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Medicinal Plants as a Potential Source of Male Contraceptive Agents

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Abstract

To control the population explosion in the world, new methods of contraception involving men is an attractive alternative. Since ancient times, plants and plant based products have been used as a valuable and safe natural source of medicines for treating various ailments. India possesses a vast reserve of medicinal plants which have been used extensively in the treatment of various diseases. The reversibility of antifertility effects of plants and its active components, play a major role in development of male contraceptive agents. The present review attempts to discuss medicinal effects of plant derived products on male reproductive system.

Keywords: Male contraception; Medicinal plants; Spermatogenesis; Antifertility effect; Testosterone.

Introduction

The world's population has risen to an alarming level especially in developing and underdeveloped countries and has detrimental effects on life supporting system [1]. Plants continue to be major source of medicines throughout human history. A wide majority of herbal plants possess pharmacological principles, which has rendered them useful as curative for numerous diseases. The World Health Organisation (WHO) reports that 70%-80% of the world's population confide in traditional medicines for primary health care [2]. Therefore, exploring traditionally reported medicinal plants to liberate their potential for the betterment of human health is of paramount importance. Several plants are reported to exert toxic effects on male reproductive organs including testis, epididymis, accessory sex glands and associated hormones [3,4]. The present review highlights the plants and their products that can be used as potential male antifertility agents.

Main Body

Plants possessing antifertility activities include the following :-

***Abrus precatorius* Linn** (Fabaceae) Eng- Indian Liquorice, Hindi- Gunchi, Rati. A climber found throughout India, upto an altitude of 1050 meters in the outer Himalayas. It's alcoholic seed extract given to sexually mature rats (100 mg/kg, p.o.) for 60 days resulted in significant lowering of sperm motility and sperm morphology (decapitation, acrosomal damage and formation of bulges on mid-piece region of sperm) [5]. Steroidal fraction of this seed injected in rats (30 mg i.m., alternating days for 20 days) caused testicular lesion manifesting in cessation of spermatogenesis [6]. A dose dependent testicular degeneration was observed with rats injected with (100, 200 and 300 mg respectively) of steroidal fraction of seeds [7]. Ethanolic extract of air dried seed powder (1 mg/ml/day, IP for 12 days) exhibited antispermatogenic activity in albino rats.

Histology of testicular follicle showed degeneration and spermatogenic arrest, reduced leydig cells and shrunken seminiferous tubules [8]. Oral administration of 50% ethanolic extract of seed (250 mg/kg) for 30 days and 60 days induced a total infertility in male albino rats, a condition which however was reversible. Suppression of sperm motility was most pronounced effect of this treatment.

Aecia auriculae formis A. Cunn ex.Benth (Minosaceae). Sperm immobilizing effects of mixture of the triterpene saponins acacia side A and B (obtained from this plant) have been studied in *in-vitro*. The lowest concentration (ED) required for immobilization of human sperm using a modified Sander-Crammer test was found to be 0.35 mg/ml. Compounds were more potent as compared to Tritonx -100 using the cervical mucus penetration test. The ED successfully prevented the sperm entry in the human cervical mucus. Electron microscopy revealed plasma membrane disintegration and dissolution of acrosomal cap of the sperm [9]. The 50% ethanolic extract of plant has been reported to have spermicidal activity. A sinuata-saponin (acacic acid) obtained from the bark was also found to exhibit spermicidal activity against human spermatozoa. Its maximum activity was observed at 0.04% dilution.

Aegle marmelos Linn (Rutaceae) Eng-Bael tree, Hindi-Bael. A moderate size slender tree, growing wildy throughout the deciduous forest of India up to an altitude of 1200 meters in height. Administration of ethanolic extract of its leaves in rats (25 and 50 ml/kg, p.o.) for 30 days led to significant decrease in weight of testis, reduced sperm count, decreased sperm motility and decrease in both protein and RNA content of testis [10].

Aeschynomene indica Linn (Fabaceae) Eng- Hard Sola, Hindi- Laugauni

An erect, slender, shrubby, annual found throughout India. It ascends up to 1500 meters in foot hills and in Andaman Islands. Fifty percentethanolic extract (in 2% concentration *in-vitro*) has been reported to possess spermicidal activity against both rat and human spermatozoa [11].

Agave cantala (Haw) (Agaraceae) Eng- Bombay aloe. A perennial stout scapigerous plant with short woody stem native to Mexico.Ethanolic extract (2%) of its rhizome and its spirostomal constituents has shown to possess spermicidal activity against human spermatozoa [12].

Aesandra butyracea (Roxb) sapotaceaeEng- Hill mahua, Indian-Butter tree, Hindi – Phalwara. Large deciduous tree found in the sub-Himalayan tract from Gharwal to Bhutan up to an altitude of 1500 meters and in Andaman Islands. Bassicacid, asapogenin isolated from the seeds has been reported to possess some spermicidal activity against human semen [13].

Albizia chinensis (Osbeck) Mimosaceae, Hindi- siran. A large deciduous tree distributed throughout the sub-Himalayan valleys up to 1200 meters altitude. They are found in Assam, West Bengal, Bihar, South India and Andaman. Ethanolic extract of bark and its triterpenic constituents possess spermicidal activity against human spermatozoa. Oleanolic acid, echinocystic acid and its two echinocystic acid based saponins led to complete immobilization of human

spermatozoa at 0.5, 0.09, 0.008 and 0.006% concentrations, respectively [14].

A. lebeck (Linn)-Ethanolic extracts of its pods and root at a concentration of 2% as well as saponinlebbekinin E exhibited spermicidal activity in rat and human semen [15].

Allium sativum Linn (Alliaceae) Eng- Garlic, Hindi-Lahsan. A hardy perennial herb is cultivated all over India. Chronic administration of garlic powder (50 mg for 70 days) resulted in inhibition of spermatogenesis in albino rats. Reduced concentration of sialic acid in testis, epididymis and seminal vesicle with decreased Leydig cells function reflected antiandrogenic nature of garlic [16].

Aloe vera Linn (Liliaceae) Eng- Indian aloe Hindi-Gheekanwar. A coarse looking perennial herb with a short stem and fleshy leaves, found wild in many parts of the country but now widely cultivated. Aloin, a glycoside isolated from its leaves was given to Presbytislangurs (62.5 mg/day, p.o.) for 120 days. A significant reduction was observed in spermatid cells (33.68%), semiferous tubules and leydig cells was observed [17].

Anagallis arvensis Linn (Primulaceae) Eng- Blue Pimpernel Hindi- Joukumari Krishna Neel. A small much branched annual herb found over the greater parts of India that growup to an altitude of 2400 meters in the hills. Anagalligenone, the sapogenin isolated from the plant, revealed spermicidal activity in human semen at a concentration of 0.008% [13].

Andrographis paniculata (Burm f) Acanthaceae) Eng-The creat, Hindi- Kalmegh. An erect annual herb found in the plains throughout India. Supplementation of dry leaf powder to male rats (20 mg/day, p.o.) for 60 days resulted in cessation of spermatogenesis, degenerative changes in semiferous tubules, epididymis, seminal vesicle and leydig cells. Results suggested anti-spermatogenic and/ or an anti androgenic effect of the plant [18].

Anethum sowa Roxb (Apiaceae) Eng- Indian Dill, Hindi-Sowa. An annual aromatic herb cultivated throughout India mainly in Punjab, UttarPradesh, Gujarat, Assam, Maharashtra and West Bengal. Volatile oil was tested for its spermicidal activity in the ejaculated human spermatozoa *in vitro*. At a dilution of 1:10 the oil exhibited spermicidal activity, in just 30 seconds [19].

Anisomeles malabarica Linn (Lamiaceae) Eng- Malabar. A densely pubescent, perennial herb commonly found in the western ghats from Maharashtra to Karnataka and Andhra Pradesh, Kerala and Tamil Nadu. Spermicidal activity in rat was observed with 5% ethanolic extract and in human semen at 2% concentration [11].

Ardisia thyriflora D. Don (Myrsinaceae). The 50% ethanolic extract of this plant (*in vitro*) showed spermicidal activity in male albino rat and human semen. The saponinsardisioside A and B isolated from n-butanol extract were reported to kill the human spermatozoa at 0.1% concentration [20].

Argemone mexicana Linn (Papaveraceae) Eng- Mexican poppy, Hindi- Piladhatura. An erect prickly annual herb naturalized throughout India up to an altitude of 1500 meters

in height. Three isoquinone alkaloids from its seeds (dihydropalmatine hydroxide I, berberine II, protopine III) given to male dogs (30 mg/kg for 70 days) resulted in inhibition of spermatogenesis at the stage XII of late spermatids. Tests showed spermatids and leydig cells were also decreased [21].

***Aristolochia indica* Linn** (Aristolochiaceae) Eng- Indian birthwort, Hindi- Isarmul. A perennial climber present throughout India in plains and lower hills. In adult male rats, administration of p-coumaric acid (50 mg/kg, p.o. for 56 days) produced loss of libido and decrease in weight of testis [22].

***Asparagus officinalis* Linn** (Asparagaceae) Hindi-Halyun. An erect widely branched perennial, native to temperate Europe and West Asia and is often grown in India. The sprost and glycosides obtained from methanolic extract of its fruits led to 100% immobilization of human spermatozoa at 1.5% concentration [23]. A. Plumosus- 2-yamogenin and 2-furostanol glycosides isolated from the alcoholic extract of root caused 100% immobilization of human spermatozoa at 1% and 1.5%, levels respectively [24].

***Azadirachta indica* A Juss** (Meliceae) Eng- margosa tree, Hindi- Neem. A large evergreen tree commonly found throughout India and is often cultivated. Spermicidal activity of nimbidinate has been studied *in vitro* in male rats and human semen. Neem oil exhibited strong spermicidal activity (within 30 second) in *in vitro* studies in Rhesus monkey and human spermatozoa [25]. Anti-fertility activity of the plant has also been reviewed by Hussain and Shiva Reddy in 1999 [26].

***Barleria prionitis* Linn** (Acanthaceae) Hindi- sahadara. A small branched, spiny shrub found growing throughout hotter parts of India. Oral administration of root extract to male rats (100mg/day for 60 days) led to reduced spermatogenesis. Spermatids production decreased by 73.6%. The extract reduced the fertility of male rats by 100%. Numbers of sertoli cells and mature leydig cells were also found reduced (36.9%) [27].

***Berberis chitria* Lindl** (Berberidaceae). A large shrub distributed in Himalayas from Kashmir to Bhutan that grow to an altitude of 1800-3000 meters. Palmitive hydroxide isolated from roots of this plant when given to male dogs (30 mg/kg/day) for 60 days resulted in impairment of primary and secondary spermatocytes and elongated spermatids (stages IV-VIII). Primary and secondary spermatocytes were reduced by 60% and 68%, respectively. Anti-spermatogenic action of palmitive hydroxide might be mediated by disturbances in Leydig cell function [28].

***Blighia sapida* Koen** (sapindaceae) Eng- Akee tree. A medium-sized tree occasionally cultivated in some parts of Maharashtra, West Bengal and Tamil Nadu. Saponins having hederagenin and oleanolic acid as sapogenin and glucose, rhamnose, arabinose and xylose as sugars, isolated from fruits were reported to have spermicidal action in human semen [13].

***Calendula officinalis* Linn** (Asteraceae) Eng- Garden marigold, Hindi- Zergul. An aromatic erect herb native to Southern Europe commonly cultivated in Indian gardens. The 50% ethanolic extract of plant showed spermicidal activity in rats at 2% concentration [11].

***Calotropis procera* (Ait) Asclepiadaceae** Eng- Madar tree, Hindi- Madar. A small erect and compact shrub found throughout India up to an altitude of 1050 meters in height. Oral administration of flower and root extracts (20 mg for alternating days x 30 days) to desert male gerbils (*Meriones Hurrianae*) revealed testicular necrosis, degeneration of spermatogonia, spermatocytes and sertoli cells [29]. Calotropin administered to gerbils (25 mg/kg) and rabbits (25 mg/kg/day) for 30 days inhibited spermatogenesis. The population of spermatids was decreased by 65% and 95% in gerbils and rabbits respectively [30].

***Caltha palustris* Linn** (Ranunculaceae) Eng- Marsh Marigold. A highly variable polymorphic aquatic herb found in the marshes throughout the Himalayas from Kashmir to Sikkim that grow to an altitude of 5000 meters in height. Butanol soluble fraction and ethanol extract of plant revealed *in vitro* spermicidal activity in human serum. Ethanol extract (2% concentration) has been observed to possess spermicidal activity in rat and human semen [11].

***Canscora decussate* (Roxb) Gentianaceae**. Hindi- Sankhaphuli. A slender, erect, somewhat flaccid annual distributed throughout India in damp locations. Spermicidal activity of fraction I and II isolated from alcohol and aqueous extracts were studied *in vitro* on human semen and rat sperm. Minimum concentrations of fraction I and II was found to kill rat sperms within 5 minutes at levels of 1:50000 and 1:200, respectively. Furthermore, aqueous extract provided an effective male antifertility agent when given to male rats for 30 days [31].

***Carica papaya* Linn** (Caricaceae) Eng- Papaya Hindi- Papita. Papaya was introduced into India in the 16th century and now it is widely cultivated throughout India. A number of studies have reported antifertility action of seeds of papaya (20 mg/rat/day) on administration for 8 weeks. Aqueous, alcoholic and chloroform extracts of seeds affecting sperm motility in rats has been noted. In male rabbits and langur monkeys, chloroform seed extracts (20-50 mg/day X 150 days) administration led to azoospermia and oligospermia [32].

***Casearia tomentosa* Roxb** (flacourtiaceae) Hindi- Chilla. A shrub/tree found throughout India, up to an altitude of 900 meters in the hills and Andaman Islands. Administration of 50% ethanolic extract of leaves in male rats (100 mg/kg, p.o. for 21 days) exhibited significant antifertility activity [33].

***Catharanthus roseus* Linn** (Apocynaceae) Eng- Madagascar Periwinkle Hindi- Sadabahar. An erect perennial herb, native to Malagasy is also commonly grown in gardens throughout India. Aqueous and alcoholic extracts of leaves have demonstrated anti-androgenic and antifertility effects in male albino rats [34].

***Celastrus paniculatus* willd** (Celastraceae) Eng- Black oil plant, Hindi- Malkangani. A large woody climbing shrub distributed almost all over India that grow up to an altitude of 1800 meters in height. Supplementation of seed oil given in rats (0.2 ml/rat for 30 days) showed an anti-spermatogenic effect. The oily extract from seeds also led to vacuolization, germ cell depletion and arrested spermatogenesis in testis of rats [35].

***Centratherum anthelminticum* Linn** (Asteraceae) Hindi-Somraj. A tall, leafy, annual herb distributed throughout India that grow up to 1677 meters in the Himalayas and Khasia hills. The seed extract has been reported to have spermicidal activity in rats but not such activity in human beings [11].

***Cheiranthus cheiri* Linn** (Brassicaceae) Eng- Gilli, Hindi-Todri-Surkh. An erect or ascending perennial herb native to southern Europe. It is sometimes cultivated in gardens in northern and western India. Oral administration of Kaempferol (250 mg/kg/day x 60 days), a compound isolated from the herb's stem, induced antifertility (71%) in male rats [36].

***Cichorium intybus* Linn** (Asteraceae) Eng- Chicory Hindi-Hinduba. An erect perennial herb native to temperate parts of the world and is found wild in Punjab and Andhra Pradesh. It is often cultivated in Bihar, Himachal, Assam, Maharashtra, Gujarat, Tamil Nadu, Orissa, Andhra Pradesh and Kerala. Chicory dry root powder extracted from the herb and administered to mice (8.7 g/kg x 10 days) demonstrated impairment of spermatogenesis [37].

***Cinnamomum zeylanicum* Nees** (Lauraceae) Eng- Cinnamon Hindi- Dalchini. A moderate sized tree, native to Sri Lanka and cultivated in southern India. The oil of cinnamon has demonstrated *in vitro* spermicidal activity against human spermatozoa at a dilution of 1:400 [19].

***Citrullus colocynthis* Linn** (Cucurbitaceae) Eng- Indian wild Gourd Hindi- Indrayan. Ascabrid perennial with prostrate or climbing angular stems and bifid tendrils found in warm, arid and sandy parts throughout India. The 50% ethanol extract of its root administered at various concentration (50, 100 and 200 mg/kg/day p.o. for 60 days) to male rats showed decreased sperm motility, density and spermatogenesis arrest. A marked reduction in serum testosterone was also observed in all treatment groups [38].

***Clerodendrum serratum* Linn** (Verbenaceae) Hindi-Bharangi. A blue flowered shrub widely distributed throughout India. The 50% ethanolic extract of the plant demonstrated *in vitro* spermicidal activity in rat and human semen [11]. An N-butanol fraction of 50% ethanolic extracts of the plant also exhibited *in vitro* spermicidal activity in humans.

Clinopodium umbrosum (BiebLabiataeaceae) Eng-Catmint, Hindi-Janglipudina. A slender, pubescent, profusely branched herb distributed in the Himalayas from Kashmir to Bhutan, Andhra Pradesh, Khasi hills and throughout the hills of peninsular India. The 50% ethanolic extract of the plant has been reported to possess spermicidal activity in rat semen *in vitro* [11].

***Colebrookia oppositifolia* Smith** (Lamiaceae) Hindi-BindaPansra. A densely tomentose hoary, widely branched shrub or small tree found throughout the hilly areas of India. Supplementation of ethanolic extract of its leaves in rats at different concentrations (100, 200 mg/kg p.o.) for 10 weeks significantly decreased the weight of testis and epididymis and reduction in spermatogenesis in rats. Reduction in sperm motility and count resulted in 100% infertility in rats by 200 mg/kg of ethanol extract [39].

Cotula hemisphaerica (Roxb) Asteraceae. An annual prostrate or erect herb that grows upto a height of 800meters, found in Indo-gangetic plain, UP, Bihar, West Bengal, Assam, Manipur and Meghalaya. The ethanolic extract (50%) of the plant has been demonstrated to possess spermicidal activity in rats [40].

Deeringia amaranthoides (Lamk) Amaranthaceae. Hindi- Latman. A climbing shrub found in the sub-Himalayan tracts from Chenab to Bhutan, Bihar, west Bengal and Assam. The 50% ethanolic extract of plant revealed spermicidal activity in rats *in vitro*. Ethanolic extract of its fruits (1%) also showed spermicidal activity against rats and human spermatozoa [41].

Derris indica (Lank) Fabaceae. Eng- Pongam oil tree Hindi- Karaj. A medium-sized, glabrous tree found almost that grows upto an altitude of 1200 meters in height. Seed oil has been reported to produce strong spermicidal activity. Motility of sperm from healthy men was completely lost (0.2%) within 20 seconds in presence of its three oil [42].

***Dimeria gracilis* Nees** (Poaceae). A perennial stout grass found in Tamil Nadu and Karnataka. The 50% aqueous ethanolic extract possess strong spermicidal activity against rat and human spermatozoa (2% concentration) *in vitro* [43].

Diploknema butyracea (Roxb) Sapotaceae. Eng – Indian Butter tree, Hindi- Phulwara. A large deciduous tree commonly found in sub-Himalayan tracts from Uttrakhand east wards to Sikkim, Bhutan and the Andaman Islands. The sapogenin (bassic acid) obtained from seeds has exhibited spermicidal activity against human spermatozoa. Its maximum activity was observed at 0.006% dilution [44].

Miscellaneous

Sarcostemma acidum- Methanol extract (100 mg) when administered to male albino rats for 60 days, caused a decrease in the number of mature leydig cells and an increase in degeneration of leydig cells [45].

Martynia annu- Ethanol extract (100 mg, 200 mg/kg) administered for 60 days resulted in Leydig cell atrophy and reduction in serum concentration of LH and testosterone [46].

Leptadenia hastate Decne- Aqueous extract of leaf and stem has been reported to reduce velocity, linearity and sperm motility of male wistar rats [47]. Leydig cell nuclear area and mature leydig cells numbers were also significantly reduced on oral administration of 70% methanol extract of *Tinospora cardifolia* stem to male rats (100 mg/rat for 60 days) [48].

Mentha piperita labialae (20 mg/L) and ***Mentha spicata labiatae*** (20 mg/L)- These herbal teas when fed to wistar rats increased serum FSH and LH levels and decreased total testosterone levels [49]. Administration of ethanol extracts of *Colebrookea oppositifolia* (200 mg, p.o. for 8-10 weeks) was associated with a decrease in the nuclear and cytoplasmic surface area of Leydig cells [50].

Conclusion

Keeping in view of the above discussion, medicinal plants can be used as effective anti-fertility agents, especially considering their effects on male reproductive physiology. Isolation and characterization of pharmacologically active compounds, safety, quality, efficacy of plant preparations are key issues, all of which need to be addressed before developing a potential herbal male contraceptive agent.

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