Eurycoma Longifolia as a potential adaptogen of male sexual health: a systematic review on clinical studies

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[ABSTRACT] Eurycoma longifolia (EL) has been well recognized as a booster of male sexual health. Over the past few decades, numerous in vivo animal studies and human clinical trials have been conducted across the globe to explore the promising role of EL in managing various male sexual disorders, which include erectile dysfunction, male infertility, low libido, and downregulated testosterone levels. The aim of the present review is to analyze and summarize the literature on human clinical trials which revealed the clinical significance and therapeutic feasibility of EL in improving male sexual health. This systematic review is focused on the following databases: Medline, Wiley Online Library, BioMed Central, Hindawi, Web of Knowledge, PubMed Central and Google Scholar, using search terms such as “Eurycoma longifolia”, “EL”, “Tongkat Ali”, “male sexual health”, “sexual infertility”, “erectile dysfunction”, “male libido”, and “testosterone levels”. Notably, only human clinical studies published between 2000 and 2014 were selected and thoroughly reviewed for relevant citations. Out of 150 articles, 11 met the inclusion criteria. The majority of articles included were randomized placebo-controlled trials, multiple cohort studies, or pilot trials. All these studies demonstrated considerable effects of EL on male sexual health disorders. Among them, 7 studies revealed remarkable association between the use of EL and the efficacy in the treatment of male sexual disorders, and remaining 4 studies failed to demonstrate sufficient effects on male sexual health. In summary, there is convincing evidence for the prominence of EL in improving the male sexual health. The review also substantiates the use of current methodology in the development of novel and more rationale natural herbal medicines for the management of male sexual disorders.

[KEY WORDS] Eurycoma Longifolia; Male sexual disorders; Erectile dysfunction; Male infertility; Sexual libido; Testosterone

[INTRODUCTION]
Eurycoma Longifolia; Male sexual disorders; Erectile dysfunction; Male infertility; Sexual libido; Testosterone


Introduction

Sexual health impacts the quality of life of males and females significantly, regardless of age, civil status, or sexual orientation. Sexual activity involves systematic coordination between various biological systems of the body. For example, hormones and neurological pathways must be in sync to perform sexual activities. Males in addition require blood vessels, nerves, and penile integrity to be intact for an adequate erection and its continuance while performing sexual activities. Similarly, physiological coordination among muscles and nerves also play a pivotal role in regulating ejaculation of sperms from the testicles [1-2].

Sexual dysfunction (inability to have pleasing sexual activity) negatively affects the quality of life and can be the leading cause of numerous medical or psychological distresses [3-4]. According to the Sexual Advice Association, one in 10 men experiences sexual problems [5]. Hence, any sexual complaint should be taken seriously and evaluated by particular health care specialist by assessing the entire possible nuisance associated with sexual desire, penile erection, ejaculation, and orgasm. In this chain of events, the most prominent male sexual dysfunctions include erectile dysfunction (ED), premature ejaculation (PE), low libido (reduced sexual desire) as well as low level of testosterone (male sex hormone) [6].

In male sexual well-being, one of the primary causes of
dissatisfaction in sexual performance is attributed to ED, which is defined as frequent and persistent incapability of male to retain penile erection during the course of performing sexual activity [1-2, 7]. Previously published data have highlighted that the prevalence of ED is greatly influenced by age [8]. ED affects approximately 30 million men in the United States, and among them, 18% are from 50 to 59 years of age. The highest ED prevalence of 50% and 75% occurs in 70’s and 80’s of age worldwide [7-8]. There are numerous potential causes of ED, including neurologial, vascular, hormonal, pharmacological, and psychiatric causes. The therapeutic intervention of ED greatly depends on the identification of precise cause of sexual dysfunction. However, before considering pharmacological intervention, medical professionals often suggest lifestyle changes, such as anticipating regular exercise, a healthy diet, smoking cessation, and restraining alcohol intake [9]. Lifestyle changes can also include the use of a more genitalia-friendly bicycle seat [9]. Several pharmacological therapies are available for the symptomatic management of ED; among them, phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, verdenafil and tadafil, have gained remarkable attention [10-11]. These drugs improve and maintain satisfactory penile erection by regulating the blood flow to the penis. Several side effects, such as visual disturbances, flushing, back pain, and muscle pain associated with the use of PDE-5, have left many men to turn to more natural options for the management of sexual problems [12-13].

Another common ejaculatory disorder is PE, manifesting as an inappropriate ejection of sperm, prostatic, and seminal fluid via urethra. The prevalence of PE approximates 20% to 30% of men [9]. Among various potential causes of PE, the prominent problems are associated with the central control of ejaculation, innervations to the seminal tract, and sensory innervations to the genitalia/prostate [1-2]. In addition, PE can also appear as an early indicator of diabetes mellitus or may develop following surgical intervention of benign prostatic hyperplasia or can be associated with the use of certain medications such as alpha-blockers or antidepressants [10-12].

An additional sexual disorder affecting the quality of life globally is male infertility. It is a multi-factorial disorder with numerous causative factors manifesting as impaired spermatogenesis, low sperm count, erection or ejaculation issues, and hormonal dysfunction [14-15]. The prevalence of the problem which lies solely in the male partner, accounts for about one in five infertile couples [16-17]. The numerous health issues and medical problems associated with male infertility include varicocele (swelling of veins that drain testicle), undescended testes, infections, hormonal imbalance, sperm duct defects, ejaculation issues, and sperm antibodies [18]. Certain lifestyles such as the use of anabolic steroids, alcohol consumption, tobacco smoking, emotional stress, obesity and prolonged bicycling can also significantly contribute to the development of male infertility [18]. Low libido which is solely associated with low testosterone is another male sexual disorder. Most males notice considerable downfall in testosterone levels and thus sexual performance by the age 60 to 65. The penis takes longer to erect and may not have normal hardness score, which in turn affects male orgasm and ejaculatory cycle [19-23].

_Eurycoma longifolia (EL) Jack, from family Simaroubaceae, has attained remarkable recognition in Malaysia, Thailand, and Indonesia as a potential natural herbal medicine in the improvement of male sexual disorders and infertility [24-27]. The remarkable attention of researchers to EL is based on its aphrodisiac prospective, which is the ability to improve libido, restore ED, and stimulate production of testosterone [28-29], thus improving the overall male sexual well-being [30-32]. The possible mechanism involved in improving male sexual performance is associated with increased conversion of pregnenolone to progesterone, cortisol, 5-dehydroepiandrosterone (DHEA), and testosterone in corpus cavernosum tissues [30-32]. In an attempt to better understand the underlying mechanism of action, different fractions of EL root extract have been tested for their effects on sexual function, using in vivo rat models [30-31]. The extracted data highlight that eupryepetide, a bioactive component of EL root extract, exhibits aphrodisiac effects prominently by elevating the testosterone levels [30-31]. In addition, human clinical investigations on EL have also shown other beneficial effects on male sexual health [26-27] as well as its action as an “energy-booster” [33].

To date, there have been numerous studies highlighting the clinical significance of EL in the treatment of male sexual health disorders [26-27, 33, 35]. The impact of EL in managing male sexual dysfunctions is mainly studied using in vivo animal models [28-32], however, only limited clinical researches have been carried out in human clinical trials [26-27, 34-38]. More clinical data related to EL and male sexual health are required to draw the attention of modern society and increase the awareness towards EL. Thus, the present systematic review was designed to summarize up-to-date researches on the clinical significance of EL in the management of male sexual health disorders. This systematic review would provide meaningful baseline information for future work and commercialization.

Methods

**Literature search strategy**

The terms, including “Eurycoma Longifolia”, “EL”, “Tongkat Ali” “male sexual health”, “male infertility”, “erectile dysfunction”, “male libido” and “testosterone levels”, were used to search the following databases: Medline, Wiley Online Library, BioMed Central, Hindawi, Web of Knowledge, PubMed Central and Google Scholar. All the retrieved articles were carefully screened for relevant citations in 2015.

**Inclusion criteria**

Original research articles, multiple cohort studies, randomized and placebo-controlled trials and randomized
cross pilot studies regarding human clinical trials focusing on the impact of EL on male sexual health were included. In order to assess the potential of EL on male sexual health, the principle parameters focused in the present systematic review included physical damage of sexual organ and clinical parameters such as erectile dysfunction, male infertility, low male sexual libido and low level of male sex hormone (testosterone).

**Exclusion criteria**

Case reports, case series, *in vitro* studies, *in vivo* animal studies, news, letters to the editor, review articles and clinical trials on women sexual health were excluded. In case of similar studies in concurrent publications, only the most recent publications were included. The data presented in the current systematic review is focused on the effect of EL on the male sexual health; the data on its effect on other diseases were not taken into account. Studies which also investigated other dietary supplements, herbal extracts, and the modern drugs used as natural male sex boosters were also excluded.

**Eligibility criteria**

The searched articles and studies were reviewed for eligibility based on their titles and abstracts and classified into two categories. Category 1 included articles revealing significant correlation between male sexual health and EL with potential outcomes including biochemical parameters and human clinical significance trials. Category 2 included articles reporting disease mechanism, organ damage, and major factors contributing to male sexual disorders. In Category 1 there were variations in the study design, sample size or aims towards the management of male sexual health disorders via EL supplementation without serious side effects. All the articles did not report on significant serious side effects. All the searched articles in Category 1 and Category 2 were obtained in full text version and assessed by all authors for relevant selection. Only articles which were agreed upon by all authors were concomitantly included in the present systematic review. Fig. 1 presents a summary of the process for the selection of articles.

**Review method**

The articles potentially meeting the inclusion criteria with independent citations were identified and screened by the three reviewers (H.E.T, A.N.S, and I.N.M). The articles with full text versions were included in the present review after they were agreed upon by all the reviewers following detailed discussion (H.E.T, P.A.J, Z.H, A.N.S, and I.N.M). Any kind of disagreement with regard to inclusion criteria was resolved by discussion with third and fourth reviewers (A.N.S and I.N.M).

**Data extraction**

Following an inflexible selection, the published articles were extracted and deliberated thoroughly. After an efficient overview of the selected studies, the data such as country name, year of publication, type of male sexual health disorder, study design, type of study, sample size, and significant findings were extracted. For systematic description, the scope, components and key features of each of the selected studies were also extracted. Additionally, for any other supplementary information required, the authors were contacted via email or telephone call. Regarding the articles which cited previous publications, the original publication was retrieved, and the relevant data were extracted. The extracted data with a P value less than 0.05 was recorded as statistically significant.

**Results**

More than 150 articles related to EL, male sexual disorders, and pharmacodynamic profiles of EL in association with male sexual health were obtained by computer search. The majority of these articles were original research articles, systematic reviews, literature reviews, multiple cohort studies, randomized and placebo-controlled trials, pilot studies, case series, and case reports. Notably, the current systematic review did not include articles published earlier than 2000. Moreover, a significant number of articles on *in vitro* cell culture studies and *in vivo* animal models were excluded. The following articles were also excluded: (a) study design that was not clearly described, (b) treatment of male sexual disorders involving other herbal or dietary supplements, (c) use of other modern drugs as male sex boosters, and (d) unable to retrieve the full text version.

Eventually, a total of 7 human clinical trials [35–36, 38, 41, 47–49] were found eligible to be included in the present systematic review. Most of these studies were original research articles, randomized and placebo-controlled trials, multiple cohort trials and pilot studies. Notably, most of the reported studies were performed in Malaysia, followed by United States of America (USA), China, and South Africa. The sample sizes varied from 13 to 350 subjects with ages ranging from young adults (30 years) to elderly (72 years). Notably, the aim of the human clinical trials included in the present systematic review was to evaluate the therapeutic potential of EL for the treatment of male sexual disorders, with penile erection, penile hardness, male sexual libido, male infertility, and determination of the testosterone level being the prime therapeutic concerns in the majority of the studies. The key data of the selected studies are highlighted in Table 1.

**Effect of EL on ED**

Among the included human clinical trials, two were aimed to determine the considerable association between the used EL and the effects on ED [35–36] Udani and co-workers [35] executed a double-blind and placebo-controlled study in 40 to 65 years old males having significant ED and followed them up for 12-weeks. The outcomes measured included penile erection, sexual pleasure, sexual performance, erectile hardness scores and sex intended frame of mind. A remarkable improvement was found in the sexual intercourse attempt diary, scores of penile erection hardness, and sexual well-being of subjects (P < 0.05; paired *t*-test). Substantially,
no significant abnormalities in the vital organs of the body such as liver and kidney were noted by laboratory evaluations.

Another randomized and placebo-controlled parallel design study also reported a positive effect of EL on ED [36]. Tambi and co-workers executed this study with the aim to compare the clinical effects of EL in the management of male sexual health with placebo groups. For that, 30 healthy male participants between the age of 40 and 65 years were recruited. Participants were required to be in a stable heterosexual relationship for at least six months. Both partners had to agree to attempt intercourse at least once a week, on average, during the study. They observed noteworthy improvement in sexual performance, including erectile function, sexual intercourse performance, and penile hardness score \( (P < 0.05, \text{paired } t\text{-test}) \).

**Effect of EL on male infertility**

In order to investigate the effect of EL on male infertility, Tambi and co-workers [38] conducted a placebo-controlled trial on 350 males with an average age of 32.7 years and having a history of idiopathic infertility of 5.3 years. A daily dose of 200 mg of soluble extract of EL was given to all patients with subsequent analysis of semen every 3 months for a total period of 9 months. The clinical significance of EL in male infertility was evaluated by assessing the principle parameters of fertility, such as semen volume, concentration of sperms, proportion of sperms having normal morphology and motility in accordance to World Health Organization (WHO) guidelines [39]. The results showed significant \( (P < 0.05, \text{paired } t\text{-test}) \) improvement in all the seminal parameters and 11 (approx. 15%) spontaneous pregnancies. Tambi et al. [40] had also highlighted an indirect effect of EL on men’s sexual health by down-regulating stress hormone profile correlated with male sexual performance.

In addition, Ismail and co-workers [41] had conducted a 12-week, randomized, and placebo-controlled trial on Malay males according to the Good Clinical Practice (ICH-6) guidelines and Declaration of Helsinki. This placebo-controlled
Table 1  Summary of the selected studies showing promising potential in improving male sexual disorders

<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>Country</th>
<th>Major effect</th>
<th>Sample size and Age</th>
<th>Subject state</th>
<th>Study duration</th>
<th>Study design</th>
<th>EL form</th>
<th>EL dosing regimen</th>
<th>Outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Malaysia</td>
<td>Improvement in penile erection</td>
<td>109 (40–65 years)</td>
<td>Healthy males</td>
<td>+6 months</td>
<td>Double blind/ Multiple cohort study</td>
<td>Water extract</td>
<td>300 mg daily</td>
<td>A significant ( P &lt; 0.05 ) increment in penile erection and sexual libido (8.4%–8.7%). A remarkable improvement in principle sexual parameters, including penile hardness, penile erection scores, and sexual libido. [35]</td>
<td>[35]</td>
</tr>
<tr>
<td>2012</td>
<td>Malaysia</td>
<td>Increase in sex hormone and penile erection</td>
<td>320 (30–64 years)</td>
<td>Hypogonadic males</td>
<td>1–6 months</td>
<td>Multiple cohort study</td>
<td>Water soluble extract</td>
<td>200 mg daily</td>
<td>A significant ( P &lt; 0.0001 ) increase in testosterone level. Noteworthy improvement in sexual performance, including erectile function, sexual intercourse performance, and penile hardness. [36]</td>
<td>[36]</td>
</tr>
<tr>
<td>2010</td>
<td>Malaysia</td>
<td>Male fertility</td>
<td>350 (45–64 years)</td>
<td>Sub-fertile couples with idiopathic infertility</td>
<td>9 months</td>
<td>Placebo-controlled trial</td>
<td>Water soluble extract</td>
<td>200 mg daily</td>
<td>A significant ( P &lt; 0.05 ) increase in principle parameters of fertility such as semen volumes, sperm concentrations, percentage of sperm morphology, and sperm motility. Noteworthy improvement in sexual health in males older than 60 years. [38]</td>
<td>[38]</td>
</tr>
<tr>
<td>2012</td>
<td>Malaysia</td>
<td>Male fertility</td>
<td>109 (30–55 years)</td>
<td>Healthy male</td>
<td>6 months</td>
<td>Double blind / multiple cohort study</td>
<td>Water extract</td>
<td>300 mg daily</td>
<td>A significant ( P &lt; 0.05 ) improvement in principle seminal parameters, including semen volume, sperm motility, sperm concentration, and sperm morphology. [41]</td>
<td>[41]</td>
</tr>
<tr>
<td>2013</td>
<td>USA</td>
<td>Increase in testosterone level and male sexual libido</td>
<td>63 (45–65 years)</td>
<td>Moderately psychological stressed male</td>
<td>24 weeks</td>
<td>Multiple cohort study</td>
<td>Hot water soluble extract</td>
<td>200 mg daily</td>
<td>Protective effect of EL on testicles and produce pro-fertility effects. A considerable ( P &lt; 0.05 ) increase in testosterone level in all sub-fertile men. Improvement in male sexual libido and sexual performance. [47]</td>
<td>[47]</td>
</tr>
<tr>
<td>2014</td>
<td>South Africa</td>
<td>Increase testosterone and ergogenic effect</td>
<td>13 (57–72 years)</td>
<td>Physically stable</td>
<td>5 weeks</td>
<td>Pilot study</td>
<td>Water extract</td>
<td>400 mg daily</td>
<td>A significant ( P &lt; 0.05 ) increase in total and free testosterone concentrations. [48]</td>
<td>[48]</td>
</tr>
<tr>
<td>2014</td>
<td>Malaysia, China and South Africa</td>
<td>Increase testosterone level</td>
<td>44 (&gt; 60 years)</td>
<td>Hypogonadic elderly male</td>
<td>12 weeks</td>
<td>Placebo-controlled trial</td>
<td>Water soluble extract</td>
<td>300 mg daily</td>
<td><em>EL</em> as natural alternative to conventional testosterone replacement therapy. Adaptogen to restore serum testosterone level. Significantly improved sexual health in males older than 60 years. [49]</td>
<td>[49]</td>
</tr>
<tr>
<td>2014</td>
<td>Malaysia</td>
<td>Increase testosterone and male sexual libido</td>
<td>109 (30–64 years)</td>
<td>Healthy males</td>
<td>+6 months</td>
<td>Double blind clinical trial</td>
<td>Water extract</td>
<td>300 mg daily</td>
<td>Substantial improvement in male sexual libido. A significant ( P &lt; 0.05 ) increase in male sex hormone, penile erection, and sexual libido. [35]</td>
<td>[35]</td>
</tr>
<tr>
<td>2012</td>
<td>Malaysia</td>
<td>Increase in sex hormone and male sexual libido</td>
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<td>Water soluble extract</td>
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<td>A significant ( P &lt; 0.0001 ) increase in testosterone level. Improvement in sexual Performance, including erectile function, sexual intercourse performance, and penile hardness. [36]</td>
<td>[36]</td>
</tr>
</tbody>
</table>
trial was performed on 109 randomized males between the ages of 30 to 55 years. The subjects ingested 300 mg of EL daily. They demonstrated significant improvement in sexual libido, sexual activities, and sexual satisfaction with considerably positive effects on seminal parameters, including volume and concentration of sperms in ejaculate and the proportion of sperms having normal motility^{[41]}. The outcomes of this randomized trial demonstrate the positive effect of EL on male fertility.

**Effects of EL on testosterone level and male sex libido**

Several studies were performed in men to evaluate the effect of EL on testosterone levels and male sex libido^{[45-46]}. Since there were a paucity of data supporting the potential role of EL in boosting testosterone level and sexual well-being, a clinical placebo-controlled trial was conducted by Talbott et al.^{[47]}. The trial was carried out in 63 subjects by supplementing them with daily 200 mg of standardized hot-water extract of EL daily for 4 weeks. Talbott and co-workers noticed significant improvements in testosterone status (+ 37%) in EL treated subjects with subsequent enhancement in sexual activities and well-being^{[47]}. Another clinical trial investigating the clinical effects of EL on testosterone level and age-related sexual impotence was performed by Henkel et al.^{[48]}. In this reported study, 400 mg of EL (water extract) was supplemented daily to 13 physically active males aged between 57 to 72 years for 5 weeks. Total free and bound testosterone, cortisol, dihydroepiandrosterone and sex hormone-binding globulin (SHBG) were analyzed as the principle parameters. Henkel and co-worker^{[48]} noticed remarkable increases in the free and bound form of testosterone in all patients. The increased level of male sex hormone, in the later phase, produced considerable effects on male sexual performance and sex libido.

The clinical significance of EL in improving male sexual libido and testosterone levels has also been supported by other published clinical studies^{[35-36, 49-50]}. Udani et al.^{[35]} highlighted noteworthy ($P < 0.05$; paired $t$-test) improvement in the majority of sexual parameters, including sexual intercourse performance, concentration of male sex hormone, sex libido, and overall sexual well-being for all the subjects. Tambi and co-workers^{[36]} also supported the testosterone-enhancing and sexual performance improving effects of EL by emphasizing substantial ($P < 0.05$, paired $t$-test) improvement in testosterone level, erectile function, sexual intercourse performance, and penile hardness. In addition, George et al.^{[49]} presented remarkable significance of EL an adaptogen to restore serum testosterone levels, compared to conventional regimen such as testosterone replacement therapy. George and co-workers further highlighted the feasibility of EL in improving male sex libido in 60-years-old patients having 40%–50% lower testosterone level than young ones. The clinical superiority of EL, compared to other testosterone-enhancing and sexual boosting regimens, has also been supported by Cyranoski^{[50]}.

**Discussion**

EL, a well-recognized herbal plant in the South-East Asian countries, is used as a popular medicinal herb for the treatment of sexual dysfunctions and improvement of sexual health. Despite having many traditional evidences, it is still lacking robust data from human clinical studies. It has been used for the treatment of various sexual dysfunctions in males; nevertheless it is noteworthy that the majority of research was exclusively based on in vivo animal studies with limited data available on human studies. Toxic effects, drug interactions or negative clinical trial results may hamper human based clinical studies being carried out on EL.

The data summarized in the present systematic review revealed substantial evidences for the firm association between the use of EL and the effects on male sexual health disorders in humans. It is noteworthy that the clinical significance of EL has been demonstrated in term of managing various male sexual disorders, including erectile dysfunction^{[35-36]}, male infertility, and low sexual libido^{[38, 41]}, with relatively bigger sample sizes of 109, 320, 350 and 109, respectively. Apart from a significant direct correlation between the use of EL and the treatment of male sexual disorders, there are several clinical studies reporting indirect association of EL in promoting male sexual well-being via enhancing testosterone level in serum^{[47-49]}. It may be agreed that the clinical studies with EL on male sexual health is not common in modern medical society. The population is unaware about the outcomes relating to EL researches and to achieve the positive findings with significant efficacy is definitely challenging. Thus, the potential findings of these descriptive or observational studies are worthy to be acknowledged in generating the hypotheses about the constructive effect of EL on the treatment of male sexual disorders. Notably, all the human clinical trials of EL presented in this review were recently conducted from the year 2010.

EL has gained remarkable attention due to its strong aphrodisiac effects observed in animals and humans in Asian countries for many years^{[35-36, 51-53]}. Udani et al.^{[35]} highlighted a remarkable prospect of EL in improving penile erection, penile hardness, and other principle parameters of male sexual health, substantiating the therapeutic feasibility of EL in the management of ED. Udani and co-workers^{[15]} further suggested that daily intake of EL can improve physical health, erectile performance, sexual desire and satisfaction as well as the meaningful improvement in overall male sexual activities, compared to placebo groups. These results were also in harmony with another human clinical trial by Tambi et al.^{[36]}, which has also shown the potential effects of EL on the treatment of ED. The findings of this study have also demonstrated a significant improvement in sexual performance, including erectile function, sexual intercourse performance, and penile hardness. The exact mechanism behind the aphrodisiac characteristics of EL is not well established.
Nevertheless, researchers have proposed that the pro-aphrodisiac effects of EL might be contributed by its glycoprotein and eurypeptide contents (via increasing testosterone levels) \[54\]. The claim originated from a patent surrounding LJ100 (a concentrated EL extract of glycoproteins and eurypeptides) \[54\]. Other investigators proposed that EL produced aphrodisiac effect via direct action on corpus cavernosa and seminal vesicles muscle tone \[55\]. In this study, researchers investigated the effect of 9-hydroxycaantline-6-one (9-HC-6-one), a \(\beta\)-carboline alkaloid isolated from EL, on penile hardness and seminal ejaculate. The results obtained clearly identified that 9-HC-6-one cause relaxation of phenylephrine induced contraction of corpus cavernosim muscles. Furthermore, endothelium disruption did not attenuate this response, precluding the involvement of nitric oxide-dependant pathway. The proposed mechanistic pathway highlighted that 9-HC-6-one, as the prime component, might have major contribution to the aphrodisiac effect of EL \[55\].

Male infertility is a multi-factorial syndrome, with numerous factors down-regulating spermatogenesis, producing immotile sperms, reducing sperm volume, and producing abnormality in sperm morphology \[15, 37\]. The quantity and quality of the sperms greatly influence male’s fertility. Low number or poor quality of sperms in male’s ejaculate significantly influences the ability of a man to cause pregnancy \[15\]. With regard to male infertility, several studies have demonstrated a positive influence of EL. Tambi et al. \[39\] reported a remarkable improvement in the principle seminal parameters, including concentration of sperms, semen volume, and the percentile of sperms with desired morphological characteristics. They further demonstrated a dose-dependent effect of this herb on seminal parameters, leading to the assumption that a daily dose of 300 mg of EL root extract was prominent and efficacious in the treatment of idiopathic infertility in men. This effect might be associated to testosterone-enhancing effect of EL; that in turn, may trigger spermatogenesis in testicles and improve the quality and quantity of sperms in ejaculate. In addition, an increase in sperm concentration in sub-fertile men might also be attributed to the suppression of apoptosis of sperms in the presence of anti-sperm antibodies \[22\], which may identify sperms as extraneous matters and attempt to eradicate them.

Ismail and co-workers \[41\], on the other hand, have also conducted a placebo-controlled trial in Malay males and highlighted a positive role of EL in improving male’s fertility in sub-fertile couples. They observed a significant improvement in sexual libido, sexual performance, and sexual satisfaction. They have also noted prominent effects of EL on seminal parameters, including concentration of sperms with normal morphology, sperm motility, and semen volume \[41\]. Although the exact mechanism of EL at cellular level is not fully understood, other researchers have correlated the positive effects of EL on male’s fertility to the high level of male sex hormone as well as its antioxidative properties \[39-40\]. Recent human clinical trials also provide evidences by exploring that the extract of EL significantly enhances testosterone and dihydroepiandrosterone levels in the serum \[56-59\]. The same studies also highlighted antioxidant characteristics of EL extract by showing superoxide dismutase (SOD) activity. Several studies have shown that antioxidant supplementation could improve male reproductive functions \[60-62\]. Thus, the antioxidant properties of EL might also contribute to the improvement of male’s fertility. Following each treatment cycle with EL, the semen analysis of sub-fertile subjects whose partners had got pregnant, demonstrated meaningful increment in percentages of sperm with desired morphology, sperm motility as well as concentration of normal sperms in semen \[61-62\]. The result of this study indicated that the male’s fertility can be improved by treating them with EL.

Testosterone is the principle male sex hormone that is primarily secreted by testicles. The key roles of testosterone in men are to develop male reproductive tissues such as the testis and prostate and to promote secondary sex characteristics including, increased muscle and bone mass and growth of body hair. The inadequate functioning of the testicles, caused by hypothalamic or pituitary disorder, results in lower production of testosterone and thus, androgen deficiency \[42\]. Among the prime reasons for androgen deficiency are aging and certain diseases such as Klinefelter’s syndrome, pituitary and hypothalamic disorders \[43\], which eventually results in reduced levels of testosterone \[43-44\]. The low levels of testosterone, as a result, manifest down-regulation of male sexual libido and sexual activities \[25\]. On the topic of the potential role of EL in boosting testosterone level and male sexual well-being, Talbott et al. \[47\] had suggested a strong physiological alliance between EL and testosterone levels. They noticed a significant improvement in testosterone levels in all the subjects treated with EL and subsequent enhancement in sexual activities and overall sexual well-being \[47\] compared to the placebo group. The precise mechanism contributing to the increased levels of total testosterone in these males is not fully understood. Nevertheless, the investigators have suggested that EL (containing prime component, eurypeptides) may have played notable role in releasing the bound-form of testosterone from SHBG \[37, 63\] that might increase free form of sex hormone in the serum. The free form of testosterone is biologically active and able to enter into cells and activate the associated androgen receptor signaling spermatogenesis in the testis. They have also postulated that the supplementation of EL might also reduce the metabolism of testosterone and thus tend to enhance free form of sex hormone \[37, 63\]. The therapeutic feasibility of EL is further stressed by demonstrating safety profile of EL after consumption of this natural product \[64-65\]. The findings showed no significant changes in EL treated patients in relevant to liver and kidney laboratory values including, albumin, alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), bilirubin,
blood urea nitrogen (BUN), creatinine clearance, and glomerular filtration rate (GFR), compared to the baseline or placebo group [64-65].

The corresponding effects observed by Henkel and co-worker [48] are also found in accordance with the report of Talbott et al. [47] which has shown noticeable increase in the free as well as bound concentrations of testosterone in the treated subjects. The increased concentration of male sex hormone subsequently produces remarkable improvement in male sexual performance. Thus, the data expressed in this review present satisfactory picture exploring the positive impact of EL in improving various male sexual health disorders. The summary of effects of EL in improving male sexual disorders is highlighted by Fig. 2.

![Fig. 2 EL and male sexual disorders: Schematic illustration showing the effect of EL in improving male sexual disorders](image)

**Strengths and Limitations of This Review**

Studies on the effects of EL on erectile dysfunction, decreased libido, low testosterone level, and hypogonadism have shown promising results in terms of improving male sexual health. In the quest of seeking newer alternative treatments against male sexual disorders, the current review is greatly relevant. Our search identified 7 clinical studies which were highly relevant and were included in the present systematic review. To the best of our knowledge, this was the first critical review which focuses on the effects of EL on male sexual disorders. The human clinical studies were focused in this review with the aim to have a relevant overview of the most recent and prospective evidences presented on this topic.

Admittedly, the present review had few limitations. The articles in languages other than English were not included; those articles may contain relevant information or supplementary evidence related to this topic, which should be considered as one of the potential limitations of our review. Concurrently, the present review included the articles published from the year 2000 to 2014, as our priority was to discuss about the current health aspect and its impact on the general population. The study design used in most of these human clinical studies did not present a clear picture of underlying mechanism of action and pharmacokinetic profile of EL on male sexual health disorders. Future research on the effect of EL in male sexual health disorder is expected to explore more relevant concerns on its pharmacokinetic and pharmacodynamic profiles. In recent years, much emphasis has been placed on EL in the treatment of male sexual disorders. Based on the prospective clinical evidence presented in the current review, it would be misleading to make any ultimate claims for the therapeutic feasibility of EL in other human clinical aspects.
Conclusion

Eventually, the global scenario of numerous human clinical trials screened in this review article, highlighted the role of EL as a potential herbal supplement against various male sexual health disorders, including erectile dysfunction, male’s infertility, low libido, and male sex hormone associated complications. Based on the evidences highlighted in the present review, EL may have a remarkable potential in renewing male sexual vitality and enhancing libido and overall sexual performance. The clinical superiority of EL against male sexual health disorders is associated with its broad safety profile and patient compliance.

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