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Nutritional Supplement and Medicinal Plant Extract for the Management of Male Sexual Dysfunction

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Abstract

Male sexual dysfunction is a prevalent condition with significant impacts on quality of life. In recent years, there has been growing interest in the use of nutritional supplements and medicinal plant extracts as alternative approaches for managing this condition. This review article provides a comprehensive overview of the role and potential benefits of herbal extracts and nutrients commonly used in the Nano Leo formulation. The proposed mechanisms of action for each component are discussed, along with supporting scientific evidence from relevant studies. Key components such as L-arginine, *Tribulus terrestris* extract, *Hypericum perforatum* extract, *Mucuna pruriens* extract, *Pinus gerardiana* extract, *Ginkgo biloba* extract, zinc, and vitamin D3 are highlighted for their ability to improve erectile function, ejaculation latency, libido, and overall sexual satisfaction. The findings suggest that these supplements may offer promising alternatives to conventional pharmacological therapies while addressing underlying physiological pathways. This review underscores the importance of exploring integrative approaches to enhance male sexual health and satisfaction.

Keywords

Male Sexual Dysfunction, Nutritional Supplements, Medicinal Plant Extracts, Herbal Extracts, Alternative Approaches

1. Introduction

Male sexual dysfunction encompasses a range of conditions that can result in the inability to engage in satisfactory sexual intercourse. It is a multifactorial disorder

that includes distinct forms such as inhibited ejaculation, premature ejaculation (PE), delayed or retrograde ejaculation, erectile dysfunction (ED), reduced libido due to arousal difficulties, compulsive sexual behavior, orgasmic disorder, and failure of detumescence. The prevalence of male sexual dysfunction is increasing globally due to various factors, including the growing aging population and the emergence of additional causes [1].

India has earned a reputation as the global epicenter of lifestyle diseases, contributing to its label as the world's "impotence capital", likely due to the significant prevalence of such ailments and its vast male population [2]. According to a study conducted by Sathyanarayana Rao TS from South India, male sexual diseases are more prevalent between the ages of 41 and 60 when compared to other age groups. Male ED was least prevalent among those aged 26 - 30 (8.6%), and most among those aged 51 - 60 (27.6%) among the age groups studied. PE was not detected in the 18 - 25 age range or among people over the age of 60. Unmarried men had a higher frequency of ED and PE, whereas married men had a higher prevalence of hypoactive sexual desire disorder [3]. According to a separate study conducted in North India by Singh AK *et al.*, the prevalence of sexual health disorders varied by age. The findings indicated that individuals above the age of 30 exhibited higher rates of loss of libido (37.0% vs. 9.3%), ED (7.6% vs. 1.9%), and PE (6.3% vs. 3.3%) compared to individuals aged 18 - 30 years old. On the other hand, individuals aged 18 - 30 showed higher rates of masturbation guilt (26.4% vs. 13.2%), nocturnal emission (19.0% vs. 6.3%), and inability to retract the foreskin (7.6% vs. 1.9%) [4].

An individual's sexuality is very important since it affects their entire well-being. Positive self-esteem and a profound sense of fulfillment are intimately linked to the experience of satisfying sexual functioning. Sexual dysfunction, on the other hand, has been linked to psychological distress and can have a negative impact on one's quality of life [5]. Despite significant advancements in pharmacological treatments, there remains a notable gap in the adoption of these therapies. This gap emphasizes the necessity for alternative supplements to address the existing need.

This review examines the current pharmacological therapies for male sexual dysfunction in brief while highlighting the significance of selected nutritional supplements, such as L-arginine, *Tribulus terrestris* extract, *Hypericum perforatum* extract, *Mucuna pruriens* extract, *Pinus gerardiana* extract, *Ginkgo biloba* extract, zinc (zinc sulphate), vitamin D3 and herbal extracts in this domain. To address this need, this review aims to evaluate the efficacy, mechanisms of action, and safety of these selected nutritional supplements and herbal extracts in managing male sexual dysfunction.

2. Pharmacological Management of Male Sexual Dysfunction

Phosphodiesterase inhibitors are usually regarded as the first-line therapy for ED. In the United States, the Food and Drug Administration has approved various

PDE5 inhibitors like avanafil, lodenafil, sildenafil, udenafil, mirodenafil, tadalafil, and vardenafil for ED. The therapeutic benefits of these treatments hinge upon the processes of sexual arousal and the attainment of penile erection. For patients who respond poorly to the first line of treatment, Alprostadil, commonly known as prostaglandin E1, is used as a backup treatment for ED. Apart from this gonadotropin replacement therapy has been approved for use in patients with hypogonadism [6].

While these medications are generally well tolerated, potential side effects include headaches, dyspepsia, nasal congestion, flushing, syncope, visual loss, priapism, and myocardial infarction [7]. Nevertheless, these medications have specific constraints, including potential interactions with food consumption and an elevated risk of hypotension when combined with alpha-blockers. In the case of nitrates, such interactions can pose life-threatening risks. It should be noted that these pharmacological treatments just treat the symptoms of ED and do not address the underlying pathophysiology. Furthermore, this line of treatment is only effective in 60% - 70% of patients, highlighting the necessity for the development of extra or alternative therapies [8].

3. Management of Male Sexual Dysfunction Using Nutritional Supplements and Herbal Extracts

This section focuses on selected Ayurvedic and traditional herbs that have a long history of use as treatments for sexual dysfunction. These plants have been used in various formulations to boost male sexual function and fertility. Numerous plants have also been examined and analyzed for their effects on sexual functions and reproductive characteristics. Many studies have investigated the active constituents that improve sexual activity and spermatogenesis while also having a positive effect on reproductive parameters.

3.1. L-Arginine

L-arginine, an amino acid synthesized in the body from L-citrulline, is essential for nitric oxide (NO) production [9]. NO is synthesized by nitric oxide synthase (NOS) enzymes mainly neuronal NOS (nNOS) and endothelial NOS (eNOS) in penile tissues [10]. During sexual stimulation, spinal impulses trigger NO release from nerve endings and an endothelial cell in the penile arteries [9]. NO diffuses into the smooth muscle cells of the corpora cavernosa and activates soluble guanylate cyclase (sGC). sGC catalyzes the conversion of GTP to cyclic GMP (cGMP), a key secondary messenger in erection. This cGMP activates protein kinase G (PKG), which opens potassium channels and lowers intracellular calcium levels. This calcium reduction causes relaxation of cavernosal smooth muscle, increasing arterial inflow and compressing veins (veno-occlusion), leading to erection. In ED, this pathway is disrupted due to reduced NO release or impaired NOS activity. Conditions like diabetes, hypertension, oxidative stress, and androgen deficiency reduce NO bioavailability and cGMP production. Thus, disruption of

the L-arginine-NO-cGMP pathway is a fundamental biochemical mechanism underlying ED [10].

L-arginine is well absorbed by the body when taken orally. It is metabolized, and its bioavailability ranges from 5% to 50% and 51% to 87%, respectively. It reaches maximum blood concentration in 20 to 30 minutes and has a half-life of 1.5 to 2 hours. In general, oral doses of up to 9 g/day of L-arginine are well tolerated, with only a small number of patients experiencing minor side effects such as slight drops in blood pressure, nausea, and vomiting. Cystic fibrosis patients may have stomach pains and bloating. Blood urea nitrogen and urea levels may rise in people with compromised renal function [9].

The natural origin of L-arginine, its good bioavailability after oral absorption, and its typically well-tolerated nature make it suitable for long-term treatment are all reasons why it is commonly used as a supplement for ED [9]. Numerous randomized, placebo-controlled trials have assessed the effectiveness of L-arginine, either alone or in combination with other compounds, in the treatment of ED. Although many of these studies involved small sample sizes and were considered pilot in nature, they provide encouraging evidence supporting the use of L-arginine, particularly in combination with other agents [9]. A notable 3-month randomized controlled trial using high-dose L-arginine (6 g/day) demonstrated significant improvements in International Index of Erectile Function-6 (IIEF-6) scores and peak systolic velocity (PSV) in patients with mild to moderate vasculogenic ED, while only IIEF-6 improvement was observed in those with severe ED [11]. Furthermore, a meta-analysis of 10 RCTs involving 540 patients confirmed the efficacy of L-arginine supplementation (1500 - 5000 mg), showing significant improvements in several IIEF subdomains excluding sexual desire with a low adverse event rate (8.3%) and no serious side effects. However, key limitations of existing studies include the exclusion of patients with severe ED, lack of clear differentiation of ED etiology, and variations in treatment dosage and duration, all contributing to study heterogeneity [12].

3.2. Tribulus Terrestris Extract

Tribulus has a history of use in traditional Chinese medicine and Ayurveda for various purposes, including alleviating chest pain, addressing heart-related issues, relieving dizziness, treating skin and eye disorders, expelling kidney stones, and acting as a diuretic and tonic. In addition, it is commonly marketed as a dietary supplement to enhance sexual function [13].

Protodioscin, a component that stimulates the increase of certain sex hormones, may be responsible for Tribulus' aphrodisiac effects. Furthermore, erectogenic effects can be induced via the conversion of protodioscin to DHEA [14] or by concentration-dependent mechanisms in the nitric oxide (NO)/NO synthase pathway and the corpus cavernosum (CC) endothelium [15]. Regardless of testosterone levels, the release of NO may explain the physiological changes observed with tribulus treatment. A luteinizing effect linked with gonadotropin-like activity

was observed in rats with ovarian cysts in a study employing tribulus extract [16].

Kamenov *et al.* recently conducted a prospective clinical experiment to investigate the efficacy and safety of a standardized extract for the treatment of males with mild to severe ED, with or without hypoactive sexual drive disorder. The 12-week trial used a double-blind, placebo-controlled design with parallel groups and involved a daily dose of three coated tablets. The change in the IIEF score following the treatment period was the trial's primary outcome. The results showed that the treatment group had a substantial improvement in erection, libido, and orgasmic function, with no significant difference in the occurrence of side effects when compared to the placebo group [17].

Two investigations have confirmed the beneficial effects of *Tribulus terrestris* and other components in medicinal products. The first study found that a dietary supplement called "Tribulus" increased anaerobic muscular power and blood testosterone levels in young men after 20 days of use [18]. Another study, a double-blind placebo-controlled experiment with older men with a history of ED and lower levels of total and free testosterone, indicated the great efficacy of a formulation known as "Tradamixin." This medicine, which included *Tribulus terrestris* as well as Alga Eckonia, D-glucosamine, and N-acetyl-glucosamine, was given to elderly men daily for two months and demonstrated improvements in libido and elevated testosterone levels. However, in all tests, it was unclear if a specific component was solely responsible for the reported biological benefits or if *Tribulus terrestris* had a role in those effects [19].

3.3. *Hypericum perforatum* (St. John's Wort) Extract

The neurotransmitter 5-hydroxytryptamine (5-HT) regulates a variety of autonomic and behavioral activities, including ejaculation. The participation of the medial preoptic area and the paraventricular nucleus of the hypothalamus, identified as regions involved in integrating sexual responses in men, is likely to assist the link between 5-HT and ejaculation. Multiple lines of evidence suggest that increased synaptic availability of 5-HT within the central nervous system inhibits ejaculation. As a result, PEis thought to be linked to a genetically preset ejaculation reflex with a lower threshold [20].

Several selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, sertraline, and fluoxetine, have been administered "off-label" for symptoms of PE. The effects of fluoxetine, paroxetine, and sertraline on intravaginal ejaculatory latency time (IELT) have been documented in placebo-controlled clinical trials. Paroxetine significantly alleviated PE-related problems in a randomized, double-blind, placebo-controlled study. Furthermore, after six weeks of treatment, all three SSRIs—fluoxetine, paroxetine, and sertraline—resulted in a much greater increase in mean IELT compared to the placebo group [21] [22].

Hypericum perforatum (St. John's wort, SJW), a natural supplement has been demonstrated pharmacologically to inhibit serotonin reuptake and delay ejaculation in a rat model of PE [23]. Two isolated compounds from *H. perforatum*-hy-

pericin and hyperforin—have been extensively studied for their potential therapeutic effects [24]-[26]. *Hypericum perforatum* influences several neurotransmitter systems that are crucial for male sexual function [27]. Its main active compound is hyperforin, strongly inhibits the synaptosomal reuptake of serotonin (5-HT), dopamine (DA), norepinephrine (NA), gamma-aminobutyric acid (GABA), and L-glutamate, thereby increasing their synaptic availability [24] [25]. This neurotransmitter modulation helps improve mood and may influence sexual behavior and ejaculatory control. Hyperforin also alters intracellular sodium (Na^+) and hydrogen ion (H^+) gradients, affecting neurotransmitter storage and release in synaptic vesicles. Though hypericin was initially believed to inhibit monoamine oxidase (MAO), this effect is not significant at in vivo therapeutic concentrations. SJW also indirectly affects sigma receptors, which may further contribute to its antidepressant and ejaculatory-delaying properties. Notably, it enhances serotonergic activity without causing the severe sexual side effects often associated with SSRIs, positioning SJW as a potential natural alternative for managing PE and other sexual dysfunctions. Its multifaceted receptor-level interactions support male sexual health with greater tolerability and fewer adverse effects [27].

Managing PE remains a clinical challenge in urology. While antidepressant medications—particularly SSRIs—are frequently utilized as part of the standard treatment approach, the therapeutic role of *Hypericum perforatum* (St. John's Wort) in PE is still under investigation. Although definitive evidence is lacking, it is hypothesized that H. perforatum may offer benefits through its antidepressant effects and its ability to modulate neurotransmitter activity, which could potentially support ejaculatory control [17].

In a pilot study conducted by Kaufman *et al.*, the effectiveness of *H. perforatum* was evaluated among sixteen subjects. The study revealed that individuals consuming hyperforin extract experienced a significant increase in the mean IELT, rising from 24,629 to 33,134 seconds ($p < 0.002$). Impressively, 87.5% of the participants (14 out of 16 men) reported an improvement in their IELT, irrespective of whether they considered PE bothersome or not. Moreover, there was a noteworthy increase in male satisfaction levels, elevating from 3.8 ± 0.27 to 4.25 ± 0.21 ($p < 0.03$). Equally notable, female satisfaction levels demonstrated a significant improvement, increasing from 4.9 ± 0.27 to 5.2 ± 0.23 ($p < 0.04$). However, the study's small sample size, lack of a placebo control, short duration, reliance on subjective satisfaction measures, and absence of systematic side effect assessment limit the reliability and generalizability of these findings [20].

Asgari *et al.* discovered substantial findings in prospective, double-blind, randomized, placebo-controlled study. The trial included a hypericum extract group and a placebo group. When comparing mean IELT values, there was a significant difference between the groups ($p < 0.001$). The IELT rose from 1.17 minutes to 5.8 minutes in the hypericum extract group. Furthermore, patients who consumed hypericum extract had significantly higher IIEF-5 scores for intercourse pleasure and overall satisfaction ($p < 0.001$). However, there were no significant group dif-

ferences in orgasmic function, erectile function, or sexual desire ratings. Mild side effects such as headache, constipation, and photosensitivity were observed by 27% of the hypericum extract group (6 individuals) [28]. *H. perforatum* can induce photosensitivity, primarily due to hypericin, a powerful photosensitizer that absorbs UVA at 300 nm and visible light in the range from 550 - 590 nm, leading to the generation of reactive oxygen species (ROS). These ROS can damage cellular structures, contributing to skin photoaging and cytotoxicity upon sun exposure. The risk of phototoxicity may increase when *H. perforatum* is taken alongside certain medications such as azithromycin, doxycycline, or ibuprofen [29]. Clinical studies evaluating oral doses of *H. perforatum* in healthy men demonstrated no significant increase in photosensitivity after 14 days of treatment. Despite achieving steady-state levels of hypericin and pseudohypericin, the minimal erythema dose (MED) remained largely unchanged in most participants. Although mild photoreactions were observed in a few individuals, the overall findings suggest that the extracts are safe when used under prescribed conditions [30].

The authors stated that *H. perforatum* could be regarded as an effective and safe therapy option for PE, probably due to its effect on neurotransmitters such as serotonin [28]. Despite these promising results, caution is warranted due to potential interactions between St. John's Wort and SSRIs, such as sertraline, paroxetine, and venlafaxine. Concurrent use may lead to serotonin syndrome, a serious condition characterized by mental status changes, tremor, gastrointestinal symptoms, autonomic instability, and restlessness. As both SJW and SSRIs inhibit serotonin reuptake through a pharmacodynamic mechanism, their combination increases the risk of excessive serotonergic activity. A reported case of a patient taking both SJW and sertraline supports this interaction. Such events highlight the clinical relevance and the need for caution required when combining these agents [31].

3.4. *Mucuna pruriens* Extract

Mucuna pruriens is a well-known herbal therapy that has traditionally been used to treat male infertility and nervous system diseases and as an aphrodisiac. *Mucuna pruriens* is a plant with a wide variety of phytoconstituents, including alkaloids, flavonoids, tannins, and phenolic compounds. These compounds contribute to several of physiological and pharmacological functions. Notably, *M. pruriens* seeds are high in L-DOPA, a non-protein amino acid that acts as a direct precursor of DA, a neurotransmitter that is necessary for mood regulation, sexuality, and movement. Other amino acids found in the seeds include glutathione, lecithin, gallic acid, and beta-sitosterol. Mature seeds contain 3.1% to 6.1% L-DOPA, as well as trace levels of serotonin, nicotine, dimethyltryptamine (DMT), bufotenine, 5-MeO-DMT, and beta-carboline. In contrast, the leaves contain about 0.5% L-DOPA, 0.006% dimethyltryptamine, and 0.0025% 5-MeO-DMT [32].

In a prospective controlled study conducted by Shukla *et al.*, the mechanism of action of *M. pruriens* in the treatment of male infertility was investigated. The study included four parallel groups of subjects: normozoospermic, oligozoosper-

mic, asthenozoospermic patient groups, and a control group consisting of 75 age-matched healthy men. The infertile men were administered *M. pruriens* seed powder orally in a single dose of 5 g/day, along with milk, for duration of three months. The study findings indicated that treatment with *M. pruriens* had a positive impact on steroidogenesis, leading to an improvement in sperm concentration. Furthermore, it was observed that the treatment contributed to enhanced semen quality by improving sperm motility [33].

In a study conducted by Ahmad *et al.*, the effects of *M. pruriens* seeds on semen profiles and biochemical levels in the seminal plasma of infertile men were investigated. The study was divided into two groups of 60 people each. The control group included age-matched healthy men with normal sperm profiles and a track record of successful pregnancies. The study group consisted of subgroups of normospermic, oligospermic, and asthenospermic people, each with 20 patients. For three months, the trial subjects were given *M. pruriens* seed powder orally at a dose of 5 g/day with milk. This treatment significantly reduced lipid peroxidation, enhanced spermatogenesis, and improved sperm motility, according to the findings [34].

Shukla *et al.* investigated the effects of *M. pruriens* on infertile men experiencing psychological stress. The study included 60 subjects undergoing infertility screening, divided into three subgroups based on semen profiles. A control group of 60 healthy men was also included. The infertile subjects received *M. pruriens* seed powder orally. The results showed that *M. pruriens* improved the antioxidant defense system, managed stress, and enhanced sperm concentration and motility in infertile men [35].

Based on these studies, it has been found that *M. pruriens* has the potential to improve sperm morphology to some degree. Importantly, no adverse effects were reported in any of these studies.

3.5. *Pinus gerardiana* (Chehelghoza) Extract

The therapeutic applications of *P. gerardiana* plant, as per the Ayurvedic Pharmacopoeia, encompass a range of conditions. They include [36]:

Epilepsy	Rheumatism
Facial Palsy	Cough
Wound	Hiccup
Anemia	Lower back pain
Intercoastal neuralgia and pleurodynia	Paralysis/Hemiplegia
Gout	Asthma

The plant's various parts contain distinct phytoconstituents. The seeds are known to contain linoleic acid, unsaturated fatty acids, oleic acid, vitamin E, Phytosterols, polyphenols, palmitic acid, lutein, lycopene, carotenoids, and several other chemical constituents. On the other hand, the bark is rich in β-carotene,

flavonoids, tannins, phenolics, and lycopene. Lastly, the leaves are reported to possess flavonoids, alkaloids, tannins, and saponins. Each part of the plant harbors its own unique composition of phytoconstituents [37].

Scientific evaluations have revealed that the plant exhibits diverse biological activities, including antioxidant, antithrombotic, anti-platelet, antidiabetic, anti-inflammatory, antifungal, and antibacterial properties [30].

Safari S *et al.*, evaluated the effectiveness of chehelghoza in rats. A total of 32 male rats were allocated into four groups at random. For fourteen days, rats in groups one, two, and three were fed daily meals containing 5%, 25%, and 50% Chehelghoza, respectively. The rats in the fourth group served as the control and were fed a conventional meal devoid of Chehelghoza for the same amount of time. The results showed that varied doses of Chehelghoza, which contained phytosterols, had the potential to reduce male fertility parameters [38].

3.6. *Ginkgo biloba* Extract

Ginkgo biloba is a widely used herbal supplement globally, renowned for its various beneficial properties. The extract derived from the leaves of the *G. biloba* tree contains compounds such as proanthocyanidins, phenolic acids, flavonoid glycosides (such as kaempferol, myricetin, quercetin, and isorhamnetin), as well as terpene trilactones known as bilobalides and ginkgolides. Additionally, the leaves of the *Ginkgo biloba* tree possess unique components like ginkgo biflavones, polyprenols, and alkylphenols. These constituents, including phytoestrogens, have been observed to modulate NO levels, support soft tissue systems, and enhance blood flow, which are crucial for women's sexual response. Some studies have investigated the effects of *Ginkgo biloba* extract GBE on sexual dysfunction SD thus far [39].

Ginkgo possesses the ability to enhance the levels of NO in the bloodstream, leading to the dilation of blood vessels and improved circulation [40]. This property of ginkgo makes it potentially beneficial for addressing different symptoms associated with sexual dysfunction by facilitating increased blood flow to specific areas of the body.

In a study conducted by Lima VBA *et al.*, the effects of *Ginkgo biloba* extract (GBE) were examined on the vas deferens (VD) contraction in mice. The results revealed that GBE exhibited inhibitory effects on certain mechanisms involved in the generation of DD contraction. Interestingly, this effect was not solely attributed to the inhibition of voltage-dependent calcium channels. These findings suggest that GBE, along with quercetin, may hold promise as potential pharmacological strategies for the treatment of PE [41].

In a pilot study conducted by Sohn M and Sikora R from Germany, fifty patients with arterial erectile impotence were treated with oral administration of 240 mg *Ginkgo biloba* extract for 9 months. Unlike previous studies relying on subjective measures, this study incorporated objective response criteria. The results revealed significant improvements: patients who previously achieved satisfactory erections

with intracavernous drug application regained spontaneous erections after 6 months of *Ginkgo biloba* treatment. They also experienced improved penile flow rates and rigidity. Among the subgroup of thirty patients who initially struggled to achieve satisfactory erections with high-dose intracavernous drug application, nineteen regained pharmacologically induced erections during the therapy, while eleven remained impotent. Notably, all patients in this subgroup demonstrated improved objective response parameters. This study was limited by its small sample size and lack of a placebo-controlled design, which may affect the validity of the results [42].

In an open trial involving 63 participants, *Ginkgo biloba* extract—known for its cognitive-enhancing effects, was examined for its effectiveness in treating antidepressant-induced sexual dysfunction, primarily caused by SSRIs. The results revealed an 84% success rate in treating this condition. Among the participants, women (n = 33) displayed a higher response rate of 91% compared to men (N = 30) at 76%. *Ginkgo biloba* exhibited positive effects on all phases of the sexual response cycle, encompassing desire, excitement, orgasm, and resolution. The trial was prompted by a geriatric patient's report of improved erections while taking *Ginkgo biloba* for memory enhancement. Dosages ranged from 60 mg qd to 120 mg bid, with an average of 209 mg/d. Common side effects encompassed gastrointestinal disturbances, headaches, and general central nervous system activation. The article also explores potential pharmacological mechanisms, including impacts on platelet activating factor, prostaglandins, peripheral vasodilation, and modulation of central serotonin and NA receptor factors [43].

3.7. Zinc

Zinc is essential for reproductive physiology, and a lack of it has been associated with decreased serum testosterone levels in men with uremia, sickle cell anemia, and infertility [44]. In a study led by Prasad AS, young men were subjected to a low-zinc diet to intentionally induce zinc deficiency. After duration of 20 weeks, testosterone levels were assessed and a substantial decline of nearly 75% was observed. Furthermore, the study explored the impact of zinc supplementation in elderly men. The results revealed that increased zinc intake resulted in nearly a twofold increase in testosterone levels among the elderly participants. These findings provide compelling evidence highlighting the significant role of zinc in testosterone production [37].

Another study investigated the impact of folic acid and zinc sulphate supplementation on hormone levels and seminal antioxidant defense in varicocelectomised patients with impaired spermatogenesis. The participants were divided into four groups and blood and semen samples were collected before and after varicocelectomy. After six months of treatment, the zinc sulphate/folic acid group showed a significant increase in inhibin B levels in peripheral blood and enhanced seminal plasma activity, suggesting that long-term administration of these supplements positively affects the hormonal status of varicocelectomised patients

[45]. Several studies have demonstrated the effectiveness of zinc on testosterone level, improvement in potency, and libido [46] [47].

3.8. Vitamin D3

Recent reports have investigated the relationship between serum 25-hydroxy (OH) vitamin D and arteriogenic ED [48] [49]. These reports have concluded that inadequate 25(OH) D levels, may be an independent risk factor for ED, particularly arteriogenic ED (A-ED). Individuals with ED should have their serum 25(OH) D levels measured regularly, and those with low vitamin D levels should consider 25(OH) D replacement treatment [41] [42].

Demirci A. *et al.* conducted a retrospective study to examine the potential benefits of incorporating vitamin D alongside daily tadalafil treatment in individuals with ED and vitamin D deficiency. The findings suggested that the addition of vitamin D to a 5 mg daily oral tadalafil regimen could enhance erectile function and sexual desire in ED patients with vitamin D deficiency [50].

These studies demonstrate that vitamin D deficiency may be an independent risk factor for ED and its replacement therapy may improve the symptoms.

The formulation containing all these herbal extracts and nutrients named "Nano Leo" was evaluated in Phase IV prospective efficacy study done at King George Medical College, Lucknow, India. In a study involving 99 men with ED (mean age 32.2 ± 4.71 years), the effects of Nano Leo, a nutrient supplement, were evaluated. The participants received daily capsules for 90 days, and the primary outcome measure was the change in erectile function using the IIEF questionnaire. Results showed a significant improvement in erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction domains of the IIEF score as early as Day 30. Testosterone levels, seminal parameters (sperm concentration and total sperm count), and quality of life domains also showed positive changes. No adverse events were reported, indicating the safety of Nano Leo. This study suggests that Nano Leo could be an effective and safe supplement for managing ED and improving sexual health [8].

The study also assessed the overall improvement in quality of life (QoL) among the participants. Results showed that there was a significant improvement in all QoL domains from baseline to 90 days. By the end of the study, 51% of patients reported their general well-being as very good, while 52% reported improvement in their overall mental/emotional state. The patient's ability to handle pressure also significantly increased to 73.6% at 90 days. Additionally, most patients (88.7% and 95.8%) rated their overall enjoyment of life and overall QoL as ranging from good to excellent by the end of the study. These findings highlight the positive impact of Nano Leo on various aspects of patients' quality of life [8].

Nano Leo, as softgelatin (SG) capsules, was dispensed to all patients as blister packs of 15 for oral administration. At initiation, a loading dose of two SG capsules was administered at bedtime for 7 days, followed by one SG capsule administered every day at bedtime for 90 days [8].

4. Place in Therapy

In recent years, the use of complementary and alternative medicines, particularly for the treatment of male sexual dysfunction, has grown in popularity. Many individuals with male sexual dysfunction turn to herbal supplements as accessible options, typically because they are hesitant to disclose their sexual problems with healthcare experts or are dissatisfied with conventional treatments. Despite having recovered erectile function, some people discontinue successful therapies due to concerns about potential side effects, aversion to drug-induced erections, high pharmaceutical costs, the need for planned sexual activity, and a lack of sexual interest [51]. Clinicians are generally cautious about endorsing herbal or alternative therapies for the treatment of medical conditions, including ED, due to the limited availability of strong scientific evidence from well-designed studies [44].

5. Summary

This review emphasizes the significance of individual herbal extracts and nutrients present in the formulation of Nano-Leo. Each component has a unique proposed mechanism of action, supported by scientific studies suggesting potential benefits. Furthermore, prospective studies on the formulation incorporating these extracts and nutrients have demonstrated its efficacy in treating male sexual dysfunction, underscoring their importance in this therapeutic context.

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Conflicts of Interest

Dr. Kapil Dev Mehta and Ms. Sarita Bajpai are employees of J B Chemicals & Pharmaceuticals Ltd.

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