REVIEW ARTICLE

Investigative parameters for the preclinical screening of potential of medicinal plants for the management and treatment of male sexual dysfunction

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Abstract

Male sexual dysfunctions manifested by disorders of sexual desire (hypoactive and hyperactive), disorders of erection (erectile dysfunction), disorders of ejaculation (premature, absent/delayed and painful ejaculation, disorders of orgasm, and failure of detumescence). Conventional medicine is the knowledge, skills, and practice of holistic health care and recognized and accepted for its role in the maintenance of health and the treatment of diseases. It is based on indigenous theories, beliefs, and experiences that are handed down from generation to generation. Conventional medicine is practiced in many countries; it has always been part of the cultural and religious life of Indian people. Herbal treatments are the most popular forms of traditional medicine and are highly lucrative in the international marketplace. Today, more than 80% population of the developing countries depends on plants for their medical needs. Therefore, the increasing search for medicinal plants used in the treatment and management of male sexual dysfunction has necessitated. There are many herbal drugs that have been used for the treatment and management of male sexual dysfunction with varying degrees of success such as *Tribulus terrestris, Withania somnifera, Eurycoma longifolia, Ginkgo biloba,* and *Myristica fragrans.* Based on historical experience in traditional system of medicines, herbal medicinal plants are recommended for the treatment and management of male sexual dysfunction, and few of them have been scientifically validated. Recently, preclinical screening models including use of small animals such as rats and mice have been developed for better assessment of the pharmacological potential of medicinal plants against male sexual dysfunction. The present article has summarized the preclinical screening parameters with their significance including mating performance analysis, changes in reproductive organs index, reproductive hormonal estimations, sperm analysis, and histoarchitecture investigations.

Key words: Male sexual dysfunctions, preclinical screening, scientific validation, traditional medicinal plants

INTRODUCTION

The normal male sexual response cycle functionally can be divided into five interrelated events that occur in a defined sequence: Libido, erection, ejaculation, orgasm, and detumescence [Figure 1].[1-3,4] Sexual dysfunction is a highly prevalent set of disorders, that is, frequently associated with a loss of self-esteem and a reduced quality of life in both male patients and their partners.[5] Many recent advances in the understanding of pathophysiology of various types of sexual dysfunction have resulted in the development of a wide array treatment options. Unfortunately, the advent of such a successful drug for the majority of men has resulted in far less diagnostic effort in discovering the cause of each individual case of sexual dysfunction.[1,6] Recently, scientist's attention on scientific validation of traditional claim of folklore as a drug for the management and treatment of male sexual dysfunction has amplified because of long years of traditional beliefs.[7,8]

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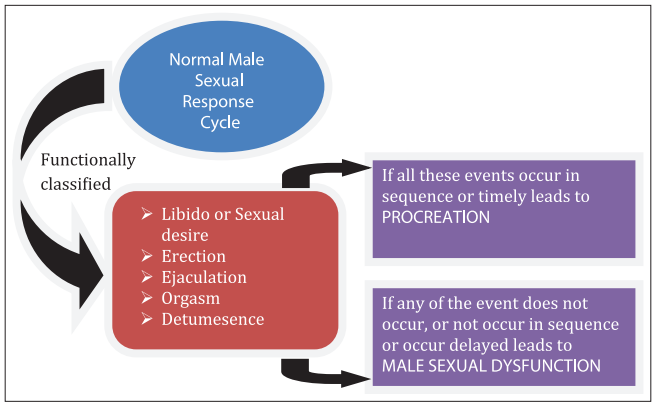


Figure 1: Normal male sexual response cycle

SCREENING PARAMETERS FOR THE ASSESSMENT OF POTENTIAL OF MEDICINAL PLANTS AGAINST MALE SEXUAL DYSFUNCTION

Test of Libido

Test of libido represents the striking frequency of male rats with the intensity of sexual desire.[9-11] A mount is operationally defined as the male assuming the copulatory position but failing to achieve intromission.[12,13]

Mating Behavior Analysis

In mating behavior analysis,[13-18] following parameters are analyzed:

Mount frequency (MF)

Mounting is defined as the climbing of one animal by another usually from the posterior end with the intention of introducing one organ into another. Mount may also be operationally defined as the male assuming the copulatory position but failing to achieve intromission. MF is therefore defined as the number of mounts without intromission from the time of introduction of the female until ejaculation.

Intromission frequency (IF)

Intromission is the introduction of one organ or parts into another (e.g., the penis into the vagina). IF is therefore defined as the number of intromissions from the time of introduction of the female until ejaculation.

Ejaculatory frequency (EF)

EF is defined as the number of times there is expulsion of semen by males after vaginal penetration - characterized by rhythmic contraction of the posterior abdomen.

Mount latency (ML)

ML is defined as the time interval between the introduction of the female and the first mount by the male.

Intromission latency (IL)

IL is the time interval from the time of introduction of the female to the first intromission by the male. This is usually characterized by pelvic thrusting and springing dismounts.

Ejaculatory latency (EL)

Ejaculation is the act of ejecting semen brought about by a reflex action that occurs as the result of sexual stimulation. EL is defined as the time interval between the first intromission and ejaculation. This is usually characterized by longer, deeper pelvic thrusting and slow dismount followed by a period of inactivity or reduced activity.

Post-ejaculatory interval (PEI)

PEI is the time interval between ejaculation and the first intromission of the following series.

Testicular Index (TI)

TI is the best primary assessment of spermatogenesis since the tubules and germinal elements account for approximately 98% of the testicular mass. A TI will be calculated for experimental animal (testis length × testis width/body weight); TI and testis width are correlated with testis weight, which reflects spermatogenesis and testosterone production.[19]

Semen Analysis[19-24]

Semen quality analysis constitutes a powerful tool to evaluate the fertility potential of males in threatened species. A semen analysis measures how much semen a man produces. It also shows the number and quality of sperm in the semen sample. A sperm quality analysis measures the health of sperm by analyzing the sperm count, sperm morphology, and sperm motility [Table 1].

Volume

This is a measure of how much semen is present in one ejaculation. The volume of sperm for a normal result should be >2 ml. A low sperm volume could indicate a low amount of sperm to fertilize an egg. An excess fluid volume could also mean the amount of sperm present is diluted.

Liquefaction time

Semen is a thick gel at the time of ejaculation. Liquefaction time is the time it takes for the semen to turn to liquid. It

should take 15-30 min before semen liquefies. While semen is initially thick, its ability to liquefy, or turns to a watery consistency, helps sperm to move. If semen does not liquefy in 15-30 min, fertility could be affected.

Sperm count

This counts the number of sperm present per milliliter of semen in one ejaculation. Sperm count, or sperm concentration to avoid confusion with total sperm count, measures the concentration of sperm in a man's ejaculate, distinguished from total sperm count, which is the sperm count multiplied with volume.

Sperm morphology

This is a measure of the percentage of sperm that have a normal shape. A normal result for sperm shape is that more than 50% of sperm are normally shaped. If a man has greater than 50% of sperm that are abnormally shaped, this reduces his fertility. A laboratory may identify abnormalities in the sperm's head, midsection, or tail. It is also possible the sperm could be immature and therefore not able to effectively fertilize an egg.

Sperm motility

This is a measure of the percentage of sperm that can move forward normally. The number of sperm that shows normal forward movement in a certain amount of semen can also be measured. This is called motile density. Sperm motility describes the ability of sperm to move properly through the female reproductive tract to reach and fertilize the woman's egg. Sperm motility studies identify the number of motile (moving) sperm seen in an ejaculate specimen.

pH

This is a measure of the acidity (low pH) or alkalinity (high pH) of the semen. A pH level should be between 7.2 and 7.8 to achieve a normal result. A pH level higher than 8.0 could indicate the donor has an infection. A result <7.0 could indicate that the specimen is contaminated or that the man's ejaculatory ducts are blocked.

White blood cell count

White blood cells are not normally present in semen. Pyospermia (also referred to as leukocytospermia) is a condition in which there are an unusually high number of white blood cells in the semen. According to the World Health Organization, pyospermia is defined as more than 1 million white blood cells per milliliter of semen. Pyospermia is an important condition in male fertility because white blood cells weaken the sperm and can damage its genetic material.

Fructose level

This is a measure of the amount of a sugar called fructose in the semen. The fructose provides energy for the sperm. Fructose is the energy source for sperm motility. Fructose is secreted from the seminal vesicles and the accessory sex glands. It is the major carbohydrate found in seminal plasma, provides over half the spermatozoa carbohydrate consumption, and appears essential for normal sperm motility.

ESTIMATION OF MALE REPRODUCTIVE HORMONES[25,26]

Serum concentration of total testosterone (T), follicle stimulating hormone (FSH), and luteinizing hormone (LH) are measures to check the fertility [Table 2].[27] Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. Both LH and FSH contribute to testicular growth, spermatogenesis, and steroid genesis.[28] The major action of FSH is promotion of spermatogenesis in the seminiferous tubules while LH regulates testosterone synthesis by the Leydig's cells. FSH also can augment the activity of LH and enhance testosterone synthesis required for spermatogenesis and maturation of sperm.[29] In male with testicular deficiency, hypergonadotrophic hypogonadism is usually present, with high levels of FSH and LH and sometimes low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia: When spermatogonia are absent or markedly diminished, FSH values are usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are within the normal range. However, for an individual patient, FSH levels do not accurately predict the spermatogenesis

Table 1: Semen analysis parameters

Semen analysis parameter	Normal values
Volume	1.5 ml or more
pH	>or equal to 7.2
Sperm concentration	15,000,000/ml or more
Total motility	40% or more
Progressive motility	32% or more
Morphology	4% or more normal forms (Strict criteria)
Vitality	58% or more live
White blood cells	Less than 1,000,000/ml

Table 2: Male reproductive hormones normal reference values

Hormones	Normal reference values
Total testosterone	2.4-12 ng/ml
LH	2-18 mIU/ml
FSH	1-18 mIU/ml

LH: Luteinizing hormone, FSH: Follicle stimulating hormone

status because male with maturation arrest histology could have normal FSH and normal testis volume and still be azoospermic.[30]

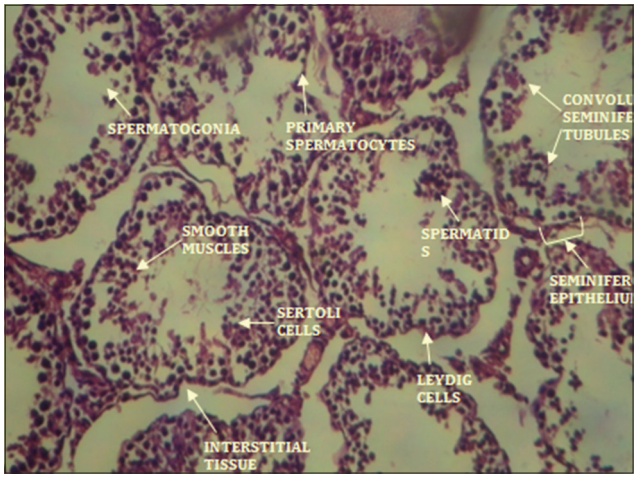
HISTOARCHITECTURE STUDIES OF TISSUES OF REPRODUCTIVE ORGANS

Histopathological studies of reproductive organs are involving the studies of changes in histoarchitecture of reproductive tissue.[31] Histopathological studies of reproductive organs such as testes, epididymis, vas deferens, seminal vesicle, and prostate gland. The testes are responsible for making testosterone, the primary male sex hormone, and for generating sperm. Within the testes are coiled masses of tubes called seminiferous tubules. These tubes are responsible for producing sperm cells.[32] Histopathology study of testes tissues involves the examination of stages of spermatogenesis, seminiferous tubules, spermatogonia, Leydig cells, and serotoli cells (Photograph 1). Epididymis is the site of sperm maturation, the process by which sperm acquire motility and the ability to fertilize an ovum. The epididymis is a long, coiled tube that rests on the backside of each testicle. It transports and stores sperm cells that are produced in the testes. Histopathology study of epididymis tissues involves the examination of histoarchitecture changes in basal (cuboidal) cells and principal (columnar) cells (Photograph 2). The vas deferens or ductus deferens is thick-walled tube in the male reproductive system that transports sperm cells from the epididymis, where the sperms are stored before ejaculation.[33] The tissue structure of the ductus deferens includes an inner lining of pseudostratified columnar epithelial tissue, a middle layer of connective tissue and visceral muscle, and an outer layer of adventitia (Photograph 3). Seminal vesicles or seminal glands are two small fibromuscular pouches lined with columnar epithelium. Seminal vesicles secret an alkaline viscous fluid that help the sperm swims toward the egg and keeps the sperm nourished during the transit process.[34,35] The seminal vesicles develop from the vas deferens. Their histological organization resembles to some extent that of the vas deferens. The mucosa shows thin, branched, anastomosing folds. The structure of the epithelium is variable appearing columnar or pseudostratified columnar (columnar cells and basal cells). The lamina propria of the mucosa is fairly thin and loose. The muscularis consists of inner circular and outer longitudinal layers of smooth muscle (Photograph 4).

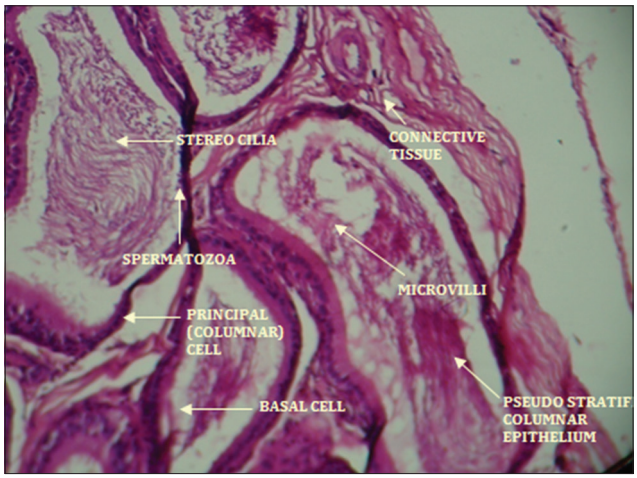
The prostate gland is a walnut-sized structure that is located below the urinary bladder in front of the rectum. The prostate gland contributes additional fluid to the ejaculate. Prostate fluids also help nourish the sperm. The urethra, which carries the ejaculate to be expelled during orgasm, runs through the center of the prostate gland. A histopathology study of prostate gland involves the examination of histoarchitecture of secretory alveoli, papillary projections of the mucosa, cuboidal or columnar and basal cells (Photograph 5).[36]

CONCLUSION

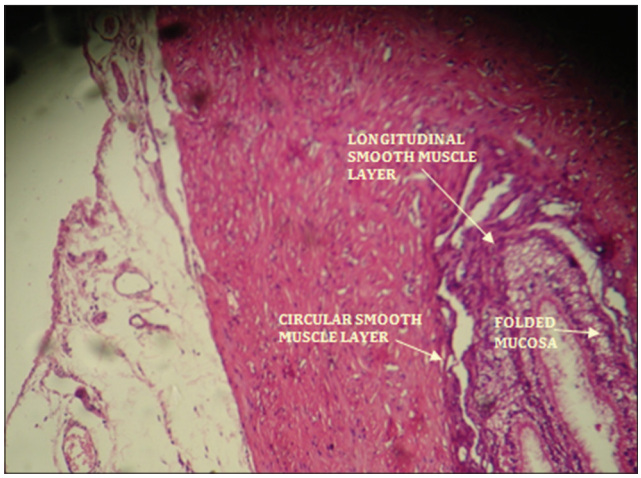
For thousands of years, man has sought healing powers from the natural world, especially from plants.[37-41] Sexual interaction is the physical manifestation of our emotional



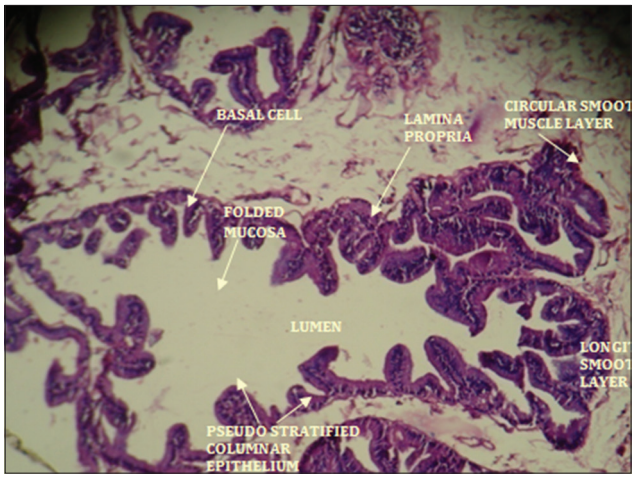
Photograph 1: Histological section of testicular tissue



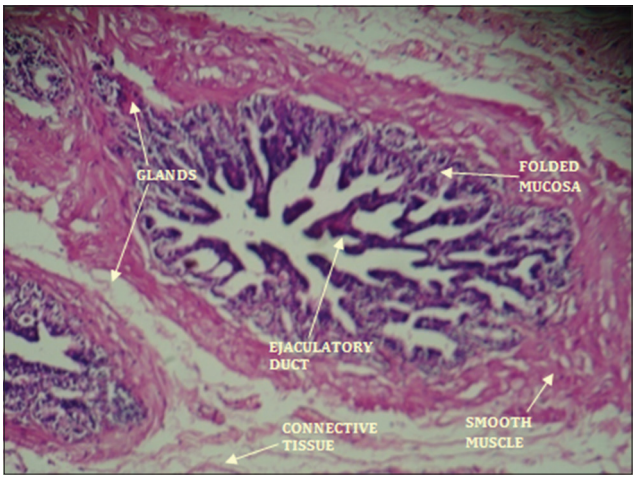
Photograph 2: Histological section of epididymis tissue



Photograph 3: Histological section of vas deferens



Photograph 4: Histological section of seminal vesicle



Photograph 5: Histological section of prostate gland

need for acceptance, our need for affirmation, and our need for life.[1] Sexual function is an important component of quality of life and subjective well-being in humans.[1,13] In recent times, it is believed that because of altered lifestyle, stressful living conditions, diverse pollutants, certain prescription and several non-prescription drugs, dietary toxins, and certain nutritional deficiencies, sexual life is negatively affected.[42-45] In ancient time, people used external agents in the form of food, drinks, and self-made preparation to maintained or enhance the sexual power. These external substances possessed pharmacological and psychological action to fortified sexual or reproductive system.[46,47] Ayurveda realized the problem of male sexual dysfunction thousands of years ago and developed a separate specialty, namely, reproductive medicine (Vaajeekarana). It realized, among other things, the role of the nervous system, cardiovascular system, and psychological aspects of fertility, and male sexual performance; it has also recommended an appropriate use of plant-based remedies, a proper lifestyle, and nutritious diet for improving overall health and treating male sexual dysfunctions.[48] Despite the use of herbal medicines over many centuries, only a relatively small number of plant species have been studied for possible medical applications. Safety and efficacy data are available for an even smaller number of plants, their extracts and active ingredients, and preparations containing them. There is little or no information regarding their phytoconstituents and the pharmacological effects of these drugs on the animal models.[49,50] Most herbal products in the market today have not been subjected to drug approval process to demonstrate their safety and effectiveness. Over 600 plants are described in the original ayurvedic compendia such as *Charaka Samhita* and *Sushruta Samhita*.[47-50] In many developing countries, medicinal plants have not been well studied, tested, or documented.[50] Most of the information is still in the hands of traditional healers, and knowledge of healers is either lost or passed to the next generation by word of mouth. Despite the vast knowledge of medicinal plants existed worldwide, only few medicinal plants were investigated for the drug discovery for the management and treatment of male sexual dysfunction. Preclinical studies are conducted before going to clinical study to investigate the biological efficacy of new drugs. Therefore, for the discovery of new drugs for the management and treatment of male sexual dysfunction, preclinical investigations are required for better understanding of the disease mechanisms in much closely similar human situation as well as for discovering newer targets and drugs for the treatment of male sexual dysfunction.

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