informal studies where the herbs were tested by women for contraception. Each herb has its own way of being taken; some are taken daily, while others are used on need based manner, after potential exposure to sperm during a fertile time. Generally, herbs that are taken on a daily basis need some time to take effect; an alternative method of birth control should be used during the waiting period to provide protection. So it's important to know how they are used, when to take them and how much to use.[2] Herbal contraceptives are a category of herbs that have an anti-fertility effect. There are many different ways in which herbs can impair fertility. Some herbs may affect the ovary, while others act upon the uterus, affect normal hormone production or block certain hormones. For several of these we don't really understand their action or how they got their reputation. Some herbs have the ability to interfere with implantation; these herbs can be taken on as needed basis, and are useful as an emergency contraceptive. There are also some herbs that have been found to interfere with normal sperm production, or mobility. Each herb is used on its own way, so it`s important to have some idea of how they are used or could be used.[2,11]

CLASSIFICATION

Herbal contraceptives are classified according to their action on male and female into:

1- Plants that affect spermatogenesis (What is spermatogenesis?)

Spermatogenesis is a complex process by which an interdependent population of undifferentiated germ cells undergoes multiplication and maturation to form functional haploid spermatozoa. Spermatogenesis includes three phases: a- the spermatogonial phase; b- the spermatocyte phase; and c- the spermatid phase. During the spermatogonial phase, the diploid spermatogonium undergoes mitosis to form stem cells and primary spermatocytes. This is followed by the spermatocyte phase, in which the primary spermatocytes undergo two rounds of meiosis to form haploid spermatids. The final phase, also called spermiogenesis, involves the differentiation of spermatids into mature spermatozoa. Spermiogenesis comprises polarization of the spermatid, formation of acrosomal cap and flagellum, cytoplasmic remodeling, and elongation of the nucleus.[12] Examples of medicinal plants that affect spermatogenesis were mentioned below in Table 1.

2- Plants that affect steroidogenesis (What is steroidogenesis?)

A steroid is a type of organic compound that contains a specific arrangement of four rings that are joined to each other. Examples of steroids include cholesterol, the sex hormones estradiol and testosterone and the anti-inflammatory drug dexamethasone. The sterane core of steroids is composed of seventeen carbon atoms bonded together to form four fused rings: three cyclohexane rings (designated as rings A, B, and C in the figure to the right) and one cyclopentane ring (the D ring). The steroids vary by the functional groups attached to these rings and by the oxidation state of the rings. Sterols are special forms of steroids, with a hydroxyl group at position-3 and a skeleton derived from cholestane.[13] Hundreds of distinct steroids are found in plants, animals, and fungi. All steroids are made in cells either from the sterols lanosterol (animals and fungi) or from cycloartenol (plants). Both lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene.[14] Steroidogenesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids. The pathways of steroidogenesis differ between different species. Several medicinal plants have been reported to affect various stages of spermatogenesis[15,16] and steroidogenesis in many different animal species such as rabbits, goats, sheep, dogs, rats, humans and monkeys.[17,18] In table 2, the most common medicinal plants affect steroidogenesis were listed.

Table 1: Examples of plants that affect spermatogenesis.

Source	Used part	Mechanism of action	Comments

	and/or active constituents		
Azadirachta indica (Neem) Family: Meliaceae	Neem oil, leaves, seeds/dry powder, *n*-hexane, EtOH extract.	*Azadirachta indica* has antispermatogenic activities and causes histological changes in testes and epididymides. It prevents pregnancy (100 %) if taken before sexual intercourse. Anti-implantational and abortifacient effects were observed in females mated by the males fed with the ethanolic extract completely abrogate pregnancy in rodents up to a concentration of 10 %. Also, the plant act by activating cell mediated immune reactions.[19-28]	**Neem Oil** The neem oil if applied vaginally acts as a spermicidal contraceptive. Neem oil has also been shown to work well both before and after sex while some purified extracts only worked before sex as a preventative.[22] **For men** should take it orally to induce temporary sterility. A direct spermicidal activity of neem oil occurs *in* vitro and *in vivo*. Intra-vas administration of neem oil results in blocked spermatogenesis without affecting testosterone production and sexual behavior.[29-31] Neem may become the first truly effective birth control "pill" for men.[22] **For women** it is used vaginally as a spermicidal, [32,33] in the form of vaginal creams (Praneem cream) and suppositories.[34] It is quickly becoming the birth control method of choice in India.[27] The studies leading to the development of these products proved that neem oil killed sperm in the vagina within thirty seconds and was effective for up to five hours. Most spermicide creams must be reapplied at least every hour.[19] **NIM-76;** is a novel vaginal contraceptive from neem oil. Study shows mechanism of spermicidal action of NIM-76, a fraction isolated from neem oil. spermicidal activity of NIM-76 was confirmed using fluorescent staining technique, it was determined NIM-76 have selectivity kill sperm without affecting normal cells makes it

			a history desirable potential vaginal contraceptive agent.[35] **Dose:** Daily oral doses of several drops of neem seed oil in gelatin capsules were given to twenty married soldiers. The effect took six weeks to become 100 percent effective, it remained effective during the entire year of the trial and was reversed six weeks after the subjects stopped taking the capsules. During this time the men experienced no adverse side effects and retained their normal capabilities and desires.[21-24,28,35] Neem leaf tablets ingested for one month produced reversible male antifertility without affecting sperm production or libido.[36]
Acacia concinna Family: Fabaceae		Spermicidal and semen coagulating activities.[37]	
Albizzia lebbek Family: Fabaceae		Spermicidal activity.[38]	
Aloe barbadensis Family: Liliaceae	Leaves, 50% EtOH extract	Anti-androgenic activity.[39]	
Anagallis arvensis Family: Myrsinaceae		Spermicidal and semen coagulating activities.[40]	
Andrographis paniculata, Family: Acanthaceae		Anti-spermatogenic and anti-androgenic effect.[41] Significant reduction in fertility and prolongation in gestation period after 3 and 4 weeks of feeding a group containing treated male Wistar mice and untreated female mice, on diets supplemented to extent of 0.75 % by powered stem.[41]	
Acacia auriculiformi Family: Fabaceae		Immobilization of sperm at lowest concentration.[42]	
Aristolochia	Roots/EtOH	Antispermatogenic and	Oral dose 100 mg/kg.[43,44]

indica, Family: Aristolochiaceae	extract	antiandrogenic effects. 100 % interceptive and anti-implantation activity.[43,44]	
Balanites roxburghii Family: Zygophyllaceae	Fruit pulp, extract/EtOH extract	Mass atrophy of spermatogenic elements due to secondary effects of hyperglycemia in dose.[45]	
Butea monosperma Family: Fabaceae	Seeds	Potential male contraceptive with minimal side effects.[46]	
Bursera sp. (Mexican copal) Family: Burseraceae	Steam and leaf extracts	Sperm aggregation.[47]	
Barleria prionitis Family: Acanthaceae		Antifertility effect on male rats.[48]	
Berberis chitria Family: berberidaceae		Impairment of germ cells.[49]	
Bursera fagaroides Family: Burseraceae		Human spermatozoa and those obtained from the mouse epididymis became agglutinated and immobilized.[50]	
Cannabis sativa Family: Cannabaceae	Dry powder of seeds.	It caused testicular lesion resulting in mass atrophy of spermatogenic elements.[51]	Dose of 14 mg/kg for 90 days.[51]
Catharanthus roseus G, *Vinca rose* Family: Apocyanaceae	The indole-indoline dimeric alkaloids	Antispermatogenic as well as antiandrogenic in male rats. The alkaloids affect spermatogenic cell line causing impairment of epididymal function.[52,53]	
Carica papaya Family: Caricaceae	Seed extract	The contraceptive characteristics of papaya seed extracts have been reported in the 1970s.[54-56] Degeneration of germ cells and germinal epithelium, reduction in the number of Leydig cells, and presence of vacuoles in the seminiferous tubules were observed when crude ripe seeds were administered orally to male Wistar rats at a dose of 100 mg per kg	

		body weight.[57] The crude chloroform extract of papaya seeds at a dose of 5 mg per animal per day for 40-60 days reduced the fertility potential to 0%, with the suppression of cauda epididymal sperm motility.[58] This suggest that contraceptive effects of chloroform extract of papaya seeds are mainly post testicular in nature without influencing toxicological profiles and libido. Administration of the chloroform extract to male rabbits for 150 days caused a decline in sperm concentration with oligospermia on the 75th day and azoospermia after 120 days.Membrane damage in the acrosome, bent mid piece, coiled tail, detached head and arrest of spermatogenesis beyond the level of spermatocytes were also observed.[59]	
Calotropis procera Family: Apocyanaceae		Antispermatogenic effect and leydig cell atrophy.[60]	
Clerodendrum serratum Family: Verbenaceae	Plants excluding root	Showed spermicidal activity.[61]	
Curcuma longa Family: Zingiberaceae	50 % EtOH extract	Interference with spermatogenesis at later stages.[62]	
Cinnamomum comphora Family: lauraceae	Nees & erbern, seed extract	Arrest and inhibition of spermatogenesis.[63]	
Cuminum cyminum Family: Apiaceae	Seeds ethanol extract	Anti-spermatogenic activity.[64]	
Citrullus colocynthis schrad	Fruit, 50 % EtOH extract,	Impairment of sperm induced reversible antifertility effects.[65]	

Family: Cucurbitaceae			
Cynomorium coccineum Family: Cynomoriaceae	Aqueous extract	Effect the epididymal sperm pattern.[66]	
Echinops echinatus Family: Asteraceae	Root 50 % alcoholic extract	Sperm antimotility, sperm density in epididymis was reduced.[67]	
Foeniculum vulgare Mill Family: Apiaceaes	Whole plant	Antiandrogenic activity.[68]	
Gossypium herbaceum (Cotton) Family: Malvaceae		Gossypol directly inhibited epididymal sperm motility *in vitro* and its injection inhibited sperm motility in vivo. Gossypol affects sperm motility by a mechanism which is related to the structure and functions of the plasma membrane. Potential vaginal contraceptive, no advese effect on blood composition, hematological parameters and urinary secretions. Co-precipitation of gossypol prevented sperm motility when applied vaginally. Gossypol inhibits spermatogenesis in many mammals. Cotton seed oil emulsion also exhibited spermatozoal motility inhibition. Gossypol reduces the level of serum testosterone and LH. Also, it blocked CAMP formation in sperm, which resulted into inhibition of sperm motility.[69,70]	**1-** Gossypol, a yellow polyphenolic compound present in the stem, seeds and roots of *Gossypium* species. **2-** Gossypol-oral contraceptive for man. **3- Dosage** – 1.250–10 mg/kg for 5–14 week for rabbit. Gossypol acetic acid produces its contraceptive effect by depressing spermatogenic function through its direct action on Leydig cells. Gossypol acetate induced sterility at dose level of 5 or 10 mg/kg daily for 12 week.[69,70]
Juniperus phoenicea Family: Cupressaceae		Decrease testosterone levels.[71]	
Mentha arvensis	Leaves/pet.	Possess reversible	

Family: Lamiaceae	ether, 50 % ethanolic extract	antifertility property without adverse toxicity in male mice. Reduces fructose synthesis in seminal vesicles, as a result of which the viability of spermatozoa seems to be altered.[72]	
Myristica fragrans Family: Myristicaceae.	EtOH extract	premature ejaculation.[73]	
Moringa oleifera Family: Moringaceae		Antifertility activity.[74]	
Nicotiana tabaccum Family: Solanaceae.		Antiandrogenic activity.[75]	
Ocimum sanctum Family: Lamiaceae	Leaves extract	Showed spermicidal activity.[76] It decreases sperm count, motility and the forward velocity of the sperm. The effects were found to be reversible upon withdrawal of treatment for 2 weeks.[76]	The extract of *Ocimum sanctum* L leaves when administered to male rats at a dose of 250 mg/kg body weight for 48 days.
Pentapanax leschenaultia Family: Araliaceae	Fruit/EtOH extract	Completely immobilized human spermatozoa.[77]	
Primula vulgaris Family: Primulaceae		Immobilized human sperm (60-120 × 10^9 sperm/ml) at dilution of 1:1000 .[78]	
Piper longum (Pepper) Family: Piperaceae	Piperine alkaloid	Piperine, an alkaloid extracted from the fruits and roots of black pepper, has been shown to cause damage to the germ cells and seminiferous tubules when administered orally for 30 days.[80] Suppression in the levels of antioxidant enzymes, and increase in the lipid peroxidation in testis and epididymis along with activation of caspase 3 and F as apoptotic proteins in testicular germ cells were	**1**- Pepper, a commonly used spice, is reported to induce sterility in laboratory male mice.[79] **2**- Laboratory studies have demonstrated a reduction in rat sperm motility, viability, and count on exposure to piperine at 10 mg and 100 mg per kg body weight.[82]

		reported.[81,82]	
Ricinus communis Family: Euphorbiaceae	Seeds/MeOH extracts, ether soluble fraction	Alteration in the motility mode of movement and morphology of sperms.[83]	
Rauwolfia series Family: Apocyanaceae		Affect the fertilizing capacity of human spermatozoa in vitro.[84]	
Trigonella fonenum graecum Family: Fabaceae	Seeds extract	Exerts both antifertility and anti-androgenic activities.[85]	Dose, 100 mg/day/male albino rat.[85]
Tripterygium wilfordii Family: Celastraceae		Anti-spermatogenic activity similar to that of gossypol (30 mg/kg in diet for 80 days).[86]	**1-** Safe reversible male antifertility agent. **2-** Induce complete infertility male rats and selected for further toxicological and pharmacological evaluation.[86]

Table 2: Examples of the plants that affect steroidogenesis.

Source	Used part and/or active constituents	Mechanism of action	Comments
Albizia lebbeck L, discussed previously.			
Allium sativum Family: Liliaceae	Total crude extract	The crude extract when administered to male rats at varying concentrations (5 %, 10 %, 15 % and 30 %) for 30 days caused an increase in the percentage of empty seminiferous tubules and brought about a decrease in serum testosterone levels, with the effects being invoked at a dose as low as 10 %. An *in vitro* study on the effects of allitridum, an active principle from garlic, has been reported to inhibit sperm motility and complete immobilization of rat, hamster and human spermatozoa at a dose of 7.5 mg/mL. A significant reduction in the levels of serum testosterone and LH was reported when crude extracts of garlic were administered to male rats for 30 days. *In vitro* studies on the crude aqueous extract of *Allium sativum* have been reported to reduce sperm viability, membrane disintegration of sperm and irreversible immobilization of ram epididymal and human ejaculated sperm at doses of 0.25 g and 0.50 g per mL, respectively.[87-89]	Graded doses of the extract induced abnormalities in the size and shape of rat sperm along with dorso-ventral constrictions in the middle region of the sperm head, which was proposed to be due to alterations in cauda epididymal milieu and androgen deficiency.[87-89]

Abelmoschus esculentus Family: Malvaceae		Decrease in serum testosterone levels.[90]	
Aegle marmaelos Family: Rutaceae		Reduced testosterone levels.[91]	
Bulbine natalensis Family: Asphodelaceae		Decreases testosterone and progesterone at high dose.[92]	
Capparis aphylla Family: Capparaceae		Reduces steroidogenic enzymes.[93]	
Chromolaena odoratum Family: Asteraceae		Decreases serum testosterone level.[94]	
Dendrophthoe falcate Family: Loranthaceae		Decrease in serum testosterone levels.[95]	
Garcinia cambogia Family: Clusiaceae		Degeneration of the leydig cells.[96]	
Jatropha curcus Family: Euphorbiaceae	Whole plant	Decrease sperm motility and decrease sperm count, abortifacient. [29]	
Psoralea corylifolia Family: Fabaceae		Decreases serum testosterone levels.[97]	
Syzygium aromaticum Family: Myrtaceae		Reduction in the steroidogenic enzymes and testosterone levels at higher dose.[98]	

3- Implantation inhibitors

Herbal contraceptive used by women manly acted as implantation inhibitors by inhibiting the implantation of a fertilized egg (Table 3). These plants cause the uterine lining to change texture and more thick, becoming too slippery or perhaps too viscous, to hold an egg to prevent implantation. Some herbal contraceptives have the ability to interfere with implantation, the actual effect in the body can vary from herb to herb, but the end result makes it difficult for the egg to implant or maintain its grip on the uterine wall. Implantation occurs about 6 days after the egg has been fertilized. If the egg is unable to get a grip on the uterine wall, it cannot survive, it begins to break down, and menstruation will arrive as usual.

Table 3: Implantation inhibitors medicinal plants.

Source	Used part and/or active constituents	Mechanism of action	Comments
Azadirachta indica (Neem), neem oil, leaves, seeds/dry powder, *n*- hexane, EtOH extract, Family: Meliaceae. Its mechanisms and dose were discussed previously			
Asparagus pubescens Family: Asparagaceae	Root/MeOH extract	0.5-1.5 g/kg protected animals from conception for 4-14 gestational periods in rabbits, rats and mice. It inhibited fetal implantation. Its effect may in part be due to its anti-implantation and/or a direct effect on the uterus.[99]	
Actaea racemosa L (Black cohosh) Family: Ranunculaceae		In rats and mice, *C racemosa* induced estrus and increased uterine weight in a dose-dependent manner.[100]	
Abrus precatorius Family: Fabaceae	Seeds dry extract	Oral contraceptive, prevents implantation of fertilized ovum by inhibiting endometrial alkaline phosphate, induces 100% sterility in mice when injected one day pre and post coitum. Sperm anti-motility activity, Steroidal fraction indirectly influenced the pituitary level, leading to decrease in production and release of testosterone, resulting in significant alterations in the testis.[101]	
Acacia catechu Family: Fabaceae		Effective oral contraceptive in rats and inhibits implantation.[102]	
Acacia arabica Family: Fabaceae		Effective oral contraceptive in rats and inhibits implantation. Aqueous solution of tannin (1–1%) has power to coagulate human cervical mucus, seminal fluid and other mucin type of glycoprotein. So, suppository was formulated from tannin ethers, benzalkonium chloride, carboxymethyl cysteine and excipients in sufficient quantities. It acts as a barrier for sperm penetration and thus enhanced the possibility for contraception	

		purposes.[102]	
Beaumontia grandiflora Family: Apocyanaceae	Leaves extract	Showed anti-implantation, abortifacient and luteolytic effects.[103]	
Citrus aurantium Family: Rutaceae	Peel	It inhabits implantation.[104]	Oral contraceptive. 0.75 mg/kg in 0.1% ethylene glycol daily on rabbit.[104]
Calendula officinalis Family: Asteraceae	Saponins employed in extract form or pure form.	Spermatocides, anti-blastocysts and abortion agents.[105]	
Centella asiatica Family: Apiaceae		Its compounds caused consistent reduction of fertility in female mice.[106]	Used as oral antifertility agents in albino mice.
Curcuma zedoaria Family: Zingiberaceae	Tubers	It inhibited implantation in 60% of animals and increased foetal loss.[107]	Administered orally at 500 ml/kg on days 1–5 of pregnancy.[107]
Datura quercifolia Family: Solanaceae		Its compounds showed dose related response. 100 mg/kg from 1–7 days of pregnancy caused 73.3% anti-implantation effect.[108]	Most effective antifertility agent. 25 mg/kg orally for 1–7 days of pregnancy.[108]
Daucus carota (Carrot) Family: Apiaceae	Seeds of a wild carrot also known as Queen Anne's lace (QAL)	The seeds inhibit the implantation of a fertilized egg cause the uterine lining to change texture and more thick, becoming too slippery or perhaps too viscous, to hold an egg to prevent implantation. The extracts of the seeds disrupt the implantation process, or if a fertilized egg has implanted for only a short period, will cause it to be released. Possesses weak estrogenic property and anti-pregnancy effect. Inhibits implantation effectively at doses 80 and 120 mg/mouse orally from day 4 to 6 post coitum.[109-113]	**1**- Women have used the seeds from *Daucus carota*, for centuries as a contraceptive, the earliest written reference dates back to the late 5th or 4th century B.C. appearing in a work written by Hippocrates. **2**- Traditionally, it has been known to be used for regulating menstrual cycle, endometriosis, prevents clotting, and tones uterus. It does not need to be used daily to be effective. If a woman knows she was exposed to sperm during a fertile time,

			QAL seeds can be used like an emergency contraceptive, an after the fact preventive. One of its biggest advantages is that it can be taken on as needed basis, making it useful for women who have sex in frequently. **Dose;** There are four dosage regimens used: **a**- Every day. **b**- Daily for three days before ovulation, during ovulation, and for at least three days after ovulation. **c**- Daily for a least seven days following sexual intercourse. **d**- Seeds should be chewed within 8 hours of being exposed to sperms with water or juice. Chewing them releases the oils, if the seeds are simply swallowed whole, they will pass right through your system, without releasing their oils and not be effective. All the women used the same dosage; one teaspoon of the seeds chewed well and rinsed down with something to drink.[109-113]
Dictamnus albus Family: Rutaceae	Root bark/MeOH and *n*- hexane extract.	Decreased fertility in rats when administered orally on day's 1-10 post-coitum. Fraxinellone showed antifertility activity by inhibition of implantation.[114]	

Dioscorea villosa (Wild Yam) Family: Dioscoreaceae		Wild yam works by thickening the outer covering of the egg's "shell" so that the sperm are unable to penetrate. Wild yam is very good for the liver and endocrine system because it tones and nourishes the liver, helping to balance hormone production. Wild Yam can be used for a variety of women's issues including menstrual irregularity, menstrual cramps, infertility, menopause and endometriosis. Its infusion is the strongest preparation to prevent miscarriage, because it relaxes the uterus and soothes the nerves. Wild yam can be used to both promote and decrease fertility, depending on the amount taken and when in the cycle it is taken and for how long. When taken between menstruation and ovulation in small doses, it increases fertility. [115]	**1**- It is a good example of a typical herbal contraceptive, taken daily, needing a period of time to establish effectiveness and mixed results reported. Doses must be taken twice daily, and never forgotten. The herb needs to be taken for a minimum of one month to allow it time to take effect, waiting two months, may even be better before relying on it for birth control.[115] **2**- As a contraceptive, take pre-packaged capsules of wild yam, 1275 mg to 1500 mg twice a day, every day or 3 size capsules, twice a day, every day. Note that antibiotics both herbal (garlic, echinacea, goldenseal, or other herbs) and pharmaceutical negate the contraceptive effect of wild yam.[115]
Echium vulgare Family: Boraginaceae		Decreased the weight of ovaries.[116]	
Ensete superpa Family: Musaceae	Seeds	Possesses antifertility activity.[117]	
Embelia ribes Family: Myrsinaceae	Seeds or fruit berries/ pet. ether, MeOH, benzene and $CHCl_3$ extract	Potent oral contraceptive. Prevent pregnancy 37–75 %, reversible male contraceptive at dose 80 mg/kg. Female antifertility principle 100 mg/kg. Control 57.5%.[118,119]	
Ferula assafoetida (Asafoetida) Family: Apiaceae	Dry powder	It has a folkloric reputation as an abortifacient and emmenagogue.[120,121]	

Foeniculum vulgare Family: Apiaceae	Seeds	On days 1-5 of pregnancy inhibited implantation in 60% of animals and increased foetal loss. Reduced secretory activity and weight of accessory sex glands.[122]	Administered orally at 500 ml/kg.[122]
Lygodium flexuosum Family: Schizaeaceae	Whole plant/alcoholic extract	Anti-ovulatory and anti-implantation activity.[123]	
*Marsdenia k*oi Family: Apocyanaceae	Whole plant/methanolic extract	Its compounds exhibited good antifertility activity.[124]	
Momordica charantia, Family: Cucurbitaceae	Seeds/petroleum ether and benzene extract	Anti-spermatogenic effect. Inhibited embryonic implantation and pregnancy.[125,126]	
Montanoa tomentosa Family: Asteraceae	Leaves/*n*-hexane, aqueous extract	Controls antifertility in female rats and anti-implantation effects for human and lower animals. Increased uterine contractions or induced labor or abortion at a dosage of 272 µg/rat produced 100% resorption of fetuses. Possess unique antifertility activity in females. Inhibited implantation in rats and mice when administered on days 1-6 and in hamsters when administered on days 4-6 of gestation.[127,128]	
Murraya paniculata Family: Rutaceae	Roots	Potent anti-implantation activity in rats at 3 mg/kg orally on pregnancy day 2.[129,130]	
Mentha pulegium (Pennyroyal) Family: Lamiaceae		Abortifacient which causes uterine muscle to contract.[29]	
Nigella sativa Family: Ranunculaceae	Seeds/hexane extract	Showed significant antifertility activity. Prevented pregnancy in Sprague-Dawley rats treated orally at 2 g/kg daily dose on day's 1-10 post-coitum.[131]	Administered orally at 500 mL/kg on days 1-5 of pregnancy inhibited implantation in 60 % of animals and increased foetal loss.[131]
Plantago ovate Family: Plantaginaceae		Forms a gel in fallopian tubes in three minutes.[132]	

Polygonum hydropiper (Smartweed leaves), Family: Polygonaceae	Leaves extract	Smartweed is used as fertility regulator. It contains rutin, quercitin and gallic acid, all of which interfere with normal pregnancy.[29]	An infusion can be prepared using 4 ounces of the fresh leaves or one ounce of the dried leaves in a quart of boiled water. Drinking freely until menstrual bleeding begins. Smartweed may be used to prevent implantation after fertilizing intercourse, or to bring on a missed period.[29]
Prunus armeniaca (Apricot Kernels) Family: Rosaceae		Suspected to have anticancer qualities which might treat the developing fetus as a foreign body, 5-10 apricot kernels three times a day immediately after following fertilizing intercourse and continuing until menstruation come.[133]	
Punica granatum (Pomegranate) Family: Lythraceae		The fruit is used by ancient women to prevent conception. The seeds of the fruit contain an oestrone identical to the natural hormone estrogen.[115,134]	
Phytolacca dodecandra Family: Phytolaccaceae	BuOH extract of sundried berries	Prevented pregnancy or decreased the embryonic count on days 1, 4 and 6 after coitus. It reduced sperm motility to 0 % at 20 µg/ml.[135]	The plant had little or no effect on pregnancy at doses 1000 µg. after 15 min. compared to 50% in a control.[135]
Ruta graveolens (Rutin) Family: Rutaceae		This is found at local health food markets. It is also known as Vitamin P. It can be used to prevent pregnancy, when taken in tablet form in doses of at least 500 mg daily for several days preceding and following ovulation, or when taken after intercourse and continue until menstruation begins. Chloroform extracts of the root stem leaf *Ruta graveolens* showed significant antifertility activity in rats.[136] Rue contains two chemicals that we know have the ability to	**1**- Rue (*Ruta graveolens*) has been used historically as tea to induce miscarriage by thousands of women all over the world from the Mediterranean, and Europe to Latin America and North America. Rue is a traditional abortifacient used by the Hispanic people in New Mexico.[136-138] **2- Dosages**: Tea, 1-3

		cause abortion during early pregnancy. One of the chemical substances is called **philocarpine**, which is used in veterinary medicine as an abortifacient for horses[137]. The other is called **Rutin**, a bioflavinoid that hardens bones and teeth, strengthening arteries and veins. **Rutin** can be used to disrupt pregnancy and as an emergency contraceptive. It is contraindicated in individuals who have poor kidney functions. When using rue, avoid long exposure to sunlight. May be irritating to the gastrointestinal tract.[136]	tsp. per cup, 3-4 times daily. Boil the water first then pour he boiled water over the dried herb. Do not boil the herb in water, as this destroys the herbs properties. For a tincture, 5-15 drops 3-4 times a day. Capsules, 1-4 capsules 3-4 times a day. Take it as a tablet in doses of at least 500 mg daily for several days preceding and following ovulation, or take it after fertilizing intercourse and continue until the menstrual flow begins.[115]
Ricinus communis Family: Euphorbiaceae	Seeds/MeOH extracts pet. ether soluble fraction,	The plant showed anti-implantation and anti-conceptive activities.[139]	Dose for adult female rats and rabbits is up to 1.2 g/kg and 600 mg/kg, respectively.[139]
Saraca indica Family: Fabaceae.		Showed anti-progestational activity in rabbits. Exhibited 33.3 % to 85.7% anti-implantation effect when given 1.25 to 50 mg/kg orally from days 1–5 of pregnancy.[140]	
Sophora japonica Family: Fabaceae		Contraceptive action or antifertility action in lab. animals.[1]	
Striga orobanchioides Family: Scrophulariaceae	EtOH extract	Exhibited slight anti-estrogenic activity. Showed dose- dependent and significant anti-implantation activity. Reduced weight of sex organs.[141]	
Tanacetum vulgare (Tansy), Family: Asteraceae		Common name is Scented Fern which is known to botanists as *Tanacetum vulgare* L., family: Asteraceae, and tansy has a long history of use in folk medicine. The dried leaves and flowering tops of tansy have been employed, usually in the form of	

		a tea, as an emmenagogue (promotes menstrual flow-often a euphemism for promoting abortion).[29]	
Vicoa indica Family: Asteraceae		Possessed antifertility activity which is dose-related and was found to be free from side effects.[142]	
Vitex negundo Family: Verbenaceae	Seeds	100% anti-implantation effects when given orally from day 4–6 pregnancy.[143]	Dose 100 mg/kg i.p. for 45 days, azoospermia achieved without altering the metabolism and (or) libido.[143]

STRUCTURE ACTIVITY RELATIONSHIP (SAR) OF NATURAL STEROIDAL CONTRACEPTIVES

A 5*β*-reduced metabolite of Δ^4, 3-keto androgens, and androsterone, a metabolite of dihydrotestosterone, as well as 17 hydroxyl group is essential for activity. Two general types of modification of androgens have been particularly useful;

1- Esterification of the 17*β*-hydroxyl group with any of several carboxylic acids decrease the polarity of the molecule, make it more soluble in the lipid vehicles.

2- Alkylation at the 17α position also allows androgens to be effective orally, because the alkylated derivatives are slowly catabolized by the liver.[3]

Many steroidal and non steroidal compounds possess estrogenic activity. The most potent naturally occurring estrogen in humans, for both ER-α and β-mediated actions, is 17*β*-estradiol, followed by *estrone* and *estriol*. Each of these molecules is an 18-carbon steroid, containing a phenolic A-ring with a hydroxyl group at carbon 3, and a *β*-OH or ketone in position 17 of ring D. The phenolic A ring is the principal structural feature responsible for selective, high-affinity binding to both receptors. Most alkyl substitutions on the A ring impairs such binding, but substitutions on ring C or D may be tolerated. Ethinyl substitutions at the C17 position greatly increase oral potency by inhibiting first-pass hepatic metabolism. Models for the ligand-binding sites of both estrogen receptors have been determined from structure-activity relationships and structural analysis.[144,145]

Non steroidal compounds with estrogenic or anti-estrogenic activity ¾ including flavones, isoflavones (*e.g.*, genistein) and coumestan derivatives ¾ occur naturally in a variety of plants and fungi. A number of synthetic agents ¾ including pesticides (*e.g.*, *p,p*-DDT), plasticizers (*e.g.*, bisphenol A), and a variety of other industrial chemicals (*e.g.*, polychlorinated biphenyls) ¾ also have hormonal or anti-hormonal activity. Many of these polycyclic compounds contain a phenolic

ring that mimics the A ring of steroids. While the affinity of these environmental estrogen for the estrogen receptor is relatively weak while their affinity is relatively weak, their large number, bioaccumulation and persistence in the environment have raised concerns about their potential toxicity in humans and wildlife.[146] Over-the-counter and prescription preparations containing naturally occurring estrogen like compounds from plants (*i.e.*, phytoestrogens) now are available.[147] Unlike the estrogens, which requires a phenolic A-ring for high-affinity binding, the progesterone receptor (PR) favors a Δ^4-3-one A-ring structure in an inverted 1β, 2α-conformation.[3]

CONCLUSION

The knowledge of medicinal plants used by the people is popular in various cultures and traditions. For centuries herbal potions and pessaries have been concocted with the goal of preventing and or disrupting pregnancy. However, taking herbal contraceptives may risk exposure to health concerns, not always 100% effective, and should not be taken with prescribed medication or having an existing health problem. Taking herbal contraceptives long term may or may not cause a health concerns. Pharmacological effects of many plants have been studied in various laboratories. However, there are many limitations regarding safety and efficacy of these preparations. Knowledge about active principles of herbal preparations is not well defined and information on toxicity and adverse effect of these formulations are lacking. Information regarding pharmacokinetics and bioavailability is not available. Assurance of safety, quality, efficacy of medicinal plant and herbal products are key issues, which needs to be addressed. Selection of plant material should be based on quality, standardization of methods of preparation, enforcement of regulation regarding appropriate labels are measures, which will improve the quality and acceptability of herbal preparation. Ecotype pharmacological evaluation is very essential when the drug is used in crude form. The relative proportion of phytochemical present in medicinal plants can vary in different ecotypes. There is also a need for documentation of research and publication of results in peer-reviewed journals. Most of the information on pharmacological study of plants are incomplete since they are published as abstract presented at conferences. Standardization of tests and methods of preparation and documentation of adverse effects of herbal medicines merits attention. Standardization of methods, quality control, data on safety and efficacy are needed for proper understanding of the used of the herbal medicines. The development of better prophylactics requires new breakthroughs of theories about this process that could only be obtained from basic researches in reproductive biology and medicines. Owing to the belief that post testicular agents have a more rapid antifertility effect and a correspondingly more rapid recovery that would agent

that acts on spermatogenesis, a dual approach was pursued. Drugs with post meiotic or post testicular action would not disturb spermatogenesis libido or any other hormonally related features. Their effects are rapid both in onset and in the return of normal sperm on withdrawal of the drug.[148] New targets for drugs interventions should be pursued through support of basis sciences, taking advantage of modern cellular and molecular biological techniques. The relatively slow emergence of fertility control technologies for practical application clearly reflects the complexities of science and the requirement of multi-disciplinary research approach. Recent biotechnological, biochemical and immunological advances have overcome some of these difficulties and know make the production and use of contraceptive vaccines feasible. They can provide a valuable alternative to currently available methods of family planning. A vaccine that targets sperm represents a promising approach to contraception. Anti-sperm antibodies (ASA) in men and women cause infertility but the antigens that are recognized by ASA are not characterized. Prostasomes (organelles secreted by human prostatic cells) are one of the major targets for ASA and that several antigens can cause antibody response associated with immunological infertility. Researchers suggested that prostasomes are available after a new set of antigens for research on male immune infertility and immunecontraception.[149]

REFERENCES

1. Unny R, Chauhan AK, Joshi YC, Dobhal MP, Gupta RSA. A review on potentiality of medicinal plants as the source of new contraceptive principles. Phytomedicine 2003; 10: 233-260.
2. Akdogan M, Ozguner M, Kocak A, Oncu M, Cicek E. Effects of peppermint teas on plasma testosterone, follicle-stimulating hormone, and luteinizing hormone levels and testicular tissue in rats. Urology 2004; 64: 394-398.
3. Hardman J.G.; Limbird L.E.; Molinoff P.B.; Ruddon R.W.; Gilman`s A.G., *The* pharmacological basis of therapeutics. 9th Ed., 2008: 1411-1457.
4. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale`s Pharmacology. 6th Ed., 2007: 445-460.
5. Pincus G, Bialy G. Drugs used in control of reproduction. *Advan. Pharmacol.*, 1965: 285-313.
6. Tyler ET. Antifertility Agents. Annu Rev Pharmacol 1967; 7: 381-398.
7. Swahn ML, Westlund P, Johannisson E, Bygdeman M. Effect of post-coital contraceptive methods on the endometrium and the menstrual cycle. Acta Obstet Gynecol Scand 1996; 75: 738-744.

8. Croxatto HB, Fuentalba B, Brache V, Salvatierra AM, Alvarez F, Massai R, Cochon L, Faundes A. Effect of the Yuzpe regimen, given during the follicular phase, on ovarian function. Contraception 2002; 65: 121-128.
9. Sharma RS, Rajalakshmi M, Jeyaraj DA. Current status of fertility control methods in India. J Biosci 2001; 26: 391-405.
10. www.ippf.org/Resources/Contraception/
11. Farnsworth N. Potential value of plants as source of new antifertility agents I. J Pharm Sci 1975; 64: 535-598.
12. D'Cruz SC, Vaithinathan S, Jubendradass R, Mathur PP. Effects of plants and plant products on the testis. Asian J Andro 2010; 12: 468-479.
13. Moss GP. Nomenclature of steroids. Pure and Applied Chem 1989; 61: 1783-1822.
14. Lichtenthaler H. 1-Dideoxy-D-xylulose-5- phosphate pathway of isoprenoid biosynthesis in plants. Annu Rev Plant Physiol Plant Mol Biol 1999; 50: 47-65.
15. Ogbuewu IP, Agoh C, Etuk IF, Okoli IC, Iloeje MU. Evaluation of the cholesterol characteristics of the liver of Dutch Belt rabbit bucks fed toasted commercial poultry diets supplemented with soy milk. Int J Agric Res Dev 2010; 2: 77-81.
16. Rahim F, Saki G, Bazrafkan M. Effect of alcohol extracts of the Ruta graveolens L.on the count, motility and in vitro fertilization capacity of rat's sperm. Asian J Plant Sci 2010; 9: 63-66.
17. Udoh P, Kehinde A. Studies on antifertility effect of pawpaw seeds (*Carica papaya*) on the gonads of male albino rats. Phytother Res 1999; 13: 226-228.
18. Liu GZ, Lyle KC, Cao J. Clinical trial of gossypol as a male contraceptive drug. Part I. Efficacy study. Fertil Steril 1987; 48: 459-461.
19. Sinha KC, Riar SS, Bardhan J, Thomas P, Kain AK, Jain RK. Anti-implantation effect of neem oil. Indian J Med Res 1984a; 80: 708–710.
20. Sinha KC, Riar SS, Tiwary RS, Dhawan AK, Bardhan J, Thomas PK, Kain AK, Jain RK. Neem oil as a vaginal contraceptive Indian J. Med. Res., 1984b; 7: 131-136.
21. Prakash AO, Tewari RK, Mathur R. Non-hormonal post-coital contraceptive action of neem oil in rats. J Ethnopharmacol 1988; 23: 53-59.
22. Riar SS, Bardhan J, Thomas P, Kain AK, Parshad R. Mechanism of antifertility action of neem oil. Indian J Med Res 1988; 88: 339-342.
23. Shaikh PD, Manivannan B, Pathan KM, Kasturi M, Ahmed RN. Antispermatic activity of *Azadirachta indica* leaves in albino rats. Current science 1993; 64: 688-689.

24. Upadhyay SN, Kaushic C, Talwar GP. Antifertility effect of neem (*Azadirachta indica*) oil by single intrauterine administration: a novel method for contraception. Proc R Soc Lond B Biol Sci 1990; 22: 242 (1305): 175-179.
25. Garg S, Doncel G, Chabra S, Upadhyay SN, Talwar GP. Synergistic spermicidal activity of Neem seed extract, reetha saponins and quinine hydrochloride. Contraception 1994; 50: 185-190.
26. Talwar GP, Raghuvanshi P, Misra R, Mukherjee S, Shah S. Plant immunomodulators for the termination of unwanted pregnancy and for contraception and reproductive health. Immunol Cell Biol 1997; 75: 190-192.
27. Garg S, Upadhyay SN, Talwar GP. Immuno contraceptive activity guided fractionation and characterization of active constituents of neem (*Azadirachta indica*) seed extracts. J Ethnopharmacol 1998; 60: 235-246.
28. Awasthy KS. Genotoxicity of a crude leaf extract of Neem in male germ cells of mice. Cytobios 2001; 106 (Suppl 2): 151-164.
29. Shweta G,Chetna R, Jinkal S, Nancy S, Hitesh J. Herbal plants used as contraceptives. Int J Curr Pharm Rev Res 2011; 2: 48-53.
30. Upadhyay SN, Dhawan S, Talwar GP. Antifertility effect of neem (*Azadirachta indica*) oil in male rats by single intra-vas administration: an alternate approach to vasectomy. J Androl 1993;14: 275-281.
31. Bardhan J, Riar SS, Sawhney RC. Neem oil-a fertility controlling agent in rhesus monkey. Indian J Physiol Pharmacol 1991; 35: 278-280.
32. Bhasin S, Woodhouse L, Casaburi, R, Singh AB, *Bhasin* D, Berman N, Chen X, Yarasheski KE. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 2001; 281: E1172-E1181.
33. Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, Speed C, Jones M. Aromatase-a brief overview. Annu Rev Physiol 2002; 64: 93-127.
34. Sharma V.P.; Praneem polyherbal cream for contraception: Safety in malaria endemic countries. Curr Sci 1996; 71: 430-435.
35. Sharma SK, Sairam M, Ilavazhagan G, Devendra K, Shivaji SS, Selvamurthy W. Mechanism of action of NIM-76: a novel vaginal contraceptive from neem oil. Contraception 1996; 54: 373- 378.
36. Deshpande VY, Mendulkar KN, Sadre NL. Male antifertility activity of *Azadirachta Indica* in mice. J Postgrad Med 1980; 26: 167-170.

37. Kamboj VP, Dhawan BN. Research on plants for fertility regulation in India. J Ethnopharmacol 1982; 6: 191-226.
38. Varshney IP, Vyas P, Srivastava HC, Singh PP. Study of *Albizzia lebbek* Benth wood saponin, Lebbekanin-E. Natl Acad Sci Lett (India) 1979; 2: 135-136.
39. Dixit VP, Joshi S. Effect of *Aloe barbadensis* and Clofibrate in triton induced hyperlipidaemic presbytis monkey. *Ind J Med Res* 1983; 78: 417-421.
40. Kamboj VP, Dhawan BN. Research on plants for fertility regulation in India. J Ethnopharmacol 1982; 6: 191-226.
41. Akbarsha MP, Manivannan B, Hamid KS, Vijayan B. Antifertility effect of *Andrographis paniculata* (Nees) in male albino rats. Indian J Exper Biol 1990; 28: 421-426.
42. Pal D, Chakraborty P, Ray HN, Pal BC, Kabir SN. Acaciaside-B-enriched fraction of *Acacia auriculiformis* is a prospective spermicide with no mutagenic property. Reproduction 2009; 138: 453-462.
43. Che CT, Ahmed MS, Kang SS, Waller DP, Bingel AS, Martin A, Rajamahendran P, Bunyapraphatsara N, Lankin DC. Studies on Aristolochia III. Isolation and biological evaluation of constituents of *Aristolochia indica* roots for fertility-regulating activity. J Nat Prod 1984; 47: 331-341.
44. Gupta RS, Dobhal MP, Dixit VP. Morphometric and Biochemical change in testes of Presbytis entellus Duferesne (Langur monkey) following aristolochic acid administration. Annals of Biology 1996; 12: 328-334.
45. Dixit VP, Bhargava SK, Gupta RA. Hyperglycemia induced testicular dysfunction after chronic administration of *Balanites roxburghii* Planch fruit pulp extract in dogs *Canis indicus* L. Indian J Exp Biol 1981; 19: 918-921.
46. Bhargava SK. Estrogenic and post coital anticonceptive activity in rats of butin isolated from *Butea monosperma* seed. J Ethnopharmac . 1986; 18: 95 (101).
47. Serrano H, Garcia-Suarez MD. Sperm aggregation by water extracts from two *Bursera* species. Arch Indrol 2001; 46: 15-20.
48. Gupta RS, Kumar P, Dixit VP, Dobhal MP. Antifertility studies of the root extract of *Barleria prionitis* in male albino rats with special reference to testicular cell population dynamics Linn. J Ethnopharmacol 2000; 70: 111-117.
49. Gupta RS, Tank R, Dixit VP. Quantitative analysis of germ cells and leydig cells in rat and dog made infertile with solasodine ($C_{27}H_{43}O_2N$). Adv Contr Deliv Syst 1989; V: 389-397.

50. Huacuja RL, Delgado NM, Carranco LA, Reyes LR, Rosado GA. Agglutinating and immobilizing activity of an ethanol extract of *Bursera fagaroides* on human and mammalian spermatozoa. Arch Invest Med (Mex.) 1990; 21: 393-398.
51. Dixit VP. Effect of *Cannabis sativa* extract on testicular function of *Presbytis entellus entellus*. Planta Med 1981; 41: 288-294.
52. Murugavel T, Akbrarsha MA. Antispermatogenic effect of *Vinca rosea*. Indian J Exp Biol 1991; 29: 810-812.
53. Averal HI, Stanley A, Murugaian P, Palanisamy A, Akbarsha MA. Specific effect of Vincristine on epididymis. Indian J Exp Biol 1996; 34: 53-56.
54. Udoh P, Kehinde A. Studies on the antifertility effect of Pawpaw seeds (*Carica papaya*) on the gonads of male albino rats. Phytother Res 1999; 13: 226-228.
55. Pathak N, Mishra PK, Manivannan B, Lohiya NK. Sterility due to inhibition of sperm motility by oral administration of benzene chromatographic fraction of chloroform extract of the seeds of *Carica papaya* in rats. Phytomedicine 2000; 7: 325-333.
56. Stokes T. Papaya male contraceptive [In brief]. Trends in Plant Sci 2001; 6:14.
57. Ogbuewu IP, Agoh C, Etuk IF, Okoli IC, Iloeje MU. Evaluation of the cholesterol characteristics of the liver of Dutch Belt rabbit bucks fed toasted commercial poultry diets supplemented with soy milk. Int J Agric Res Dev. 2010; 2: 77-81.
58. Lohiya NK, Goyal RB. Antifertility investigations on the crude chloroform extract of *Carica papaya* Linn. seeds in male albino rats. Indian J Exp Biol 1992; 30: 1051-1055.
59. Lohiya NK, Mishra PK, Pathak N, Manivannan B, Jain SC. Reversible azoospermia by oral administration of the benzene chromatographic fraction of the chloroform extract of the seeds of *Carica papaya* in rabbits. Adv Contracept. 1999; 15: 141-161.
60. Gupta RS, Sharma N, Dixit VP. Calotropin-a novel compound for fertility control. Anc Sci Life 1990; 9: 224-230.
61. Setty BS, Kamboj VP, Garg HS, Khanna NM. Spermicidal potential of saponins isolated from Indian medicinal plants. Contraception 1976; 14: 571-578.
62. Purohit A. Contraceptive efficacy of *Curcuma longa* (50 % EtOH extract) with special emphasis on testicular population dynamics. J Curr Biosci 1991; 8: 129-134.
63. Singh SP. Effect of *Cinnamomum camphora* leaf extract on testicular function of house sparrow (Passer domesticus L). Indian J Phy Nat Sci 1990; 10: 22-25.
64. Sharma J, Sharma S, Jain R. antifertility activity of *Cuminum cyminum* on reproductive organs on male albino rats (Rattus norvegicus). *In: National Symposium Reproductive Biology*

and Comparative Endocrinology Vadodara Gujarat 2001; 69.

65. Chaturvedi M, Dixit VP. Antifertility effect of *Citrullus colocynthis* Schrad in male albino rats. Indian J Environ Sci 1997; 1: 89-92.
66. Qian SZ, Zhong CQ, Tu X. Effect of *Tripterigium wilfordii* Hook. f. on the fertility of rats. Contraception 1986; 33: 105-110.
67. Chaturvedi M, Mali PC, Dixit VP. Fertility regulation in male rats with the help of *Echinops echinatus* (Roxb.) root extract. J Phytol Res 1995; 8: 115-118.
68. Farooq T, Vanithakumari G, Bhuvaneswari G, Malini T, Manonayaki S. Effects of anethole on seminal vesicle of albino rats. Ancient Sci Life 1991; 11: 9-11.
69. Coutinho EM. Gossypol: a contraceptive for men. Contraception 2002; 65 : 259-263.
70. Gupta RS, Sharma R. A review on medicinal plants exhibiting antifertility activity in male. Nat Prod Rad 2006; 5: 389-410.
71. Shkukani H, Salhab A, Disi A, Shomaf M, Al Quadan F. Antifertility effect of ethanolic extract of *Juniperus phoenica* in male albino rats. J Herbal Pharmacother 2007; 7: 179-189.
72. Sharma N, Jacob D. Antifertility investigation and toxicological screening of the petroleum ether extract of the leaves of *Mentha arvensis* L. in the male albino mice. J Ethnopharmacol 2001; 75: 5-12.
73. Misra DN, Shukla GD. Vitafix in premature ejaculation. A controlled trial. Ind Pract 1980; 33: 81-86.
74. Hukla B, Sha H, Wang C, Yu D, Wu X, Yu X. Proton NMR identification of Yuanhuatin-an antifertility significant component. Bopuxue Zazhi 1984; 1: 477-480.
75. Londonar RL, Srinivasreddy P, Somanathreddy P, Patil SB. Nicotine induced inhibition of the activities of accessory reproductive ducts in male rats. J Ethnopharmacol 1998; 60: 215-221.
76. Ahmed M, Ahamed RN, Aladakatti RH, Ghosesawar MG. Reversible anti-fertility effect of benzene extract of *Ocimum sanctum* leaves on sperm parameters and fructose content in rats. J Basic Clin Physiol Pharmacol 2002; 13: 51-59.
77. Pant G, Panwar MS, Rawat MSM, Negi DS. Spermicidal activity and chemical examination of *Pentapanax leschenaultii* (DC) seem fruits. Herba Pol 1988; 34: 161-162.
78. Primorac M, Sekulovic D, Antonic S. In vitro determination of the spermicidal activity of plant saponins. Pharmazie 1985; 40: 585.
79. Munshi SR, Rao SS. Antifertility activity of an indigenous plant preparation ROC-101). I. Effect on reproduction. Indian J Med Res 1972; 60: 1054-1060.

80. Malini T, Manimaran RR, Arunakaran J, Aruldhas MM, Govindarajulu P. Effects of piperine on testis of albino rats. J Ethnopharmacol. 1999; 64: 219-225.
81. D'Cruz SC, Vaithinathan S, Saradha B, Mathur PP. Piperine activates testicular apoptosis in adult rats. J Bioche Mol Toxicol 2008; 22: 382-388.
82. D'Cruz SC, Mathur PP. Effect of piperine on the epididymis of adult male rats. Asian J Androl 2005; 7: 363-368.
83. Sandhyakumary K, Bobby RG, Indira M. Antifertility effects of *Ricinus communis* (Linn) on rats. Phytother Res 2003; 17: 508-511.
84. Chan SYW, Tang LCH. Effects of reserpine on fertilising capacity of human spermatozoa. Contraception 1984; 30: 363-369.
85. Kamal R, Yadav R, Sharma JD. Efficacy of the steroidal fraction of fenugreek seed extract on fertility of male albino rats. Phytother Res 1993; 7: 134-138.
86. Huynh PN, Hikim AP, Wang C, Stefonovic K, Lue YH, Leung A, et al. Long-term effects of triptolide on spermatogenesis, epididymal sperm function, and fertility in male rats. J Androl 2000; 21: 689-699.
87. Chakrabarti K, Pal S, Bhattacharyya AK. Sperm immobilization activity of *Allium sativum* L. and other plant extracts. Asian J Androl 2003; 5: 131-135.
88. Qian YX, Shen PJ, Xu RY, Liu GM, Yang HQ. Spermicidal effect in vitro by the active principle of garlic. Contraception 1986; 34: 295-302.
89. Hammami I, Nahdi A, Mauduit C, Benahmed M, Amri M. The inhibitory effects on adult male reproductive functions of crude garlic (*Allium sativum*) feeding. Asian J Androl 2008; 10: 593-601.
90. Olatunji-Bello II, Ijiwole T, Awobajo FO. Evaluation of the deleterious effects of aqueous fruit extract of *Abelmoschus esculentus* (Okro fruit) and some male reproductive parameters in Sprague Dawley rats. J Phytol 2009; 1: 461-468.
91. Chauhan A, Agarwal M. Reversible changes in the antifertility induced by *Aegle marmelos* in male albino rats. Syst Biol Reprod Med 2008; 54: 240-246.
92. Yakubu MT, Afolayan AJ. Reproductive toxicologic evaluations of *Bulbine natalensis* Baker stem extract in albino rats. Theriogenology. 2009; 72: 322-332.
93. Sarathchandran I, Manavalan R, Akbarsha MA, Kadalmani B, Karar PK. Effect of ethanolic extract of *Capparis aphylla* (Roth) on testicular steroidogenesis in rat. J Biol Sci 2007; 7: 582-584.

94. Yakubu MT, Akanji MA, Oladiji AT. Evaluation of antiandrogenic potentials of aqueous extract of *Chromolaena odoratum* (L.) K. R. leaves in male rats. Andrologia 2007; 39: 235-243.

95. Gupta RS, Kachhawa JB. Evaluation of contraceptive activity of methanol extract of *Dendrophthoe falcata* stem in male albino rats. J Ethnopharmacol 2007; 112: 215-218.

96. Ogbuewu IP, Unamba-Oparah IC, Odoemenam VU, Etuk IF, Okoli IC. The potentiality of medicinal plants as the source of new contraceptive principles in males. N Am J Med Sci 2011; 3: 255-263.

97. Takizawa T, Mitsumori K, Takagi H, Nasu M, Yasuhara K, et al. Sequential analysis of testicular lesions and serum hormone levels in rats treated with a *Psoralea corylifolia* extract. Food Chem Toxicol 2004; 42: 1-7.

98. Mishra RK, Singh SK. Safety assessment of *Syzygium aromaticum* flower bud (clove) extract with respect to testicular function in mice. Food Chem Toxicol 2008; 46: 3333-3338.

99. Nwafor PA, Okwuasaba FK, Onoruvwe OO. Contraceptive and non-estrogenic effects of methanolic extract of *Asparagus pubescens* root in experimental animals. J Ethnopharmacol 1998; 62: 117-122.

100- Foster S. Black cohosh (*Cimicifuga racemosa*): A literature review. Herbalgram 1999; 45: 35-49.

101. Ratnasooriya WD, Amara sekera AS, Perera NSD, Premakumara GAS. Sperm antimotility properties of a seed extract of *Abrus precatorius*. J Ethnopharmacol 1991; 38: 85-90.

102. Chowdhury AKA , Khaleque RA , Chakder SK . Antifertility activity of traditional contraceptive pill comprising *Acacia catechu, Acacia arabica* and *Traqia involucerta*. Indian J Med Res 1984; 80: 372-374.

103. Choudhary DN, Singh JN, Verma SK, Singh BP. Antifertility effects of leaf extracts of some plants in male rats. Indian J Exp Biol. 1990; 28: 714-716.

104. Ghosh BP, Mukerjee AK, Banerjee S. New pyrone derivative, Cirantine, oral contraceptive . Naturwissenschaften 1955; 42: 77

105. Pakhurst RM, Stolzenberg SJ. Saponin containing spermatocidal compositions. U.S. 3, 886, 272 (Cl. 424-180, A01N) 27 May, Appl. 384, 101, July 30, 1973: 8.

106. Dutta T, Basu UP. Crude extract of *Centella asiatica* and products derived from its glycosides as oral antifertility agents. Indian J Exp Biol 1968; 6: 181-182.

107. Seshadari C, Pillai SR. Antifertility activity of a compound: Ayurvedic preparation. J Sci Res Plants Med 1981; 21: 1-3.

108. Chandhoke N, Gupta S. Estrogenic activity of DQ, a steroidal lactone isolated from *Datura quercifolia*. Indian J Exp Biol 1978; 16: 48-52.

109. http://www. sisterzeu.com/index.html.

110- Riddle.; John M.; Eve's Herbs-A History of Contraception and Abortion in the West Cambridge, Ma., Harvard University Press; 1997.

111. Chu Y, Zhou M, Li Q, Bao Y. Antifertility effect of volatile oil from *Daucus carota* seeds. Shengzhi Yu Biyun 1985; 1: 37-40.

112. Sharma MM, Lal G, Jacob D. Estrogenic and pregnancy interceptory effects of carrot *Daucus carota* seeds. Indian J Exper Biol 1976; 14: 506-508.

113. Tung CY, Hsu L-C, Chu H-W, Chou Y. Studies on the antifertility constituents in carrot seeds (*Daucus carota* L.). Chung Ts'ao Yao 1981; 12: 13.

114. Woo WS, Lee EB, Kang SS, Shin KH, Chi HJ. Antifertility principle of *Dictamnus albus* root barks. Planta Med 1987; 53: 339-401.

115- Ana S. Fertilility: Conception and Contraception A handbook for the Muslim Family. 89-97. http://www.ummah.net/islam/taqwapalace.

116. Man'ko IV, Poskalenko ON, Korkhov VV, Baikova VV. Preparation and investigation of "CES" series agents with contraceptive activity from plants of the borage family (Boraginaceae Don.). Farm Zh (Kiev). 1977; 3: 60-65.

117. Amonkar AJ, Trivedi GK, Bhattacharya SC. Structure of Kadalin, a biologically active component of Banakadali (*Ensete superba*). Indian J Chem Sec B 1978; 16B: 12-15.

118. Purandare TV, Kholkute SD, Gurjar A, Joshi UM, Dattatreyamurty B, Sheth AR, Swamy XR, Jayaraman S, Munshi SR. Semen analysis and hormonal levels in bonnet macaques administered *Embelia ribes* berries, an indigenous plant having contraceptive activity. Indian J Exper Biol 1979; 17: 935-936.

119. Krishnaswamy M, Purushothaman KK. Antifertility properties of *Embelia ribes* (embelin). Indian J Exper Biol 1980; 18: 1359-1360.

120. Zhi-da M1, Qi-Fi M, Mizuno M, Tanaka T, Iinuma M. Polysulfanes in the volatile oils of *ferula* species. Planta Med 1987; 53: 300-302.

121. Tetsuya Kajimoto, Yahiro K, Nohara T. Sesquiterpenoid and disulphide derivatives from *Ferula assafoetida*. Phytochemistry 1989; 28: 1761-1763.

122. Farooq T, Vanithakumari G, Bhuvaneswari G, Malini T. Effects of anethole on accessory sex tissue of albino rats. J Res Ayurv Siddha 1997; 15: 161-170.

123. Gaitonde BB, Mahajan RT. Antifertility activity of *Lygodium flexuosum*. Indian J Med Res 1980; 72: 597-604.

124. Yuan JL, Ding WP, Shi JP, Lu ZZ, Zhou BN, Erdelmeier CA, Cordell GA, Fong HH, Farnsworth NR. Studies on the antifertility components from *Marsdenia koi*. J Tongji Med Univ 1991; 11: 165-168.

125. Chan WY, Tam PPL, Choi HL, Ng TB, Yeung HW. Effects of momorcharins on the mouse embryo at the early organogenesis stage. Contraception 1986; 34: 537-544.

126. Naseem MZ, Patil SR, Patil SB. Antispermatogenic and androgenic activities of *Momordica charantia* in albino rats. J Ethnopharmacol 1998; 61: 9-16.

127. Hahn DW, Ericson EW, Lai MT, Probst A. Antifertility activity of *Montanoa tomentosa* (Zoapatle). Contraception 1981; 23: 133-140.

128. Levine SD, Hahn DW, Cotter ML, Greeenslade FC, Kanojia RM, Pasquale SA, Wachter M, Mc Guire JL. The Mexican plant zoapatle (*Montanoa tomentosa*) in reproductive medicine. Past, present and future. J Reprod Med 1981; 26: 524-528.

129. Kong YC, Ng KH, But PPH, Li Q, Yu SX, Zhang HT, Chen KF, Soejarto DD, Kan WS, Waterman PG. Sources of the anti-implantation alkaloid yuehchukene in the genus *Murraya*. J Ethnopharmacol 1986a; 15: 195-200.

130. Kong YC, Ng KH, Wat KH, Wong A, Saxena IF, Cheng KF, But PPH, Cheng HT. Yuehchukene, a novel antiimplantation indole alkaloid from *Murraya paniculata*. Planta Med 1985; 4: 304-307.

131. Kong YC, Xie JX, But PPH. Fertility regulating agents from traditional Chinese medicines. J Ethnopharmacol 1986; 15: 1-44.

132. Nandi RC, Singh S, Sarin JPS, Malviya B, Chandra H, Khanna NM. A carrier material for delivery of chemicals for contraception purposes in females or vas in males. Indian IN 1982; 150: 468-475.

133. Bennet RR. Wild Carrot Seeds for Herbal Contraception. Northeast Herbal Assoc. Newsletter 1994; 6: 32-34.

134. Prakash AO, Shukla S, Gupta A , Mathur R. Effect of embelin, an antifertility agent of plant origin on some biochemical constituents of rat uterus in the presence and absence of estradiol dipropionate and progesterone. Comp Physio Ecol 1986; 11: 4-10.

135. Stolzenberg SJ, Parkhurst RM, Reist EJ. Blastocidal and contraceptive actions by an extract and compounds from *Phytolacca dodecandra*. Contraception 1976; 14: 39-51.

136. Kong YC, Lau CP, Wat KH, Ng KH, But PPH, Cheng KF, Waterman PG. Antifertility

principle of *Ruta graveolens*. Planta Med 1989; 55: 176-178.

137. Farnsworth NR, Bingel AS, Cordell GA, Crane FA, Fong HHS. Potential value of plants as source of new antifertility agents I. J Pharm Sci 1975; 64: 535-598.
138. Conway GA, Slocumb JC. Plants used as abortifacients and emmenagogues by Spanish New Mexicans. J Ethnopharmacol 1979; 1: 241-61.
139. Salhab AS, Shomaf MS, Gharaibeh MN, Amer NA. Effects of castor bean extract and ricin-a chain on ovulation and implantation in rabbits. Contraception 1999; 59: 395-399.
140. Suganthan D , Santhakumari G . Antifertility activity of indigenous preparation Ayush-47. Indian J Med Res 1979; 70: 504-516.
141. Hiremath SP, Badami S, Swamy HKS, Patil SB, Londonkar RL. Antiandrogenic effect of Striga orobanchoides. J Ethnopharmacol 1997; 56: 55-60.
142. Dhall K, Dogra M. Phase I and II clinical trials with *Vicoa indica* (Banjauri), a herbal medicine, as an antifertility agent. Contraception 1988; 37: 75-84.
143. Bhargava SK. Antiandrogenic effects of a flavanoid-rich fraction of *Vitex negundo* seeds: a histological and biochemical study in dogs. J Ethnopharmacol 1989; 27: 327-339.
144. Harrington WR1, Sheng S, Barnett DH, Petz LN, Katzenellenbogen JA, Katzenellenbogen BS. Activities of estrogen receptor alpha- and beta-selective ligands at diverse estrogen responsive gene sites mediating transactivation or transrepression. Mol Cell Endocrinol 2003; 206: 13-22.
145. Pike AC1, Brzozowski AM, Hubbard RE. A structural biologist's view of the oestrogen receptor. J Steroid Biochem Mol Biol. 2000; 74: 261-268.
146. Makela S.; Hyder S.M.; Stancel G.M.; *Handbook of Experimental Pharmacology*, Vol. 135, Springer-Verlag, Berlin, 1999, pp. 613-663.
147. Fitzpatrick LA. Soy isoflavones: hope or hype?. Maturitas 2003; 44: S21-S29.
148. Waites GM. Development of methods of male contraception: impact of the World Health Organization Task Force. Fertil Steril 2003; 80:1-15.
149. Carlson L, Nilsson BO, Ronquist G, Lundquist M, Larsson A. Identification of prostasomal antigens recognized by autoantibodies from immune infertile man: Abstract of the Third European Congress of Andrology. Andrologia 2004; 36: 141-262.