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Rising trends towards the development of oral herbal male contraceptive: an insight review

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Abstract

Background: Acknowledging population control to be an essential step for global health promotes wide research study in the area of male contraception. Although there are a great number of synthetic contraceptives available in the market, they have plenty of adverse effects. Different potential strategies for male contraception were investigated over a long period time consisting of hormonal, chemical, and immunological interventions, although these methods showed good antifertility results with low failure rates relative to condoms.

Main text: This review is based upon the concept of herbal contraceptives which are an effective method for controlling the fertility of animals and humans. This review has highlighted herbal medicinal plants and plant extracts which have been reported to possess significant antifertility action in males. The review considers those plants which are used traditionally for their spermicidal and antispermatogenic activities and imbalance essential hormones for fertility purposes and plants with reported animal studies as well as some with human studies for antifertility effect along with their doses, chemical constituents, and mechanism of action of the antifertility effect of the plants. This review also explains the phases of sperm formation, hormone production, and the mechanism of male contraceptives.

Conclusion: As far as the relevance of the current review is discussed, it might be quite useful in generating monographs on plants and recommendations on their use. A lot of the plant species listed here might appear promising as effective alternative oral fertility-regulating agents in males. Therefore, significant research into the chemical and biological properties of such less-explored plants is still needed to determine their contraceptive efficacy and also to possibly define their toxic effects so that these ingredients can be utilized with confidence to regulate male fertility. The new inventions in this field are necessary to concentrate on modern, more potent drugs with less harmful content and that are self-administrable, less costly, and entirely reversible.

Keywords: Antifertility, Family planning, Herbal contraceptives, Herbs, Mechanisms, Oral male contraceptives, Overpopulation

Background

Today, overpopulation is a matter of extreme concern for developed nations along with developing countries [1, 2]. In the year 2011, the world population was estimated at 6,928,198, 253 and increasing rapidly at a rate of 83 million citizens per year [3]. Among developing countries, India is densely populated and it is estimated that it will reach about 9.2 billion by the year 2050 [1, 2]. The year 2012 witnessed population figures reaching 1,210,193,422 [1] with an increment of 18 million to the total population every year [2]. According to India's population in 2019, figures are 1,372,717,495 [4]. Increasing population leads to an increase in the demand for resources like water and food, starvation, malnutrition, and consumption of natural resources. Since natural resources are limited, control of the increasing population is a mandatory step [5]. Family planning is an easy and important tool for controlling population burden [6]. On other hand, in

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the USA, the unwanted pregnancy rate is approximately 45% with the help of the various contraceptive options provided to women [7]. Although female contraceptives are much effective in preventing unplanned pregnancy, giving high yielding results, it cannot be used by a greater proportion of sex due to their profuse adverse effects [8].

Talking about extreme measures, the World health Organization has initiated a population control program that includes trials linked to traditional medical activities [2]. Many methods for induction of infertility are implemented over a long period that involves biochemical, biological, and immunological pathways [9] with the least impact but minimal inadequacy [5]. During ancient times, the human reproduction system was not fully established. Hence, the progress in research could not be put into practice due to unclear mechanisms related to human hormones [10].

Main text

Methods and materials

The present study has been geared up with wide-ranging facts of curative plants inhabiting all over the world concerning their accepted tradition by countless ethnic groups for fertility regulation in males. To date, no examination has analyzed the dose, constituents of elements, and mechanism of action of the antifertility effect of plants.

So, information concerning this article has been systematically gathered from the sources of scientific literature, including PubMed, Google Scholar, Science Direct, and Scopus. Simply applicable studies available in the English language were considered. The botanical and English names are considered after validation from available text and database. The criteria followed for the choice of information in this evaluation deliberate folk plant:

1. Found in Ancient Indian medicines
2. With recorded animal studies for effects on infertility as well as those with human studies of antifertility effect

Plants, their parts, or their extracts traditionally used for spermicidal and antispermatogenic activities and those that imbalance essential hormones for fertility purposes have been considered as antifertility agents. Furthermore, compounds isolated from plants with attributed potential for fertility regulation are also classified into 6 categories:

1. Phytoconstituents with spermicidal activity
2. Phytoconstituents with antispermatogenic activity
3. Phytoconstituents acts through Sertoli cells
4. Phytoconstituents acts through Leydig cells
5. Phytoconstituents with antimotility activity
6. Phytoconstituents acts by unbalancing hormones

The following keywords were used to search the literature in the data sources: oral male contraceptives, herbal contraceptives, antifertility, and male contraception.

The need of male contraceptives-a boon for society!!!

Acknowledging population control to be an essential step for global health promotes an opportunity for a large-scale research study in the field of male contraceptives [11]. Male contraceptives originated with the use of a condom in ancient times in Imperial Rome. Researches on male contraception initiated with the sole objective of taking easy targets to the male reproductive system by stopping either the sperm or the testis to function [10]. Although there are a great number of synthetic contraceptives available in the market, they have plenty of adverse effects [5].

Moreover, there is a rise in the need for male contraceptives to avoid unwanted pregnancies because not many men wish to take responsibility for family planning [8]. Also due to the adverse effects of synthetic male contraceptives, the quest for a modern, more effective, more reliable, and less expansive approach is the priority as well as objectives for the pharmaceutical and medical sciences not to forget an unusual self-administration and long-lasting effect of male contraceptives [9]. The new inventions in this field often concentrate on modern, more potent drugs with less harmful content and that are self-administrable, less costly, and entirely reversible [12].

Why not herbals???

Since ancient times, plants are always regarded as a potent source of nourishment that we require for staying healthy along with their valuable components commonly used for food and nutrition, beverages, cosmetics, dyes, medicines, etc. Herbs are excellent examples of being one of the richest sources of nutrients that aim at protecting and restoring a healthy life [13]. As specified by the World Health Organization (WHO) statistics, almost 65–80% of the world's population relies on plant species and their health care products due to the lack of modern facilities and poor conditions. There is a total of 422,000 plant species that have been recorded all over the world, out of which 20,000 species are acclaimed as wild edible species and less than 20,000 of the same community is consumed as a food supplement for 90% of people around the world, contributing to almost 25% of drug formulations from plants or their extracts [14]. The herbal preparations have been used as an oral tradition. It is becoming more popular and useful in modern times as demand for natural remedies/medicines is increasing every day because of the belief of people that they do not have any adverse effects, a boon in disguise [15]. Continuing the traditional system of medicines, more than 35,000 plant species are being used worldwide for medicinal purposes. Following which, more than 80% of the world population is turning to herbal preparations that contain plant extracts for primary health care [2].

Herbal contraceptives are plant-based contraceptives which are effective methods for controlling the fertility of animals and humans [16]. The chemical constituents of plants such as flavonoids, terpenes, tannins, quinines, diterpenoids, and lactones are apprehended to possess antifertility action through a different mechanism [17]. Different potential mechanisms for male contraception have been studied over a long period of time consisting of hormonal, chemical, and immunological strategies [2, 18] though these methods have shown better results of antifertility effects with minimum failure rates than condoms.

In recent years, plants have been reported to be used in the regulation of male fertility because of the better compatibility with the human body, better cultural acceptability, and lesser adverse effects giving it an upper hand [19]. As a result, herbal products attract scientists as a primary source of naturally occurring antifertility agents due to little or negligible adverse signs [17]. For instance, in India, several herbal plants have been reported to have antifertility effects that act through the mechanism by suppression of spermatogenesis or by prevention of implantation [20].

Phases for sperm formation

Testicular carries out two primary goals:

1. Testosterone production
2. Spermatogenesis (origin of haploid germ cells) [8] (Fig. 1)

Flow sheet for production of hormones [21] (Fig. 2)

Pituitary gonadotrophins regulate the functions of the testicles, with luteinizing hormones (LH) acting on the testosterone and producing interstitial cells and the follicle-stimulating hormone (FSH) affecting the cells of the seminiferous tubules. Including the seminiferous epithelium's structural elements, the movement of nutritional growth factor to the haploid germ cells with a near junction in the epithelium for consecutive cells is known as the "blood-testis barrier." Well-performing Sertoli cells supply sufficient mitogens, distinct factors, and energy sources to the growing germ cell, as well as shielding them from the host's own immune system from harmful agents. The number and function of the present Sertoli cells define the spermatogenesis rate and quality [22].

Male contraceptives might work as follows:

1. Suppress sperm production by antispermatogenic
2. Prevention of maturation of sperm
3. Prevention of the flow of sperm through vas deferens
4. Prevention of deposition of the sperm [1]

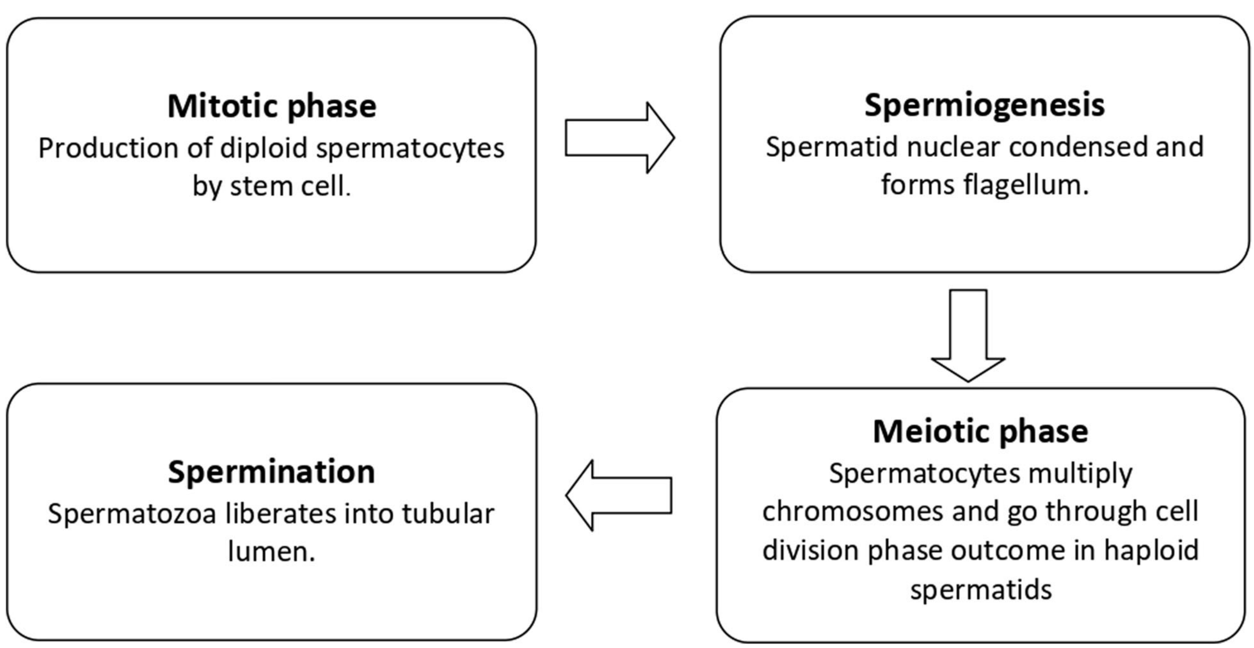

Fig. 1 Different phases by which sperm formation takes place

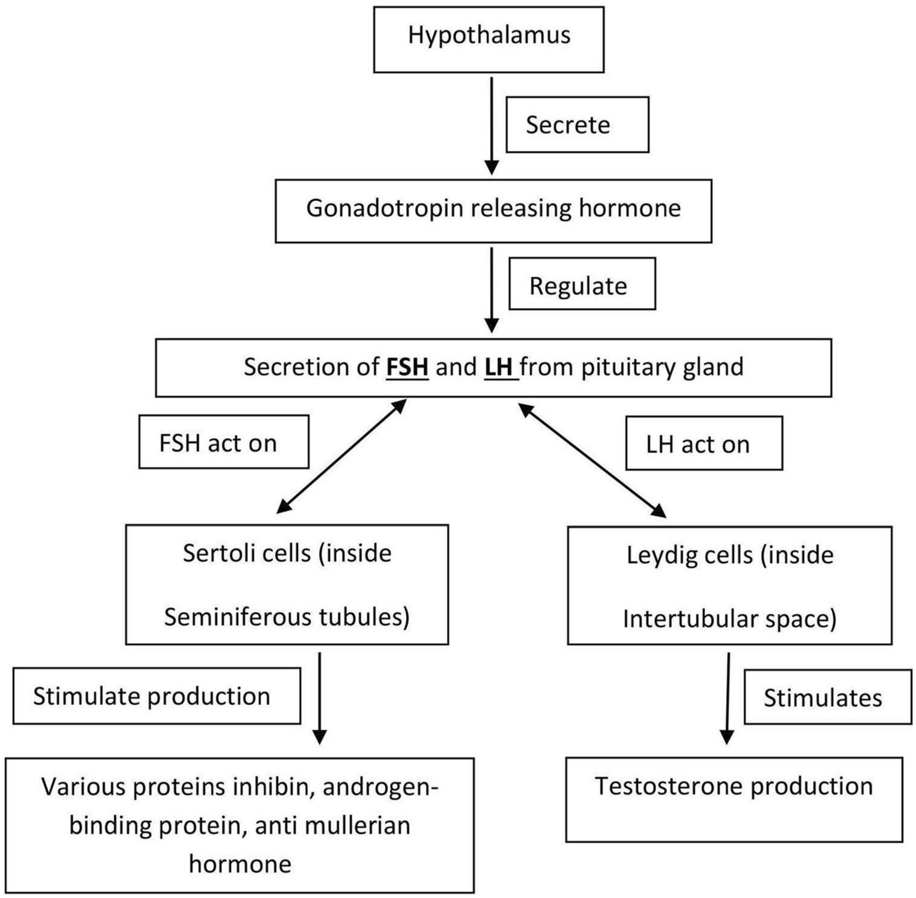

Fig. 2 Release and production of different hormones from glands

Phytoconstituents with spermicidal agents

Ideal spermicidal characteristics include the following: would rapidly and irreversibly achieve sperm immobilization, are not harmful to the vaginal and penile mucosa, do not have any side effects on the growing fetus that are free from long-term topical and systemic toxicity, and should not be ingested systemically [23]. A typical lipid bilayer consisting of outer, intra, and transmembrane proteins is a key component of the plasma membrane of sperms. This lipid bilayer associate with saponin molecules, impacting cell membrane glycoproteins and altering ionic movement across the membrane, resulting in many plants (*Phytolacca dodecadra*, *Calendula officinalis*, and *Acacia caesia*) differing [24]. Sperm immobilization can be caused by the acid pH of lemon juice through the denaturation of ATPase dyein [23].

Phytoconstituents with antispermatogenic activity

The spermatogenesis process involves a complex process:

1. Spermatocytogenesis
2. Spermatidogenesis
3. Spermiogenesis

A diploid spermatogonium undergoes mitotic division in the process of spermatocytogenesis and develops two diploids known as primary spermatocytes. Every primary spermatocyte divides into two haploid secondary spermatocytes by meiosis. Spermiogenesis is the process of spermatid differentiation into mature sperm. It indicates interference in the steroidogenesis when the cholesterol level rises and sudanophilic lipid accumulates [25].

Phytoconstituents acts through Sertoli cells

Sertoli cells are columnar with oval or pear nuclei and thin mitochondria; at the base of their cytoplasm, they have lipofuscin and lipid droplets. The main feature of Sertoli cell structural support for germ cell development is the blood test barrier, which is situated between neighboring Sertoli cells in close junctions. Sertoli cells play an important part in the process of spermatogenesis and adult life as a whole. The plant extracts kill the viability and work of Sertoli cells and have various effects on spermatogenesis, such as reducing the nuclear and cytoplasmic volume and vacuolizing Sertoli cells [26].

Phytoconstituents acts through Leydig cells

Leydig cells are polyhedral with a large prominent nucleus, an eosinophilic cytoplasm, and various vesicles packed with lipids. The hormone-releasing gonadotropin, secreted and synthesized by the hypothalamus, produces and releases LH and FSH from the pituitary gland. LH induces the production of testosterone in the testis Leydig cells [27].

Phytoconstituents with antimotility activity

The sperm passes through three sections of the caput, corpus, and cauda epididymis that are important for sperm maturation [28]. Therefore, the production and secretion of proteins through the epididymis and the completion of various morphological, biochemical, and motile properties during the transformation from epididymis are important for the spermatozoa's full capacity to fertilize [29].

Phytoconstituents acts by unbalancing hormone

Hypothalamus, pituitary gland, and testis secrete the various hormones which regulate spermatogenesis [30]. The Leydig cells synthesize and secrete the major male sex hormone testosterone under the influence of pituitary gonadotropin luteinizing hormone (LH). Several plant products are considered to contain enzymes that are used in androgen synthesis [31]. Quassia Amara's blunt methanol extract shows lower levels of testosterone, LH, and hormone-stimulating follicles (Fig. 3) (Table 1)

Epidemiological studies have shown that the use of combination oral contraceptives increases the possibility of brain thrombosis; enhances the serum triglyceride, high-density lipoprotein (HDL), and cholesterol levels; and also increases family mortality related to cardiovascular diseases as well as malignant tumors in any organ, low resistance to glucose or insulin, diarrhea, abdominal pain, fatigue, hypertension, and menstrual shifts [2].

Patents available are shown Table 2.

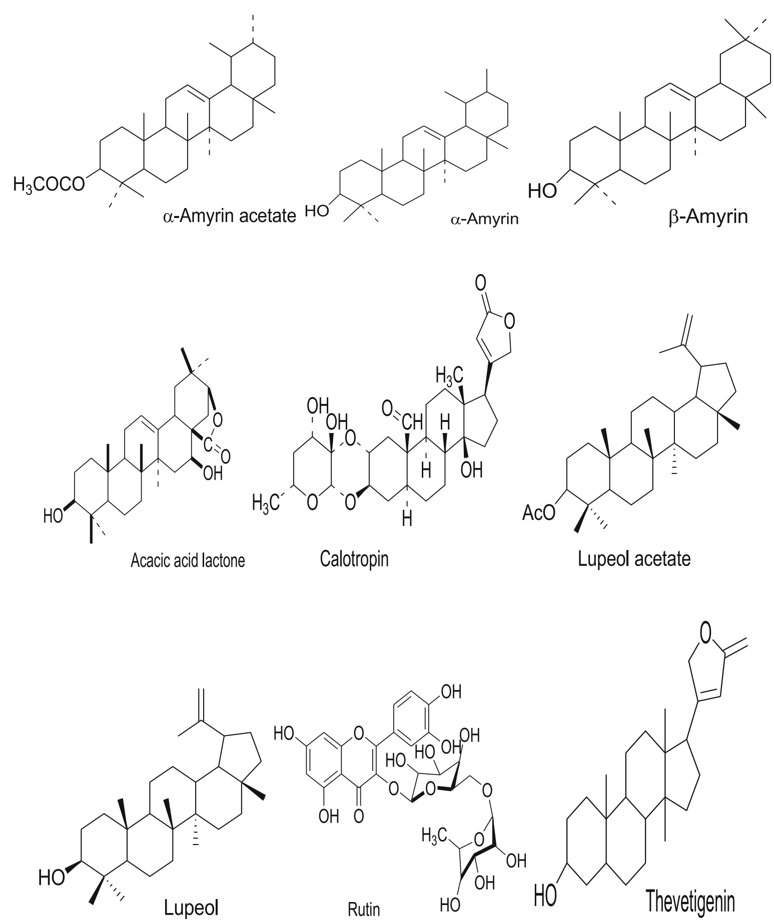

Fig. 3 Isolated compounds from plants having antifertility activity

Table 1 List of traditional plants and isolated chemical compounds from plants having antifertility activity

Sr. no.	Botanical name	Common name	Family	Part used	Subject	Dose	Active constituents	Duration of administration (days)	Mechanism of action	Antifertility activity	References
Phytoconstituents having spermicidal activity											
1.	*Acacia auriculiformis* Benth.	Ear leaf acacia	Fabaceae	Seeds	Human sperm	0.35 mg/ml	Acacic acid lactone	–	Disintegrate sperm plasma membrane and immobilize sperm	–	[32]
2.	*Aegle marmelos* (L.) Corrêa	Bael	Rutaceae	Leaves	Rat	200 and 300 mg/kg Body weight (B.W.) /day	Coumarins, tannis, phenols, rutin	60	Suppress gonadotropic hormone	Reversible	[33]
3.	*Albizia lebbeck* (L.) Benth	Bhandi	Fabaceae	Pods	Rat	100 mg/kg B.W.	Labbekanin-E, saponins	60	Reduce sperm density and sperm motility and decrease testes and prostrate size	–	[34]
4.	*Allium sativum* L.	Lahsun	Lilliceae	Bulb	Human sperm	0.25 and 0.5 g/ml	Allitridum	–	Disrupt membrane architecture	Irreversible	[20]
5.	*Cananga odorata* (Lam.) Hook. f. & Thomson	Ylang yalang	Annonaceae	Root bark	Rat	1 g/kg B.W./day	52-kd protein	60	Decrease androgen production, increase 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase activity, and decrease 3β-hydroxy steroid dehydrogenase enzyme activity	Reversible	[35]
6.	*Cestrum parqui* (Lam.) L'Hér.	Chilean cestrum	Solanaceae	Leaves	Human semen	40, 62.5, 100, 150, and 250 μg/ml	Saponin	–	Disrupt sperm plasma membrane sterol	–	[36]
7.	*Chenopodium album* L.	Lamb's quarters	Chenopodiaceae	Fruits	Rat/rabbit	2 mg/ml	Oleanolic acid, glucuronic acid	–	Disintegrate sperm plasma membrane and cause the dissolution of acrosomal cap causing sperm death	–	[37]
8.	*Chromolaena odoratum* (L.)	Tivra gandha	Compositae	Leaves	Rat	250 and 500 mg/kg B.W.	–	14	Decrease biomolecule concentration and disrupt seminiferous tubules	–	[38]
9.	*Colebrookia oppositifolia*	Bhinda	Lamaceae	Leaves	Rat	100 and 200 mg/kg	5,6,7,4′-tetramethoxy flavones, 5,6,7-trimethoxy flavones, 5,7,4′-trihydroxy flavones 3-o-glucoside	56–70	Reduce sialic acid, fructose concentration, and ascorbic acid	–	[39]
10.	*Juniperus phoenica* (L.)	Cedar	Cupressaceae	Ripe red cones	Rat	400 and 800 mg/kg	α-Pinene, δ-3-carone, β-phellandrene	21	Inhibit LH and gonadotropin-liberating hormone	–	[40]
11.	*Mollugo pentaphylla* L.	Five-leaved carpetweed	Molluginaceae	Aerial part	Human sperm	10, 30, 100, and	Mollugogenol-A (saponin)	–	Plasma membrane-losing osmo-regulatory properties and	–	[41]

Table 1 List of traditional plants and isolated chemical compounds from plants having antifertility activity *(Continued)*

Sr. no.	Botanical name	Common name	Family	Part used	Subject	Dose	Active constituents	Duration of administration (days)	Mechanism of action	Antifertility activity	References
						300 μg/ml			enhance superoxide ions and lipid peroxidation		
12.	*Quassia amara* L.	Bitterwood	Simaraubaceae	Stem wood	Rat	0.1, 1.0, and 2 mg/kg B.W.	Quassin, 2-methoxycanthin-6-one	56	Decrease serum level testosterone, LH, and FSH	Reversible	[42]
13.	*Sapindus mukorossi* Gaertn.	Reetha	Sapindaceae	–	Human Semen	0.05%, 0.1%, 1.25%, and 5%	Saponins, digitonin	–	Disruption and erosion of membrane	–	[32]
14.	*Terminalia chebula* Retz.	Chebulic myrobala	Combretaceae	Dry fruits	Rat	50 and 100 mg/kg/day	Anthraquinones, ellagitamic acid, 4,2,4-chebulyl-β-D-glucopyranose, ellagic acid, gallic acid	60	Inhibit acrosomal enzyme and sperm hyaluronidase enzyme	Reversible	[43]
15.	*Tinospora cordifolia* (Willd)	Guduchi	Menispermaceae	Stem	Rat	100 mg/rat/day	–	60	Reduce plasma level of testosterone and inhibit glycolysis in spermatozoa	–	[44]
16.	*Ziziphus mauritiana* Lam.	Ber	Rhamnaceae	Barks	Human semen	0.1 and 0.5 mg/ml	Saponin	20 s–20 min	Disrupt lipid within sperm membrane	–	[45]
Phytoconstituents with antispermatogenic activity											
1.	*Bacopa monnieri* (L.) Wettst.	Brahmi	Scrophulariaceae	All part	Mice	250 mg/kg B.W. /day	–	28 and 56	Decrease fructose level and inhibit spermatogenesis	Reversible	[46]
2.	*Barleria prionitis* L.	Vajra-danti	Acanthaceae	Root	Rat	100 mg/kg	Barlerin, acetyl barlerin, apigenin-7-o-glucoside	60	Reduce glycogen, protein, and sialic acid content and deplete germinal and Leydig cell constituents	–	[47]
3.	*Cannabis sativa* L.	Ganja	Cannabinaceae	Seeds	Rat	20 mg/day	Cannabinoids	20	Act on cannabinoids receptors	–	[48]
4.	*Chrysophyllum albidum* G.Don	White star apple, vdara	Compodeoidea	Root bark	Rat	100 and 200 mg/kg	Alkaloids, tannis, saponin, phenol, flavonoids	147	Reduce gonadotropins level (FSH and LH) and inhibit spermatogenesis	–	[49]
5.	*Citrullus colocynthis* (L.) Schrad.	Tumba	Cucurbitaceae	Root	Rat	50, 100, and 200 mg/kg B.W./day	Hentriacontane, n-octacosanol, 1,2,6-hexa-cosanediol	60	Inhibit pituitary gonadotropin secretion and reduce sialic acid and protein	Reversible	[50]
6.	*Crotalaria juncea* L.	Sunn hemp	Papilionaceae	Seed	Mice	25 mg/100 g/day	–	30	Reduce seminiferous tubular fluid and decrease protein content, FSH, and LH	–	[51]
7.	*Cuminum*	Jeera	Apiaceae	Seed	Rat	100 mg/	–	60	Sloughing or death of epithelial	–	[52]

Table 1 List of traditional plants and isolated chemical compounds from plants having antifertility activity *(Continued)*

Sr. no.	Botanical name	Common name	Family	Part used	Subject	Dose	Active constituents	Duration of administration (days)	Mechanism of action	Antifertility activity	References
	cyminumin L.					rat/day			cells and reduce glycogen content		
8.	*Curcuma longa* L.	Haldi	Zingiberaceae	Rhizomes	Mice	600 mg/kg B.W./day	–	56 and 84	Inhibit gonadotropin secretion and decrease serum level	Reversible	[53]
9.	*Fadogia agrestis* Schweinf. ex Hiern	Nagbitenga	Rubiaceae	Stem	Rat	18, 50, and 100 mg/kg B. W.	Alkaloids, anthraquinones, flavonoids, saponin	28	Increase cholesterol level and reduce glycogen content	Reversible	[54]
10.	*Hibiscus rosasinensis* L.	Gudhal	Malvaceae	Flower	Mice	150 and 300 mg/kg	–	20	Decrease androgen synthesis and reduce spermatogenic element	–	[55]
11.	*Lepidium meyenii* Walp.	Maca	Brassicaceae	Root	Rat	66.7 mg/ml	–	14	Enhance epididymal weight and reduce stages I–VI of seminiferous epithelium	–	[56]
12.	*Leptadenia hastata*	Cheila	Asclepediaceae	Leaves and stem	Rat	100, 200, 400, and 800 mg/kg	–	60	Reduce Leydig cell and imbalance LH, prolactin, and testosterone serum level hormones	–	[57]
13.	*Momordica charantia* L.	Karela	Cucurbitaceae	Seed	Rat	25 mg/100 g B.W.	–	35	Inhibit gonadotrophins (FSH) and enhance cholesterol level and sudanophilic lipids	–	[58]
14.	*Mondia whitei* (Hook.f.) Skeels	La racine	Periplocaceae	Root	Rat	500 and 1000 mg/kg B.W.	Steriods, triterpenes	30	Reduce intratesticular concentration of cholesterol	Reversible	[59]
15.	*Morinda lucida* Benth.	Brimstone tree	Rubiaceae	Leaves	Rat	400 mg/kg/day	Anthraquinones, anthraquinols	28 and 91	Reduce serum testosterone level and inhibit acetylcholinesterase	Reversible	[60]
16.	*Mucuna urens* L.	Ibaba	Cannabaceae	Seed	Rat	70, 140, and 210 mg/kg B.W.	Flavonoids, anthranoid, anthraquinones, polyphenols	14	Inhibit endogenous gonadotrophic activity	–	[61]
17.	*Ocimum gratissimum* L.	African basil, ram tulsi	Lamiaceae	Leave	Mice	11–88 mg/kg	Eugenol, citral, linalol, charvicol, thymol, gerianol	7, 14 and 28	Deplete Leydig and Sertoli cells and destroy cell membrane	–	[62]
18.	*Parkinsonia aculeate* L.	Vilyati babul	Caesalpiniaceae	Stem bark	Rat	50, 100, and 200 mg/rat/day	α-Amyrin acetate, β-amyrin acetate, 6-hydroxypentacosylpentanoate ethynoma decanoate, 6-hydroxytritriacontan-3-one	60	Reduce testosterone level and Leydig cell diameter and seminiferous tubular diameter	–	[63]
19.	*Piper nigrum* L.	long pepper	Piperaceae	Fruits	Mice	25 and 100 mg/	Piperine	20 and 90	Reduce sialic acid level and decrease fructose concentration	Reversible	[64]

Table 1 List of traditional plants and isolated chemical compounds from plants having antifertility activity *(Continued)*

Sr. no.	Botanical name	Common name	Family	Part used	Subject	Dose	Active constituents	Duration of administration (days)	Mechanism of action	Antifertility activity	References
						kg B.W./ day			in seminal vesicle		
20.	*Ruta graveolens* L.	Rue	Rutaceae	Leave	Rat	500 mg/ kg B.W.	–	60	Reduce serum androgen level and degenerate Leydig cells	–	[65]
21.	*Semecarpus anacardium*	Bhilawa	Anacardiaceae	Fruit	Rat	100, 200, and 300 mg/kg/ day	–	60	Decrease sialic acid content and androgen production (LH)	–	[66]
22.	*Terminalia bellirica* (Gaertn.) Roxb.	Baheda	Combretaceae	Fruit	Rat	10 and 25 mg/ 100 g B.W.	Triphala	50	Reduce androgen level and increase cholesterol level	–	[67]
23.	*Thevetia peruviana*	Lucky nut, Mexican oleander	Apocynaceae	Stem bark	Rat	100 mg/ rat/day	α-Amyrin acetate, lupeol acetate, α-amyrin, β-amyrin, lupeol, thevetigenin	60	Deform and impair Leydig cell and reduce androgen concentration	–	[68]
Phytoconstituents acts through Sertoli cells											
1.	*Azadirachta indica* A.Juss.	Neem	Meliaceae	Leaves	Rat	100 mg/ rat/day	–	48	Degenerate germ cells	Reversible	[69]
2.	*Dendrophthoe falcate* (L.f.) Ettingsh.	Banda	Loranthaceae	Stem	Rat	100 mg/ kg B.W./ day	Quercitrin (quercetin-3-o-rhamnoside), kaempferol, rutin	60	Decrease seminiferous tubular fluid and reduce androgen synthesis and sialic acid	-	[70]
3.	*Thespesia populnea* (L.) Sol. ex Corrêa	Tulip tree	Malvaceae	Leaves	Mice	400 mg/ kg B.W.	–	15	Elongate seminiferous tubules	–	[71]
4.	*Tripterygium wilfordi* Hook. f.	Yellow vine root	Celastraceae	Root	Rat	100 mg/ kg/day	–	–	Degenerative changes of seminiferous epithelium and reduce reproductive cells in testes	Irreversible	[72]
Phytoconstituents acts through Leydig cells											
1.	*Berberis chitria* Buch.-Ham. ex Lindl.	Daruhaldi	Berberidaceae	Root	Dog	30 mg/ kg/day	Palmitine hydroxide	60	Decrease postmeiotic germ cells and decrease androgen binding protein of Sertoli cells via FSH	–	[73]
2.	*Calotropis procera*	Camelweed	Asclepiadaceae	Roots	Gerbil/ rabbit	25 mg/ kg B.W.	Calotropin	30	Suppress testicular function by decreasing androgenic parameter	–	[74]
3.	*Garcinia cambogia*	Malabar tamarind	Cluciaceae	Seed	Rat	100 and 200 mg/ kg B.W.	Biflavonoid, xanthone	42	Enhance interstitial spaces and reduce Leydig cells in interstitial space and seminiferous tubules contraction	–	[75]
4.	*Malvaviscus conzattii* Greenm.	Turk's cap mallow	Malvaceae	Flower	Rat	800 mg/ kg B.W. /day	–	30	Reduce germ cells and impairs function of epididymides	–	[76]

Table 1 List of traditional plants and isolated chemical compounds from plants having antifertility activity *(Continued)*

Sr. no.	Botanical name	Common name	Family	Part used	Subject	Dose	Active constituents	Duration of administration (days)	Mechanism of action	Antifertility activity	References
5.	*Martynia annua* L.	Scorpion	Martyniaceae	Root	Rat	50, 100, and 200 mg/kg B.W.	–	30	Reduce scrum concentration of LH and testosterone	Reversible	[77]
6.	*Ocimum sanctum* L.	Tulsi	Lamiaceae	Fresh leaves	Rabbit	2 g/day	–	30	Reduce pH, mucoprotein, and alkaline phosphatase and make non-viable spermatozoa	Reversible	[21]
Phytoconstituents with antimotility activity											
1.	*Carica papaya* L.	Papita	Caricaceae	Seeds	Monkey	50 mg/kg B.W. /day	–	360	Hasten sperm transport leading to ejaculation and affect composition of epididymal fluid and their enzymes on spermatozoa	Reversible	[78]
2.	*Echinops echinatus* Roxb.	Utakatira, oontkateli	Asteraceae	Roots	Rat	50, 100, and 200 mg/kg B.W. /day/rat	Echinopsine, echinopsidine, echinozolinone	60	Reduce concentration of protein in the cauda epididymis and testicular glycogen level and reduce ascorbic acid content of the adrenal gland	–	[79]
3.	*Gossypum herbaceum*	Cotton	Malvaceae	Fruit	Rabbit	20 mg/day	Gossypol acetic acid	84	–	–	[80]
4.	*Lagenaria breviflora* (Benth.) Roberty	Molina	Cucurbitaceae	Whole fruit	Rat	1000, 2000, 4000, and 8000 mg/kg B.W.	–	14	Degenerate seminiferous tubules	–	[81]
Phytoconstituents acts by unbalancing hormones											
1.	*Abelmoschus esculentus* (L.) Moench	Okra	Malvaceae	Fruit	Rat	70 mg/kg B.W./day	Flavonoids, saponins	28	Reduce serum testosterone level and spermatogenesis	Reversible	[82]
2.	*Abrus precatorius* L.	Coral bead vine, rosary pea, ratti	Leguminosae	Seed	Rat	250 mg/kg	Abridine	30 and 60	Impair function of sperm plasma membrane, suppress oxidative/energy metabolism, and reduce sperm motility	Reversible	[83]
3.	*Bulbine natalensis* Baker	Bulbine	Asphodelaceae	Stem	Rat	25, 50, and 100 mg/kg B.W.	Alkaloids, tannis, anthraquinones	7	Reduce serum testosterone and progesterone levels	–	[84]
4.	*Curcuma longa* L.	Haldi	Zingiberaceae	Rhizomes	Rat	500 mg/kg/day	–	60	Decrease androgen synthesis and Leydig cell nuclei diameter and inhibit Leydig cell function	–	[85]

Table 1 List of traditional plants and isolated chemical compounds from plants having antifertility activity *(Continued)*

Sr. no.	Botanical name	Common name	Family	Part used	Subject	Dose	Active constituents	Duration of administration (days)	Mechanism of action	Antifertility activity	References
5.	*Psoralea corylifolia* L.	Babchi	Leguminosae	Seeds	Rat	10 g/kg B.W.	Corylin, bavachin, psoralen, isopsoralen, psoralidin	84	Decrease serum testosterone and FSH levels and suppress pituitary testicular axis	–	[86]
6.	*Stevia rebaudiana*	Sugar leaf	Asteraceae	Leave	Rat	2 ml/rat	Stevioside	60	Decrease androgen level	Irreversible	[87]
7.	*Syzygium aromaticum* (L.) Merr. & L.M.Perry	Lavang	Myrtaceae	Flower buds	Mice	15, 30, and 60 mg/kg B.W.	Eugenol, β-caryophyllene	35	Destroy germ cells and inhibit spermatogonia	–	[88]

Conclusion

Different potential strategies for male contraception were investigated over a long period time consisting of hormonal, chemical, and immunological interventions, although these methods showed good antifertility results with low failure rates relative to condoms. The present study showed the literature data that there is majority of plants, which are traditionally used as antifertility agents and their effects have not been thoroughly studied on animals. The majority of tests have been performed on conscious animals and relatively few tests have had their efficacy confirmed in humans. Herbal contraceptives are safer and cheaper methods for population overcoming. To summarize, a lot of the plant species listed here might appear promising as effective alternative oral fertility-regulating agents in males. Among plant parts, leaves have been maximally utilized for controlling fertility. As far as the relevance of the current review is discussed, it might be quite useful in generating monographs on plants and recommendations on their

Table 2 List of patents on a male contraceptive

Summary of invention	Patent number	Inventor/assignee
Substituted acylanilides and methods of use thereof	AU2015264895B2	Dalton, James, Miller, Duane D.
Styrene maleic anhydride based formulation for male contraception and prostate cancer	EP 2 268 290 B1	Guha, Sujoy Kumar
Lonidamine analogs and their use in male contraception and cancer treatment	EP 2 502 624 A1	Chakrasali, Georg, Jakkaraj, Tash
Orally active 7-alpha-alkyl androgens	EP1212345B1	Louw Van Der, Leysen, Buma Bursi
Methods of making the 4-n-butylcyclohexanoic and the undecanoic acid esters of (7 alpha, 11 beta)-dimethyl-17 beta-hydroxy-4-estren-3-one and their medical use	EP1272196B1	Blye, Kim
Oral pharmaceutical composition comprising 15-hydroxytestosterone and its analogues	EP1551415B1	Bunschoten, Coelingh Bennink, Van Der Linden
Male contraceptive formulation comprising norethisterone	US20020103176A1	Eberhard Nieschlag, Axel Kamischke, Michael Oettel, Alexander Ruebig, Ekkerhard Schillinger, Habenicht Ursula-Friederike
Male contraceptive method and composition	US20020164368A1	Ronald Zimmerman
Androgen as a male contraceptive and non-contraceptive androgen replacement	US20020193359A1	Alfred J. Moo-Young
Reversible infertility in male mice following oral administration of alkylated imino sugars: a non-hormonal approach to male contraception	US20040019082A1	Aarnoud C. Van Der Spoel, Mylvaganam Jeyakumar, Terry D. Butters, Raymond A. Dwek, Frances M. Platt
Non-hormonal compositions and methods for male contraception	US20190290615A1	Guillaume Ei Glaoui, Mehdi Ei Glaoui, Philippe Perrin, Stéphane Droupy, Véronique Agathon–Meriau
Reversible male contraception	US4252798	Donald J. Tindall
Male contraceptive steroids and methods of use	US4297350	John C. Babcock; J. Allan Campbell, Thomas J. Lobl,
Oral male contraceptive	US4381298	Patricia B. Coulson, Sheffield Dr.
Male contraceptive implant	US5733565	Alfred J. Moo-Young, Saleh I. Saleh
Male contraceptives	US5854254	Susan H. Benoff
Buccal drug delivery system for use in male contraception	US6180682	Virgil A. Place
High-strength testosterone undecanoate compositions	US9480690	Chandrashekar Giliyar, Basawaraj Chickmath, Nachiannan Chidambaram, Srinivansan Venkateshwaran
Male contraceptive comprising a prolactin inhibitor and a sex steroid	WO1999066935A1	Lincoln, Kirkton Cottages, WU
A pulmonary drug delivery composition containing a progestogen and androgen for use in a contraceptive method in males	WO2003068315A1	Coelingh Bennink, Van Der Linden
Novel spermicidal and anti-infective contraceptive device	WO2007074478A1	Jain Rajesh, Jindal Kour Chand
Substituted (5,6)-dihydronaphraalenyl compounds as reversible male contraceptives	WO2008137081A1	Wolgemuth Debra J., Reczek Peter R.
Inhibitors of eppin/semenogelin binding as male contraceptives	WO2009042565A2	O'rand Michael G., Widgren Esther Elaine, Richardson Richard, Temple Brenda
Non-hormonal male contraceptive agents and methods using same	WO2016205539A1	Yan Wei
Piperidine-dione derivatives for use as contraceptives	WO2018211276A1	Sieng Bora, Lundvall, Steffi, Claudia Alejandra

use. Therefore, this review has highlighted the significant antifertility activity of herbal medicinal plants and their extracts. Moreover, this review can concentrate the interest of researchers on toxicity studies of phytoconstituents and their clinical trials, which may serve as an alternate potential antifertility agents with milder or fewer side effects and can be developed into suitable contraceptive formulations. Therefore, significant research into the chemical and biological properties of such less-explored plants is still needed to determine their contraceptive efficacy and also will possibly define their toxic effects so that these ingredients can be utilized with confidence to regulate male fertility.

Abbreviations
LH: Luteinizing hormonesFSHFollicle-stimulating hormoneHDLHigh-density lipoproteinB.W.Body weight

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Authors' contributions
We declare that this work was done by the authors named in this article: SV conceived and designed the study. AY carried out the literature collection of the data and writing of the manuscript. AY and SV assisted in the data analysis and corrected the manuscript. The authors read and approved the final manuscript.

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