

Need of Clinical studies on the efficacy of Nutraceuticals for treating Drug-Induced male Sexual Dysfunction

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Nutraceuticals to prevent Male Sexual Disorders:

Male sexual dysfunction (MSD) is a physical or psychological problem which has an impact on the quality of life. Infertility is a global problem affecting about 8–12% of couples worldwide. Idiopathic male infertility is a common disorder with almost no definite medicinal treatment¹. MSD is a repeated inability to achieve normal sexual intercourse, includes various forms such as premature ejaculation, retrograded, retarded or inhibited ejaculation, erectile dysfunction (ED), arousal difficulties (reduced libido), compulsive sexual behavior, orgasmic disorder and failure of detumescence². There are various underlying causes such as cardiovascular leakage, diabetes mellitus, obesity, and/or drugs for impotence³.

In recent decades, interest in the use of nutraceuticals and functional foods has risen substantially. This is because of their safety, adequate efficacy, and potency⁴. A nutraceutical product is a substance, which brings physiological benefit or provides protection against chronic diseases⁵. There is growing need of alternative medicines to treat ED as well as improve libido because in Pakistan, the currently available synthetic products such as tadalafil (Cialis) and sildenafil (Viagra), the phosphodiesterase type-5 inhibitors (PDE5is), not only sold with higher prices in black market but also produce serious adverse effects. These drugs have been used and advertised widely since the 1997s in the USA. Moreover, treatments for MSD are not adequate and their curative potential is unsatisfactory⁶. On the other hand, psychological stress, insufficient physical exercise, certain nutritional deficiencies, and various etiological factors may leads to incapability to have sexual pleasure². Hormonal imbalance, genetic, and environmental factors may contribute to development of idiopathic male infertility. More than 1000 genes are involved in spermatogenesis, but just a few of them are known⁷. Moreover, there is some evidence that diet affects the reproductive system also on the transcriptome level⁸. In this context, there is growing interest in the use of traditional natural therapies for the prevention of sexual disorder including ED and improving libido for patients who have low sexual drive.

Folk remedies for male ED have been used long time ago, with some being advertised widely since the 1930s. Previously, it has been shown that various phytochemicals within traditional dietary foods and herbs have demonstrated many pharmacological properties in experimental models, which are predictive of human clinical efficacy. Aqueous crude extract of *Zea mays* (maize) administered at doses of 25, 50, and 75 mg/kg produced aphrodisiac effects by acting at the 2 main levels of the central nervous system that control ejaculation, the brain and the spinal cord in Wistar rats⁹. Enhanced aphrodisiac activity as observed by increased mounting, intromission, and erection frequencies in rats

administered with aqueous extracts of *Crocus sativus* (Saffron) at doses of 80, 160, 320 mg/kg body weight¹⁰. It has been reported that oral administration of *Withania somnifera* (Indian ginseng) at dose of 470 mg/kg body weight for 6 days induced testicular development and spermatogenesis in immature Wistar rats; and improved prosexual behavior (chasing, nosing, and genital sniffing) and sperm production as well as serum testosterone levels in sluggish mice^{11,12}. Administration of hydro-alcoholic and aqueous extract of the roots of *Asparagus racemosus* (*Asparagus*) at doses of 200 and 400 mg/kg showed strong aphrodisiac potential and increased sexual performance in male Wistar rats. Penile erection, measured by Penile Erection Index, improved considerably and other indicators of sexual performance such as latency in mount, intromission, and ejaculation and hesitation time was reduced while mount frequency was increased¹³. Oral administration of *Mucuna pruriens* (velvet bean) seed extracts improved sperm concentration and motility by inhibiting lipid peroxidation and recovered the levels of plasma lipids, cholesterol, antioxidant vitamins, and fructose in oligospermic patients¹. Male rats administered with extract of *Ferula asafetida* (Stinking gum) oleo–gum–resin at various dosages (25, 50, 100, and 200 mg/kg) for 6 weeks showed improved sperm count, motility, viability and morphology¹⁴. Enhanced sexual behavior in the form of increased penile erection and reduced hesitation time, arousal, vigor, and libido has been observed in rats treated with the aqueous extracts of the roots of *Chlorophytum borivilianum* (White musli) at doses of 125 and 250 mg/kg body weight for 60 days which was attributed to its testosterone-like effects. Increased erection also indicated a possible role of nitric oxide¹⁵. *Curculigo orchioides* (Black musli) is another medicinal plant whose ethanolic extracts of rhizome at dose of 100 mg/kg for 30 days have shown remarkable improvement in penile erection, mating performance and vigor, mount frequency, and ejaculation. It has spermatogenic potential and has anabolic effects which are seen in the form of increased weight of reproductive organs¹⁶. *Curculigo orchioides* also plays a significant role in overcoming physically induced sexual dysfunction, such as testicular damage, by enhancing the reduced spermatogenesis¹⁷. Administration of ethanolic extracts of *Abelmoschus manihot* (sunset hibiscus) at doses of 100 and 200 mg/kg for 7 days have increased penile erection, index, sperm count, sexual performance, and vigor and enhanced mount and intromission frequency in mice due to its spermatogenic and anabolic effects¹⁸. Administration of ethanolic extract of seeds of *Bryonia lacinosa* (Bryony) at doses of 50, 100, and 150 mg/kg body weight for 28 days improved sexual behavior, such as frequency and latency of mount and intromission, increased weights of the reproductive organs and increased spermatogenesis and sperm count, and increased serum levels of fructose, testosterone and LH were reported, thereby reflecting the androgenic activity of the extract as well as its effect on the hypothalamic–pituitary–gonadal axis in rats. The probable mechanism of action appears to be the stimulation of gonadotropins through hypothalamus activation¹⁹. The root, flower and leaf of *Argyreia*

speciosa (woolly morning glory) have been shown to possess aphrodisiac properties as evaluated by an increased mounting in mice²⁰. A polyherbal drug consisting of dried roots of *A. speciosa* has been shown to be an effective treatment towards male impotency and sterility as observed by increased testosterone levels²¹. Therefore, nutraceuticals and herbs have aphrodisiac potential and protect the spermatogenesis against various damages. The philosophy behind the use of nutraceuticals is to focus on prevention of disease, as said by Hippocrates “let food be your medicine and medicine be your food”⁴.

Nutraceuticals for the Treatment Male Sexual Disorders:

Drug-induced sexual dysfunction is a common side effect of psychoactive medication, many frequently prescribed medicines, chronic medical conditions as well as sex stimulants. Traditional medicine presents various food and remedy options for treating male sexual and erectile disorder. We report here a case of 30-year-old man with history of use of Tadalafil (Cialis 10mg), a PDE5 inhibitor, for three years. His sperm analysis showed severe oligozoospermia. After taking a nutritional therapy he had a remarkable improvement in his sperm parameters, libido, and sexual behavior. Drug was discontinued for 3 months before start of (nutritional) therapy. The patient was put on traditional medicine, treated with “APHRO84” compound for 12 weeks because spermatogenesis takes 75 days. About 7g of (herbal) confection was taken once daily in the evening (17:00 to 18:00 hrs) with a cup of hot milk. This compound is a combination of cinnamon (25%), Black cumin (15%), Tribulus terrestris (15%) and ginger (10%), which are prepared in a powder form and mixed with honey (35%).

This nutraceutical having both a vegetable source (phytochemical) as well as an animal origin (metabolite complex) possess pharmacologically active substances which have inherent therapeutic properties due to the natural active principles of recognized effectiveness which they contain. The mode of action of aphrodisiacs involves 3 types: increase sexual strength and libido, improve potency and/or enhance sexual pleasure. Honey is a popular aphrodisiac used for centuries to bring romance in marriages. It is believed to have aphrodisiac potential^{22, 23}. It has been shown that administration of Cinnamomum cassia (cinnamon) at dose of 100 mg/kg for 28 days produced erectogenic and aphrodisiac effects due to its potential to inhibit arginase activity and increase smooth muscle collagen ratio in the rat penile tissue²⁴. *Nigella sativa* (Black cumin) increases spermatogenesis in rats, sexual weakness and aphrodisiac⁶. *Zingiber officinalis* (ginger) increases sexual potential and also has aphrodisiac effects²⁵. *Tribulus terrestris* (tribulus) possess stimulatory effect on sperm quantity and quality in males with moderate idiopathic oligozoospermia⁶. It has androgen enhancing property. Protodioscin (phytoconstituent of *T. terrestris*) improves sexual desire and enhances erection in males by the conversion of protodioscin to DHEA (De- Hydro-Epi- Androsterone). *T. terrestris* increases cGMP and intracavernosal pressure in vivo²⁶.

Amongst the nutraceuticals and functional foods used for the treatment of loss of libido (male infertility) and ED as well as aphrodisiac effects include, but are not limited to almonds, pistachios, hazelnuts, coconut, cashew nut, sesame, frankincense, alyssum, and gingers⁷. An appropriate use of plant-based remedies, a proper lifestyle as well as healthy and nutritious diet for improving overall health and treating MSD is also recommended.

Conclusion:

Considerable evidence suggests that majority of nutraceuticals possess

multiple pharmacological properties to help treat sexual disorders. However, clinical studies on the use of these nutraceutical compounds in preventing and treating sexual disorders are lacking. In addition, the possible biochemical and molecular mechanism(s) of action should be investigated to develop new, effective, and safe drug for the management and treatment of MSD. The major imperative of the nutraceutical industry is to effectively translate insights gained from basic research into new medicines. On the basis of our results, we believe that this natural aphrodisiac has the potential to become ‘an established nutraceutical’ after there are sufficient clinical data to demonstrate such an aphrodisiac benefit.

Conflict of Interest: There are no conflicts of interest

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