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MALE INFERTILITY: A MAJOR PROBLEM WORLDWIDE AND ITS MANAGEMENT IN *AYURVEDA*

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ABSTRACT

Infertility is a major reproductive health problem today, affecting 10 to 15 percent of couples seeking to have children. Male infertility problems may be contributory to 30 to 40 percent of infertile couples. The infertile male partner has qualitative or quantitative abnormalities of sperm production and other sexual disorders as major factors responsible for infertility. There have been no drugs available from western medicine system (Allopathic system of Medicine), evaluated clinically to improve the sperm count or to improve libido so as to be used as aphrodisiac. The therapies adopted to improve sperm count or to improve libido are accompanied by serious side effects. The importance of sexuality in human life is well recognized in *Ayurveda* as '*Vajikarana adhikara*' or virilification therapy. "*Vajikarana"* is the branch of *Ayurveda*, which deals with all types of physical and psychological sexual problems like impotence, libido, poor erection, and early ejaculation in males. *"Vajikarana"* includes the utilization of plants and other substances from natural sources as aphrodisiacs for erectile dysfunction, infertility, impaired spermatogenesis, methods of correcting defective semen and sexual satisfaction. *Ayurveda* describes the aphrodisiac substances as "*Vajikara*". There is a list of the plant drugs used as *Vajikarana Aushadhi* in *Ayurveda*. Some of the examples of the class are *Butea monosperma* (Palash), *Curculigo orchiodes* (Kali musli), *Pedalium murex* (Bada Gokhru), *Asparagus racemosus* (Shatavari), *Panax ginseng* (man root), *Nigella sativa* (Kalijiri), *Chlorophytum borivilianum* (safed musli), *Myristica fragrans* (nutmeg), *Tribulus terrestris* (Chhota Gokhru), *Zingiber officinale* (Ginger), *Mucuna pruriens* (atmagupta) etc. These herbs are reported in the scientific literature for their aphrodisiac and spermatogenic activity.

KEYWORDS: Male infertility, Ayurveda, *Vajikarana*, Aphrodisiac, spermatogenic.

INTRODUCTION

Infertility is defined as the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year. Infertility is a major reproductive health problem today, affecting 10 to 15 percent of couples seeking to have children[1-3]. Male infertility problems may be contributory to 30 to 40 percent of infertile couples. When a man has several normal parameters for semen and sperms, eventhough sexual dysfunction may lead to the state of infertility. Thus male infertility is defined as the inability of a male to achieve a pregnancy in a fertile female. In humans it accounts for 40 to 50 percent of infertility[4]. The infertile male partner has qualitative

or quantitative abnormalities of sperm production as one of the factors responsible for infertility[5-9]. The male factor infertility may be because of the abnormalities in semen or in sperms. When the concentration of sperms is below 20 million sperms per ml of semen, the male is said to be infertile i.e. pregnancy cannot be easily achieved in normal fertile woman. Male factor infertility accounts for mainly two reasons: Sperm abnormalities and male sexual disorders. Sperm abnormalities Sperm motility is the prime functional parameter that determines the fertilizing ability of spermatozoa. The cause underlying loss of sperm motility may be either hormonal, bio-chemical, immunological or infection[10-13]. Male sexual disorders are classified as disorders of desire, erectile dysfunction, disorders of ejaculation, and Failure of detumescence[14].

It is evident from most of the studies that, the average sperm count has dropped to 66 million spermatozoa per millilitre in 1990 from 113 million in 1940. The analysis also showed 18 per cent of men in the 1980s had sperm counts below 20 million spermatozoa, the lower limit of the normal count at that time, compared with 6 per cent between 1930 and 1950. The number of men with high counts, more than 100 million, also dropped dramatically from 50 per cent to 16 per cent over the same period[15].

Studies carried out in India confirmed deterioration in vital semen parameters of Indian males too[16]. These studies provided evidences that quality of semen was deteriorated in the region probably due to environmental, nutritional and life style related reasons. In India, the overall prevalence of primary infertility ranges between 3.9% and 16.8%[17]. It was also estimated that infertility vary widely among Indian states from 3.7% in Uttar Pradesh, Himachal Pradesh and Maharashtra to 5% in Andhra Pradesh and 15% in Kashmir[18]. Indian couples seeking fertility treatment, the male factor is the cause in approximately 23% cases[19]. A study comprised of retrospective as well as prospective analysis of infertility cases over a period of 20 years (Aug 1990 to July 2005) on Indian population, showed that overall incidence of male infertility over those two decades varied from 8.97% to 14.63%[20].

SPERMATOGENESIS

Spermatogenesis is the process by which the male gametes called spermatozoa (sperms) are formed from the primitive germ cells (spermatogonia) in the seminiferous tubules of the testes. It takes 74 days for the completion of the process. The process starts at the age of 14 years in male[21]. In the testes, the germ cells are located in tubules of which their inner side is covered by the seminiferous epithelium containing somatic sertoli cells which provide nourishment and support germ cells. Before a sperm can leave the testes, it has to pass through several stages of maturation.

Spermatogenesis process includes the following stages:

a) Stage of proliferation- Each spermatogonium contains diploid number of chromosomes. In man, there are 23 pairs of chromosomes. One member of each pair is from maternal origin and the other one from paternal origin. The 23 pairs include 22 pairs of autosomal chromosomes and one pair of sex chromosomes. The sex chromosomes are one X chromosome and one Y chromosome. During the proliferative stage, spermatogonia divide by mitosis without any change in chromosomal number. In male there are usually seven generations of spermatogonia. The last generation enters the stage of growth as primary spermatocyte[21].

b) Stage of growth- In this stage, the primary spermatocyte grows into a large cell.

c) Stage of maturation- After reaching the full size, each primary spermatocyte quickly undergoes meiotic or maturation division. It includes division of primary spermatocyte into two secondary spermatocytes. The significance of the first meiotic division is that each secondary spermatocyte receives only the haploid or half the number of chromosomes. 23 chromosomes include 22 autosomes and a X or Y chromosome. After this, each secondary spermatocyte undergoes second meiotic division resulting in two smaller cells called spermatids. Each spermatid has haploid number of chromosomes.

d) Stage of transformation- There is no further division. The spermatids are transformed into matured spermatozoa (sperms) by means of spermatogenesis and released into the lumen of the seminiferous tubules.

Hormonal Control of spermatogenesis[21]:

Spermatogenesis is influenced by many hormones which act directly or indirectly. Although the initiating factors are not known, at puberty certain hypothalamic neurosecretory cells increase their secretion of Gonadotropin Releasing Hormone (GnRH). This hormone in turn, stimulates gonadotrophs in the anterior pituitary to increase their secretion of the two Gonadotropins, Luteinizing hormone (LH) and Follicle Stimulating Hormone (FSH). Figure 2 explains the hormonal control over testes and spermatogenesis. Below are the hormones necessary for spermatogenesis.

Follicle Stimulating Hormone (FSH)

FSH is responsible for initiation of spermatogenesis. It binds with sertoli cells and spermatogonia and induces proliferation of spermatogonia. It also stimulates formation and secretion of Androgen Binding Protein (ABP) from sertoli cells and releases it in the lumen of the seminiferous tubule and into the interstitial fluid around the spermatogonia. ABP binds to testosterone, thereby keeping the concentration of testosterone high near the seminiferous

tubules. Testosterone stimulates the final step of spermatogenesis. Once the spermatogenesis is over, sertoli cells release inhibin.

Testosterone

This steroid hormone is synthesized from cholesterol in the testis and is the principal androgen. Testosterone is responsible for sequence of lateral stages (stages from 7 to 14) in spermatogenesis. It is also responsible for maintenance of spermatogenesis. Testosterone also acts in a negative feedback manner to suppress secretion of GnRH by hypothalamic neurosecretory cells. It is also essential for the growth of external genitalia viz. penis and scrotum and other accessory sex organs namely genital ducts, seminal vesicles and prostate gland. Testosterone is also responsible for the distinguishing characters of masculine body, increase in the size of male sex organs, bone growth, broadening of shoulders, lengthening of pelvis, thickening of skin, melanin pigmentation on body surface, male type hair distribution on whole body, hypertrophy of laryngeal muscles, enlargement and lengthening of larynx, thickening of vocal cord etc.

Luteinizing hormone

LH binds to specific membrane receptors located on the surface of the leydig cells of the testis, which causes an increase in second messengers (c-AMP and ca^{2+}), activation of protein kinases, phosphorylation and synthesis of proteins, which ultimately results in an increased conversion of cholesterol to pregnenolone. The conversion of cholesterol to pregnenolone, known as cholesterol side chain cleavage (CSCC) reaction, takes place in the mitochondria, catalyzed by the cholesterol side chain cleavage enzyme complex and is generally considered as the rate limiting step in steroid production. Pregnenolone leaks out of the mitochondria and is converted to several other steroids, including testosterone as the main end product in leydig cells[22].

Growth hormone

Growth hormone is essential for general metabolic processes in testis. It is also necessary for proliferation of spermatogonia[22].

Inhibin

It is a peptide hormone secreted by sertoli cells upon stimulation by FSH. It plays an important role is spermatogenesis by inhibiting FSH secretion through feedback mechanism. So when the rate of spermatogenesis increases, there is simultaneous increase in inhibin secretion also. Inhibin in turn acts on anterior pituitary and inhibits secretion of FSH leading to decrease in the pace of spermatogenesis[22].

Role of different cells in spermatogenesis

Sertoli cells are known as nurse cells of testis present in walls of seminiferous tubules. These cellas are distinguished from adjascent cells through the presence of dark nucleous after staining. Sertoli cells provide structural and metabolic support to spermatogenic cells. They form tight junction and thus afford protection to spermatononia. Sertoli cells, under the influence of FSH secrets Androgen Binding Protein (ABP). These cells secret Inhibin and some components of testicular fluid[23].

Leydig cells or interstitial cells of leydig are present in lumen of seminiferous tubule. Leydig cells are major site of steroidogenesis in testis. The main function of leydig cells is to produce androgens for the paracrine regulation of spermatogenesis within the testis, and for the various systemic endocrine effects, androgenic and anabolic, outside the testis. Under the influence of LH, leydig cells synthesize testosterone. Leydig cell would respond to LH and function normally, only if, the critical protein necessary for steroid genesis, from LH receptor, cholesterol transporting proteins as well as various steroidogenic enzymes would synthesize without any mistake in their amino acid sequence[24-25].

Normal values of semen parameters in human:

A 2010 World Health Organization report described normal human semen as having a volume of 1.5 ml or greater, pH of 7.2 or more, sperm concentration of $15x10^6$ spermatozoa/ml or more, sperm count of $39x10^6$ spermatozoa per ejaculate or more and motility of 32% or more within 60 minutes of ejaculation[26].

When the concentration of sperms is below 11 million sperms per ml of semen, the male is said to be infertile i.e. pregnancy cannot be easily achieved in normal fertile woman. Sperm motility is the prime functional parameter that determines the fertilizing ability of spermatozoa [10,11,13,27].

Table 1: Normal values of semen parameters

Semen Parameter	Reference value
Volume	≥ 1.5 ml
pH	7.2 to 7.8
Concentration	≥ 15 X 10^6 /ml
Total spermatozoa per ejaculate	≥ 39X 10^6
Progressive Motility	≥ 32 % motile
Total Motile	≥ 40% (Progressive + Non Progressive)
Vitality	≥ 58% live spermatozoa
Normal Spermatozoa	≥ 4%

Sperm Morphology

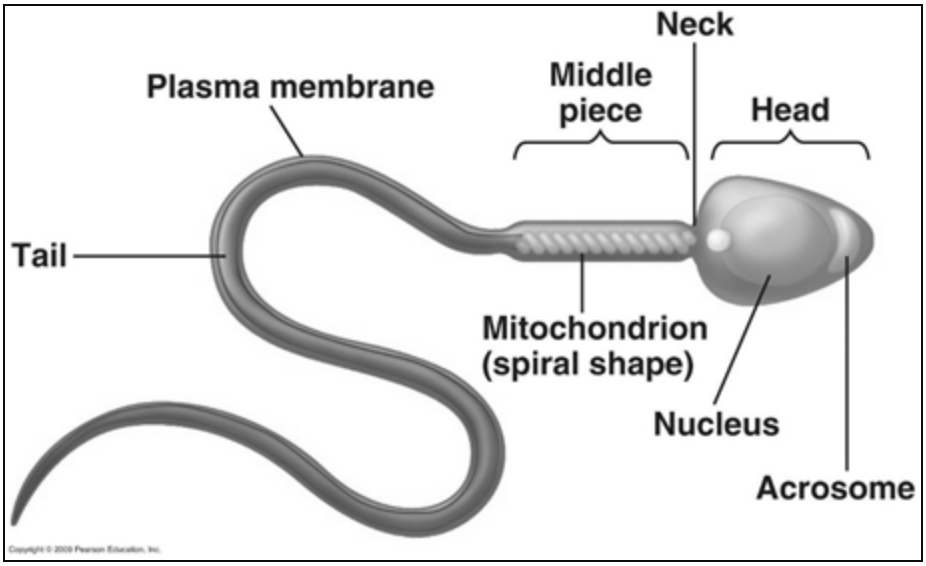

Figure 1: Normal spermatozoa

Sperm morphology is a term that refers to the shape and size of sperm cells. Abnormal sperm morphology is the term used when a sperm does not fit the expected description, whether the abnormal characteristic is size, shape or features. Teratozoospermia is the term used for sperm with abnormal morphology.

During the sperm analysis exercise, only recognizable sperm are included in a morphology count. The following are few of the initial observations, proved a sperm to be abnormal.

- The normal sperm head should be oval with no irregularities
- There should be a well-defined acrosomal region (40-70% of head area)
- There should be no neck, mid-piece or tail defects
- There should be excess residual cytoplasm no more than 1/3rd the size of a normal sperm head

Disorders related to semen and sperm abnormalities

If a man is not having normal types of semen and sperm characteristics then he could be suffering from disorder related to semen and sperm abnormalities which can lead to infertility.

Oligospermia or Oligozoospermia: This condition is indicated when sperm concentration falls below 10 million/ml. it may be due to loss of a portion of a ejaculate, partial obstruction of the genital tract, drugs or genetic abnormalities. Around 31% of male are suffering from this condition[14].

Azoospermia: This condition is indicated when there is complete absence of spermatozoa in semen. This may be due to the obstruction of the sperm transport, hypogonadism, antiandrogenic

causes, such as chemotherapy or idiopathic factors, which are most probably genetic in origin[28]. Azoospermia is present in less than 1 % of all men and in 10 to 15% of infertile men[29].

Aspermia: This condition is indicated by the complete lack of semen. This can be the result of impaired seminal gland function or destruction of the seminal glands caused by injury[14].

Teratospermia: This condition is indicated by the increase in sperm with abnormal morphology[14].

Asthenozoospermia: This condition is indicated by the reduced sperm motility[14].

HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD):

Male sexual disorders are classified as Hypoactive sexual desire disorder (HSDD), erectile dysfunction, disorders of ejaculation, and Failure of detumescence[14]. Hypoactive sexual desire disorder (HSDD) affects both men and women. HSDD may be defined as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. Sexual desire disorders are under recognized, under-treated disorders leading to a great deal of morbidity in relationships[30]. The National Health and Social Life Survey in USA, found that 15 % of men lacked sexual interest for several months within the past one year of study[31]. A descriptive epidemiological study on a sample size of 1529 (742 males and 787 females) reported that about 21.15% of the male subjects were diagnosed to be suffering from one or more male sexual disorders. Prevalence of male HSDD was revealed to be 2.56% among the subjects diagnosed with sexual disorders. Due to complex nature of HSDD and difficulty in diagnosis, the authors predicted more than the reported prevalence of male HSDD[32].

Brain and neurochemical basis of sexual behavior

Drugs affecting sexuality can either act on the central nervous system (Brain) and/or on the peripheral nervous system. Drugs affecting the brain and presumably sex centers are generally attributed with an increase or decrease in sexual arousal. Drugs that affect peripheral nerves will not affect arousal directly but may affect sexual function. In some cases, drugs action is direct and involves chemical alteration of the neurons, which governs sexual arousal or function. Alternatively, some drugs may act indirectly by altering blood flow to the genitalia. Most hypotheses concerning the neurochemical basis of sexual behavior are derived from studies in animals, but in some cases support has been provided by clinical studies. Five major neurochemically distinct systems are supposed to work together for increasing sexual arousal. The transmitters include norepinephrine, dopamine, serotonin, acetylcholine, and histamine[33]. The most widely endorsed hypotheses suggest that both serotonin and dopamine are involved in the neurochemical control of sexual behavior with serotonin playing an inhibitory role and

dopamine an excitatory role. Dopamine plays a crucial role in the central control of sexual behavior in males[34]. Increase in the activity of central dopaminergic systems correlates with sexual activity[35]. *In vivo* microdialysis in conscious male rats revealed that dopamine transmission increased sharply in the striatum, nucleus accumbens, and medial preoptic area during copulation[36-38]. This change in central neurotransmission may be permissive to a series of motor responses including penile erection. It may also modulate the activity of brain nuclei directly involved in the control of penile erection[39]. For example, drugs such as levodopa, which increase levels of dopamine in the brain, tend to be associated with increase libido and enhanced sexual function in patients suffering from abnormal dopamine activity such as that associated with Parkinson's disease. In contrast, drugs blocking dopamine function such as haloperidol, causes loss of sexual arousal. It has been long suspected that monoamines play a crucial role in the regulation of sexual behaviour, particularly that of dopaminergic transmission which is facilitatory to masculine activity and both dopaminergic and adrenergic receptors are involved. Yohimbine, bromocriptine, and reserpine are alpha-adrenergic receptor blocking agents whereas yohimbine, bromocriptine, amphetamine, and apomorphine all comet with the neurotransmitter dopamine for binding to membrane sites[40]. Furthermore, some studies have also suggested that the dopamine release is also increased during sexual activity in the paraventricular nucleus of the hypothalamus and that in this hypothalamic nucleus dopamine facilitates penile erection and sexual behaviour by activating NO production in the cell bodies of oxytocin neurons controlling penile erection and sexual motivation, which project to extrahypothalamic brain areas and to the spinal cord[41-44].

Causes and treatment of male sexual disorders

There have been tremendous advances in the understanding of the physiology and pathophysiology of male sexual function in last three decades. Each male sexual disorder can be individually treated by various therapeutic agents.

Causes of male sexual disorders[44]

Causes of various male sexual disorders are as below:

- Psychogenic (*e.g.*, depression, marital discord leading to desire deficiency, performance anxiety leading to excitement inhibition, obsessive-compulsive sexuality, excessive sex-seeking in association with affective disorders, addictive sexuality, sex impulsivity)
- CNS disease (partial epilepsy, Parkinson's, poststroke, adrenoleukodystrophy)
- Androgen deficiency (primary or secondary), androgen resistance

- Drugs (antihypertensives, psychotropics, alcohol, narcotics, dopamine blockers, antiandrogens)

Treatment of hypoactive sexual desire disorders (HSDD)

Deficient sexual desire or hypoactive sexual desire is currently being treated by following means:

a) *Psychological and behavioral counseling:* psychotherapy is the way to treat the decreased libido which arises from the fear of failure, lack of self confidence, mental stress etc. Consultation of psychiatrist is the one and sole option for the treatment. Review showed that desire disorders have poorer response to the psychotherapy.

b) *Hormonal replacement:* several studies have indicated improvement in libido and spontaneous erection with testosterone replacement[44]. Male sexual dysfunction caused by insufficient androgen levels can be treated by testosterone replacement therapy. Excessive androgen intake may rise in hematocrit levels in men with chronic obstructive lung disease and heavy smoking habit. It also decreases the serum concentration of high density lipoprotein (HDL) cholesterol. Both these risk can lead to coronary artery disease. There is also increased risk of prostate cancer with initiation of testosterone replacement therapy[45].

c) *Pharmacological agents:* Libido can be increased by administration of various dopamine agonists like apomorphine, bromocriptine and pergolide or dopamine precursor like levodopa[46-50]. Cabergoline is a new dopamine agonist shown to increase the libido[51]. Bupropion and nomifensin, antidepressant, have shown libido increasing effect[52]. Serotonergic drugs like trazodone, venlafaxine and fenfluramine hace also shown an increase in sexual desire[53-54].

***Ayurveda* and concept of *Vajikarana* therapy**

Ayurveda is the ancient Indian Science of medication. It is considered as the oldest literature for the treatment of various diseases. The importance of sexuality in human life is well recognized in *Ayurveda* under the name '*Vajikarana adhikara*' or virilification therapy. Srikantha Bhavaprakasaha of Bhavamisra[55] describes the Vajikarana adhikara- virilification therapy. *Vajikarana Chikitsa* is the branch of *Ayurveda*, which deals with all types of physical and psychological sexual problems like impotence, libido, poor erection, and early ejaculation in males. *Vajikarana therapy* includes the utilization of aphrodisiacs from natural sources for erectile dysfunction, infertility, impaired spermatogenesis, methods of correcting defective

semen and sexual satisfaction[56]. *Ayurveda* describes the aphrodisiac substances as "*Vajikara*". They are believed to increase sex power[57].

***Klaibya* or Impotence[55]**

It is the term used for Impotence. Kliba is the person who is incapable of copulation and incapacity for copulation is known as Klaibya (Impotence/infertility). As per *Ayurveda,* it is of seven kinds.

a) First type: *manasa klaibya (psychological impotence)*: Man desirous of copulation, getting hurt in his mind by many causes which are unpleasant to the mind, makes his penis to lie down (not getting erect and stiff) resulting in impotence; known as *manasa klaibya***.**

b) Second type: More use of foods which are pungent, sour and salty, give rise to increase of pitta which in turn causes decrease (or loss) of sukra (semen) resulting in impotence *(Sukraksaya*-oligospermia*)*.

c) Third type: the person who indulges in too much of copulation and do not use any drugs (foods) which make for virilification, develops *dhvaja bhanga* (non erection of the penis- erectile dysfunction); this is known as klaibya due to loss or decrease of sukra (semen)**.**

*d) Fourth type***:** due to major diseases of the penis.

e) Fifth type: Marmachedaja (impotence due to damage of vital part): impotence due to rupture (damage) of the channels of semen resulting in non-erection of the penis, known as *marmachedaja.*

f) Sixth type: occurs in strong persons of perverse mind who abstain from copulation, this is called impotence due to control of semen;

g) Seventh type: sahaja klaibya: the impotence which is born along with birth of man is known as *sahaja klaibya* (congenital impotence).

Sahaja klaibya (congenital impotence) and *Marmachedaja* (impotence due to damage of vital part) these two kinds of impotence are incurable.

***Sukrameha* or Spermatorrhea[58]:**

The individual who does not control his desires and indulges in unnatural sexual intercourse loses his vital strength and semen. This finally develops into a fatal disease called as Sukrameha (spermatorrhea). It is a condition of excessive, involuntary ejaculation.

Because of indigestion, loss of physical exercises and constipation and because of taking heavy meals in dinners, because of riding elephants, horses and camels that cause rubbing on male genital organs individual gets the disease sukrameha.

The symptoms of this disease include the easy discharge of semen with slight sexual excitement even due to emotion, dreams, memory and the like. Because of putting pressure on stomach while trying to pass constipated stools, because of retaining the urge of passing urine and stool this disease can also manifest. In this disease individual discharges semen even while his organ is not erected. This condition is also called "*Ratrimeha*". A prolonged condition of this disease can also result in the disease called *Dhvajabhanga* or Erectile dysfunction.

Aphrodisiacs:

An aphrodisiac is defined as any food or drug that arouses the sexual instinct, induces veneral desire and increases pleasure and performance. This word is derived from *Aphroditaeí* the Greek Goddess of love and these substances are derived from plants, animals or minerals and since time immemorial they have been the passion of man[59]. Aphrodisiacs can be classified by their mode of action into three types: Those that increase libido, potency, or sexual pleasure. Various substances of animal and plant origin have been used in folk medicines of different cultures to energize, vitalize and improve sexual function, and physical performance in men, out of these very few have been identified pharmacologically[60]. The meaning of vajikarana could be understood like this, 'vaja'= semen, the person who has (sukra) semen is called 'vaji'= one possessing semen, the person who does not possess semen is called 'avaji'. Increase the growth of 'vaji' (semen) through drugs is called vajikarana.

"Vajikara ausadhas" or "**aphrodisiacs"** are the drugs, foods or medicines which make man capable of copulating like a horse with females. They increase sex power.

Below is the list of diseases/ technical terms mentioned in Ayurvedic Formulary of India with their English terminology[61].

Plant drugs in *Ayurveda* described as *Vajikarana*

There is a list of the plant drugs used as *Vajikarana Aushadhi* in *Ayurveda*. Some of the examples of the class are *Butea monosperma* (Palash), *Curculigo orchiodes* (Kali musli), *Pedalium murex* (Bada Gokhru), *Asparagus racemosus* (Shatavari), *Panax ginseng* (man root), *Nigella sativa* (Kalijiri), *Chlorophytum borivilianum* (safed musli), *Myristica fragrans* (nutmeg), *Tribulus terrestris* (Chhota Gokhru), *Zingiber officinale* (Ginger), *Mucuna pruriens* (atmagupta) etc. These herbs are reported in the scientific literature for their aphrodisiac and spermatogenic activity.

Table 2: Correlation between Ayurvedic Sanskrit terms for male sexual disorders and their corresponding English terminology

Sanskrit terms	Corresponding English terminology
Dhvajabhanga	failure of Penile Erection or Erectile Dysfunction
Ksinasukra / Sukraksaya	Oligospermia
Napunsakata / Klaibya	Impotence
Sukrameha	Spermatorrhea
Sukradosa	Diesease of semen

Table 3: List of plants used as *"Vajikarana"* with their common names, botanical names and parts used

Sr. No.	Common names	Botanical names	Parts used
1	Agaru	*Aquilaria agallocha*	Heart wood
2	Ajamoda	*Apium leptophyllum*	Fruit
3	Amalaki	*Emblica officinalis*	Fresh fruit pulp, dried fruit
4	Ashvagandha	*Withania somnifera*	Root
5	Atibala	*Abutilon indicum*	Root
6	Ativisa	*Aconitum heterophyllum*	Root
7	Atmagupta	*Mucuna prurita*	Seed
8	Bhallataka	*Semicarpus anacardium*	Fruit
9	Canda	*Angelica archangelica*	Root
10	Cavya	*Piper retrofractum*	Stem
11	Citraka	*Plumbago zeylanica*	Root bark
12	Devadaru	*Cedrus deodara*	Heart wood
13	Dhataki	*Woodfirdia fruticosa*	Flower
14	Draksa	*Vitis vinifera*	Fruit
15	Durva	*Cynodon dactylon*	Root
16	Elavaluka	*Prunus avium*	Seed
17	Gambhari	*Gmelina arborea*	Root bark, fruit, stem, stem bark
18	Goksura	*Tribulus terrestris*	Root, fruit
19	Jati	*Jasminum officinale*	Leaf
20	Jatiphala	*Myristica fragrans*	Seed
21	Jivak	*Malaxis acuminate*	Pseudo bulb
22	Kakoli	*Lilium polyphyllum*	Tuberous roots
23	Kancanara	*Bauhinia variegata*	Stem bark
24	Kantakari	*Solanum xanthocarum*	Whole plant
25	Karkatsringi	*Pistacia chinensis*	Gall
26	Karcura	*Curcuma zeodaria*	Rhizome
27	Kasa	*Saccharum spontaneum*	Root stock
28	Kaseru	*Scirpus kysoor*	Rhizome
29	Kharjura	*Phoenix dactylifera*	Fresh fruit, dried fruit
30	Kokilaksa	*Hygrophila spinosa*	Seed
31	Kusa	*Desmostachya bipinnata*	Root stock
32	Kustha	*Saussurea lappa*	Root

33	Lavanga	*Syzigum aromaticum*	Flower bud
34	Lodhra	*Symplocus racemosa*	Stem bark
35	Mahabala	*Sida rhombifolia*	Root
36	Mahameda	*Polygonatum cirrhifolium*	Root and rhizome
37	Manjistha	*Rubia cordifolia*	Stem
38	Marica	*Piper nigrum*	Fruit
39	Masaparni	*Teramnus labialis*	Whole plant
40	Mudga	*Phaseolus radiatus*	Seed
41	Musta (nagarmoth)	*Cyperus rotundus*	Rhizome
42	Nagakesar	*Mesua ferrea*	Stmn
43	Nagavalli	*Piper betle*	Leaf
44	Padmaka	*Prunus cerasoides*	Heart wood
45	Pattanga	*Ceasaplinia sappan*	Heart wood
46	Prasarini	*Paderia foetida*	Whole plant
47	Prasniparni	*Uraria picta*	Whole plant
48	Punarnava (rakta)	*Boerrhavia diffusa*	Whole plant
49	Punarnava (sveta)	*Boerrhavia verticillata*	Root
50	Riddhi	*Habenaria intermedia*	Tubers
51	Salmali	*Bombax ceiba*	Root, stem bark
52	Sarala	*Pinus roxburghii*	Root, heart wood
53	Sveta sariva	*hemidesmus indicus*	Root
54	Sveta candana	*Santalum album*	Heart wood
55	Tagara	*Valeriana wallichii*	Rhizome
56	Talisa	*Abies webbiana*	Dried leaf
57	Udumbara	*Ficus racemosa*	Leaves, bark
58	Usira	*Vetiveria zizanioides*	Root
59	Vaca (vaj)	*Acorus calamus*	Rhizome
60	Vidari	*Pueraria tuberose*	Tuberous root
61	Vidanga	*Emblia ribes*	Fruit
62	Vijaya	*Cannabis sativa*	Leaf
63	Vridhadaru	*Argyreia speciosa*	Root
64	Yasti	*Glycyrrhiza glabra*	Leaf

Current literatures on some medicinal plants described as *Vajikarana*

Here below information describes the current status of various herbs mentioned in ayurvedic or traditional literature for the use as aphrodisiac. The review includes the research carried out on the plants related to its aphrodisiac or spermatogenetic activity and its Phytochemistry.

Asparagus racemosus:

Asparagus racemosus, commonly known as Shatavari, is belonging to family Liliaceae. It is a climbing plant which grows in low jungles areas throughout India. It is useful for infertility, decreased libido, threatened miscarriage, menopause and leucorrhea. Mishra et al. found that Shatavari root extract in the dose of 3000 mg/kg b.w. significantly increased the number of mounts and mounting frequency in adult male albino rats[62]. Mayank and his group also

conducted a comparative study on aphrodisiac activity of *Asparagaus racemosus*, *Chlorophytum borivilianum* and *Curculigo orchiodes. A*dministration of 200 mg/kg body weight of aqueous extract of roots of *Asparagaus racemosus and Chlorophytum borivilianum* and rhizomes of *Curculigo orchiodes* improved sexual performance in male albino rats. The anabolic effects were observed positive evidenced by weight gain in body and organ coupled with presence of steroidal saponins in the extracts suggestive of testosterone intervention of the drug extracts. Improvement in body weight is generally attributed to steroid genesis and is biological indicator of for effectiveness of the herbal drugs in the genesis of steroidal hormones[63].

Argyreia speciosa:

The aphrodisiac property of *Argeria nervosa* was studied in male mice by **Subramoniam** et al. in 2007[64]. The root, flower and, to some extent, leaf (homogenate in 2% gum acacia) of the plant showed aphrodisiac activity as evidenced by an increase in mounting behavior of mice. When different extracts of the root were tested, the activity was found in the alcohol extract (200 mg/kg; p.o, single dose). The extract, 1 hr after administration, stimulated mounting behavior of male mice in a concentration-dependent manner. The root- or flower-treated male mice also exhibited a remarkable increase in mating performance. Further, the number of males was found to be more among the pups fathered by the herbal drug-treated mice compared to those by the control mice. Thus, the plant has promising potential to be developed into an effective medicine for stimulating male sexual activity with an influence on sex ratio favoring males.

Butea superba:

Butea superba (*B. monosperma*) is commonly known as flame of forest in India. It is recognized as palash in Sanskrit. Ancient literature described the use of root and stem bark for the treatment of male impotence. Tocharus et al. in 2005 investigated that long term treatment with ethanolic extract of Butea superba root (0.01, 0.1 or 1.0 mg/kg BW/day) significantly increased the number of sperm, prolonged the sperm motility *in vitro* while producing no change in sperm morphology in adult male rat and mice[65].

Chlorophytum borivilianum:

This plant is known as safed musli in Indian system of medicine and is regarded as powerful aphrodisiac in male. It is a member of a special group of ayurvedic herbs known as *Vajikarana Rasayanas.* The comparative study on aphrodisiac activity of roots of safed musli is also conducted by Mayank et al in 2009[63].

Curculigo orchiodes:

Curculigo orchiodes is commonly known as Kali Musli. It is very well known herbal medicine in the treatment of male infertility. Dixit and Chauhan[66] carried out study to evaluate ethanolic extract of *Curculigo orchiodes* rhizomes for its effect on orientation behavior and spermatogenesis in albino rats. Administration of 100 mg/ kg b.w. of ethanolic extract had pronounced effect on orientation of male rats towards the female. Males treated with the extract displayed more frequent and vigorous anogenital sniffing and mounting as compared to untreated animal. The increased spermatogenesis in treated group was confirmed by change in histoarchitecture as evidenced by increase in number of spermatocyte and spermatids.

Hygrophila spinosa:

Effect of seeds of *Hygrophila spinosa* on the sexual behaviour of male albino rats was studied[66] in 2009. The ethanolic extract of seeds was administered to groups of rats in 100, 150 and 200 mg kg^{-1} doses for a period of 28 days, and the action compared with control rats. The changes in body and organ weight, sexual behaviour, histo-architecture and fructose levels of seminal vesicles were observed. The sexual behaviour was assessed by determining parameters such as mount frequency (MF), intromission latency, mount latency (ML) and post-ejaculatory latency. The ethanolic extract exhibited pronounced anabolic effects in treated animals, as evidenced by gains in the body and reproductive organ weights. Increased spermatogenesis due to treatment with extracts was also witnessed in transverse section. The treatment further markedly affected sexual behaviour of the animals, as reflected by the reduction of ML, increase in MF and enhanced attractability towards females. A significant increase in the sperm count as well as fructose levels of seminal vesicles was noted. Vyas and Raval also studied effect of Alkaloidal fraction of seeds of *Hygrophila spinosa* on testosterone production by leydig cells in vitro. Alkaloidal fraction was further evaluated *in vivo* for spermatogenic and aphrodisiac potential using rat as an experimental animal. Increase in weight of reproductive organs, biochemical evaluation of selected parameters, histological studies of testes and sexual behavioral studies were selected as evaluation parameters for in vivo studies. The results, of in vitro studies confirmed ability of the fraction to stimulate normal testicular cells to secrete testosterone. Increased level of serum testosterone in test animals confirmed in vitro findings. Stimulation to leydig cells and increased serum testosterone level might be responsible for higher number of spermatozoa in testicular lumen as seen in testicular histology as well as increased libido as observed in behavioral studies[68-69].

Panax ginseng:

Ginseng is the root of the perennial herbs of *Panax ginseng* and P*anax quinquefolium* which contain a series of tetracyclic triterpenoidal saponins (ginsenosides) as active ingredients. Ginseng is an essential constituent in traditional Chinese medicine for the treatment of sexual impotence. Experimental studies have indicated a specific action for such an effect. Chen and his group have shown that ginsenosides relax rabbit corpus cavernosum and this effect is mediated by nitric oxide, released from endothelial or neural cells. These endothelial and/or neurogenic effects of ginsenosides in including relaxation of the corpus cavernosum may account for the aphrodisiac effect of Ginseng. A clinical study has confirmed the positive effects of ginseng on sexual impotence[70].

Pedalium murex:

The plant is commonly known as Bada Gokhru in traditional medicinal system of India. Ayurveda claims the use of fruit as an aphrodisiac (Vajikarana). Petroleum ether extract of *Pedalium murex* was evaluated by Balamurugan et al. for its ability to increase aphrodisiac activity and to cure ethanol induced germ cell damage and infertility in male rats. Doses of 200 and 400 mg/kg of extract showed a significant increase in mating and mounting behavior in male rats[71].

Myristica fragrans:

Myristica fragrans, commonly known as Nutmeg, have been mentioned in Ayurveda as 'Jatiphala'. Nutmeg has been traditionally used as an important aphrodisiac drug. It is mentioned in numbers of ayurvedic formulations used as Vajikarana. Tajuddin et al. had carried out an experimental study of sexual function improving effect of nutmeg[72]. The result showed that oral administration of the extract of the nutmeg kernels in the dose of 500 mg/kg produced significant augmentation of sexual activity in male rats. It significantly increased the mounting frequency, intromission frequency, intromission latency, and caused significant reduction in the mounting latency and post ejaculatory interval. The extract was also observed to be devoid of any adverse effects and acute toxicity. Thus nutmeg kernels ethanolic extract (50%) possessed aphrodisiac activity increasing both libido and potency.

Nigella sativa:

The seeds of *Nigella sativa* Linn. (Ranunculaceae herbaceous plant), commonly known as black seed or black cumin, are used as herbal medicine all over the world for the treatment and prevention of a number of diseases and conditions like asthma, diarrhoea and dyslipidaemia. Mohammad et al. (2009) studied the effect of aqueous extract of seeds of *Nigella sativa* in the

dose of 300 mg/kg of body weight on spermatogenesis[73]. The seeds of *Nigella sativa* induce a significant increase in the weight of reproductive organs as compared to control animals (P<0.01). The sperm motility and count in cauda epidydimides and testicular ducts were significantly increased (P<0.01). Spermatogenesis was increased at primary &secondary spermatocyte stages. Epididymides showed eleveted number of spermatozoa. Lumen of vas deference was full of sperms. The secretary activities of seminal vesicle and ventricular prostate were also increased. A significant increase (P<0.01) in spermatogenesis activity was observed in seminiferous tubule. Treated rats testicular cell population showed a increase in number of spermatocytes and spermatids (P<0.001) when compared to control animals. Aqueous extracts of *Nigella sativa* have increased spermatogenesis of male albino rats.

Tribulus terrestris:

Tribulus terrestris is known as "Chhota Gokhru" in India. It is called as "Goksura" in Ayurveda. Its roots and fruits are used in various vajikarana formulations. Gauthaman et al. also evaluated the hormonal effects of *Tribulus terrestris* in primates, rabbits and rat to identify its usefulness in the management of erectile dysfunction[74]. *Tribulus terrestris* extract was administered intravenously, as a bolus dose of 7.5, 15 and 30 mg/kg, in primates for acute study. Rabbits and normal rats were treated with 2.5, 5 and 10 mg/kg of extract orally for 8 weeks, for chronic study. The result showed that in rabbits, the increase in testosterone (52%), Dihydrotestosterone (31%) and dehydroepiandrosterone (29%) at 7.5 mg/kg were statistically significant. In rabbits both testosterone and Dihydrotestosterone were increased compared to control, however, only the increase in Dihydrotestosterone (by 30% and 32% at 5 and 10 mg/kg) were statistically significant. In castrated rats, increase in testosterone levels by 25% were observed with *Tribulus terrestris* extract, which was significant statistically. *Tribulus terrestris* increased some of the sex hormones, possibly due to the presence of protodioscin in the extract.

Adaikan et al. (2000) investigated that oral treatment of *Tribulus terrestris* extract on the isolated corpus cavernosal tissue of New Zealand white rabbits showed an enhanced relaxant effect[75]. They also found that protodioscin, a constituent of *Tribulus terrestris,* had a proerectile activity. The enhanced relaxant effect observed is probably due to increase in the release of nitric oxide from the endothelium and nitrergic nerve endings, which may account for its claims as an aphrodisiac.

Tribulus terrestris is reported to have several steroidal saponins with protodioscin the most dominant as well as alkaloids and flavonoids. Ganzera et al. (2001) determined the steroidal saponins in *Tribulus terrestris* by Reverse Phase High Performance Liquid Chromatography and

Evaporative Light Scattering Detector[76]. They determined the content of Marker compound, protodioscin in fruits of *Tribulus terrestris* using RP-18 column in water acetonitrile gradient mobile phase.

Zingiber officinale:

Ginger rhizome (Zingiber officinale R., family: Zingiberaceae) is used medicinally and as a culinary spice. Ginger and its constituents are stated to have antiemetic, antithrombotic, antihepatotoxic, anti-inflammatory, stimulant, cholagogue and antioxidant. It has been used since ancient time as medicinal and food origins it contain antioxidative and androgenic activities and have well effect in diseases treatment in more countries world-wide. As an antioxidant's ginger has a useful effect on spermatogenesis and sperm parameters. All major active ingredients of Z. officinale, such as Zingerone, Gingerdiol, Zingibrene, gingerols and shogaols, have antioxidant activity[77]. Besides, other researches showed that ginger oil has dominative protective effect on DNA damage induced by H_2O_2 and might act as a scavenger of oxygen radical and might be used as an antioxidant[78]. Both antioxidative[79] and androgenic activity[80] of Z. officinale were reported in animal models.

The major active phenolic ingredients isolated from Z. officinale (Zingerone, Gingerdiol, Zingibrene, gingerols and shogaols) have antioxidant activity[79-81]. Others reported that Z. officinale extracts have a potent androgenic activity in male rats[82].

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