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Original Research Article

Kaempferia parviflora ethanol extract improves self-assessed sexual health in men: a pilot study

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ABSTRACT

Background: Sexual health positively correlates with overall wellbeing. Existing therapeutics to enhance male sexual health are limited by factors that include responsiveness, adherence and adverse effects. As the population ages, safe and effective interventions that preserve male sexual function are needed. Published research suggests that various preparations of *Kaempferia parviflora*, a plant in the Zingiberaceae (ginger) family, support cardiovascular health and may ameliorate erectile function.
Objective: The aim of this study was to examine the effects of KaempMax™, an ethanol extract of the *K. parviflora* rhizome, on erectile function in healthy middle-aged and older men.
Design, setting, participants and interventions: We conducted an open-label, one-arm study on 14 generally healthy males aged 50–68 years with self-reported mild erectile dysfunction, who were not using prescription treatments. Participants took 100 mg KaempMax™ daily for 30 days.
Main outcome measures: Evaluations were conducted at baseline and on the final study assessment. Primary efficacy analyses included the International Index of Erectile Function (IIEF); secondary efficacy analyses included the Global Assessment Question about erectile function.
Results: Thirteen participants completed the 30-day study. Supplementation with KaempMax™ resulted in statistically significant improvements in erectile function, intercourse satisfaction and total scores on the IIEF questionnaire. KaempMax™ was well tolerated and exhibited an excellent safety profile.
Conclusion: Our results suggest that KaempMax™ may improve erectile function in healthy middle-aged and older men. While the effects were not as pronounced as what might be seen with prescription medication, most participants found them satisfactory. Additional, longer and placebo-controlled clinical trials will be needed.
Trial registration: Clinicaltrials.gov identifier NCT03389867.

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1. Introduction

Kaempferia parviflora is a medicinal plant from the Zingiberaceae family that has been used for centuries in folk medicine [1]. The plant is native to Malaysia, Sumatra, Borneo Island and Thailand [1]. In Thailand, it is also known as Thai ginseng, Krachai dam or black Ginger [2]. *K. parviflora* extracts have been used traditionally to treat hypertension, an effect that was validated in several studies [3–5], and various other ailments [6]. Several mechanisms explain the cardiovascular benefits of *K. parviflora*. In isolated rat aortic rings that had been pre-contracted with methoxamine, exposure to 5,7-dimethoxyflavone (DMF) from *K. parviflora* rhizomes caused concentration-dependent relaxation [7]. *K. parviflora* and their bioactive components inhibited the phenylephrine-induced contraction of rat aortic rings [8], at least in part, in a nitric oxide (NO)- and cyclic guanosine monophosphate (cGMP)-dependent manner [7,9], and inhibited the influx of Ca^{2+} into cells [7]. An ethanol extract of *K. parviflora*, administered orally at a dose of 100 mg/kg body weight, to rats with streptozotocin-induced diabetes, for four weeks, reduced oxidative stress, increased NO bioavailability and preserved aortic

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endothelium-dependent relaxation [10]. In an *in vitro* part of this study, aortic rings exposed to the *K. parviflora* extract at concentrations of 1, 10 and 100 μg/mL showed a significant decrease in the production of superoxide anions and an increased relaxation in response to acetylcholine, which is experimentally used to measure vascular relaxation [10]. In middle-aged rats, the chronic oral administration of a *K. parviflora* ethanol extract increased NO production in blood vessels, leading to decreased vascular responsiveness to phenylephrine and increased acetylcholine-induced vascular relaxation [3]. *K. parviflora* reduces the adhesion of monocytes to endothelial cells, lowers the plasma level of some inflammatory cytokines, and shows antioxidant activities *in vitro*, which are thought to inhibit the development and progression of atherosclerosis [11]. In human umbilical endothelial cells, *K. parviflora* ethanol extract promoted NO production [12], and in isolated rat hearts, the extract prevented myocardial ischemia-reperfusion injury [13].

Cardiovascular health is intimately linked to erectile function, and many of the modifiable risk factors that lead to pathological changes are shared between the two [14–17]. Decline in erectile function is a common and often undertreated condition [18]. Advancing age is an independent risk factor for erectile dysfunction (ED) [18,19], and ED prevalence increases by about 10% per decade after age 40 [20,21]. The most frequent cause of ED, regardless of age, is thought to be vascular disease [20,22]. Cardiovascular diseases and ED are connected at the level of the vascular endothelium [23], and NO has been recognized as a key mediator for both cardiovascular health and erectile function [24]. ED, an important marker of advanced vascular age, can predict cardiovascular disease and other chronic conditions and may be the earliest clinical manifestation of subclinical cardiovascular disease [14,25,26].

The benefits of *K. parviflora* for endothelial function and cardiovascular health, and the intimate connection between these two and male sexual health, open the promise of using *K. parviflora* for supporting erectile health. Several *in vitro*, animal and human studies support the use of *K. parviflora* for improving sexual health.

The major active components of *K. parviflora* are DMF, 3,5,7,3′,4′-pentamethoxyflavone and 4′,5,7-trimethoxylflavone [27]. Methoxyflavones isolated from *K. parviflora* showed an inhibitory effect against the phosphodiesterase type 5 enzyme (PDE5), and DMF was a potent inhibitor when tested *in vitro* [1,28]. Because these *in vitro* studies have identified DMF as an important mediator of *K. parviflora*-induced PDE5 inhibition and vasorelaxation, it was suggested that DMF might be an option in the development of PDE5 inhibitors for the treatment of ED [7,28].

In male rats, an alcohol extract of *K. parviflora* showed aphrodisiac activities, possibly by increasing the blood flow to the testis [29]. In another rat study [9], 100 mg/kg of *K. parviflora* extract given intravenously led to effects similar to those caused by sildenafil citrate; specifically, the *K. parviflora* extract significantly increased cGMP levels and temporarily decreased the Ca^{2+} concentration in ventricular myocytes. Another study [30], on aging male rats, reported that a single oral administration of 200 mg/kg body weight of *K. parviflora* extract increased the frequency of intromission, ejaculation and mounting, and decreased the latency between these behaviors; similar effects were observed after the daily administration of *K. parviflora* extract for two weeks.

Among Thai men, *K. parviflora* has long been used for sexual enhancement [31]. The clinical use of *K. parviflora* for human sexual enhancement is supported by a few studies. In one study [32], 15 elderly male volunteers, with a mean age of 65 years, received 90 mg of a *K. parviflora* extract per day, and exhibited statistically significant decreases in the response latency to erotic visual stimuli. Participants also showed increased flaccid and erect penile size. In another human study [33], 45 healthy elderly volunteers were randomized to receive a placebo or *K. parviflora* extract (25 mg or 90 mg) once daily for eight weeks. The result showed that supplementation decreased oxidative stress.

In our open-label pilot study, we investigated the effects of KaempMax™, an ethanol extract of *K. parviflora*, on International Index of Erectile Function (IIEF) domain scores in 13 generally healthy male volunteers aged 50–68 years who completed the trial. While there are two clinical studies [32,33] that support the use of *K. parviflora* for erectile function, our study is positioned differently and addresses new questions. Previous clinical studies assessed erectile function by measuring the response latency to visual erotic stimuli, the size and length of the penis [32], or physical fitness and oxidative status, which are indirect indicators of endothelial and sexual health [33]. Our study used the IIEF scores and the Global Assessment Question (GAQ) as measures of the primary and secondary outcomes, respectively, which are established and standardized measures of erectile health and directly assess sexual function. While the previous two clinical studies, like our study, enrolled overall healthy elderly volunteers [32,33], participants of our study presented mild ED, validating the intervention for this particular population. Furthermore, our study assessed several additional parameters, including vital signs (systolic and diastolic blood pressure, heart rate, body temperature and weight), fasting blood tests and a male hormone, which have not been comprehensively interrogated in previous clinical studies that examined *K. parviflora* extracts for male sexual health.

2. Materials and methods

2.1. Study agent

In this open-label, one-arm, pilot study we used KaempMax™, a *K. parviflora* rhizome extract standardized to 5% DMF. Participants were instructed to take one capsule containing 100 mg of KaempMax™ daily [32].

2.2. Primary and secondary efficacy analyses

We used the IIEF questionnaire as the primary efficacy analysis and the GAQ as the secondary efficacy analysis.

2.2.1. IIEF

The IIEF questionnaire is used to assess treatment outcomes related to erectile function. The questionnaire has 15 questions: 6 relate to erectile function (questions 1–5 and 15), 3 relate to satisfaction with intercourse (questions 6–8), 2 relate to orgasmic function (questions 9 and 10), 2 relate to sexual desire (questions 11 and 12) and 2 relate to overall sexual satisfaction (questions 13 and 14). The minimum total score is 5 and the maximum total score is 75, with a higher score indicating better erectile function [34].

2.2.2. GAQ

The GAQ utilized in this study is as follows: “Has the product you have been taking (over the past four weeks) improved your erections?”

2.3. Study participants

We enrolled 14 generally healthy men and obtained informed consent from each participant. The inclusion criteria included: healthy male volunteers between the ages of 50 and 70 years; having been (or attempted to be) sexually active for at least the previous 6 months; having been in a stable sexual relationship for the preceding 6 months or more; willing to attempt intercourse approximately twice every 8 days with a minimum of at least

6 times during the 30-day study period; and being able to comply with a 14-day washout period of all sexual performance-enhancing medications, nutritional supplements, or herbs prior to the first day of randomization. Exclusion criteria included: having a body mass index (BMI) greater than 34.9 kg/m^2; currently receiving or having received treatment in the past 6 months for any sexual disorder or dysfunction, including treatment for ED, intercourse satisfaction, orgasmic function, or sexual desire; attaining a score $\leq$16 on the IIEF-5 questionnaire; and having a primary diagnosis of another sexual disorder (such as premature ejaculation). The study was approved by the investigational review committee. KaempMax™ was dispensed to study participants, who were asked to maintain their existing diet and activity levels, and to contact the research center immediately if experiencing adverse effects. We performed evaluations at baseline and on the final study assessment, at day 30. These evaluations included: GAQ and IIEF questionnaires; vital signs (blood pressure, heart rate, body temperature and weight); and fasting blood tests including a standard blood chemistry panel, kidney and liver function panels, complete blood count and a male hormone panel (free and total serum testosterone, estradiol, dehydroepiandrosterone sulfate (DHEA-S) and prostate-specific antigen (PSA). LabCorp (Tampa, Florida) performed all laboratory testing.

2.4. Statistical analyses

The null hypothesis (H_0) stated that there are no differences in the mean domain score changes of the questionnaires between baseline and day 30. A *P*-value of less than 0.05 (two-tailed) was deemed to be statistically significant. Student's *t*-test was used to test the differences. The SAS Version 9.4 software (SAS Institute Inc.) was utilized in the statistical analyses.

3. Results

3.1. Baseline characteristics

Of the 14 participants enrolled, 1 dropped out due to noncompliance, and 13 completed the 30-day study. Data from the 13 subjects who completed the study were included in the statistical analyses. Subjects who completed the study had a mean age of 58 years, a mean height of 176.3 cm, a mean weight of 80.9 kg, and a mean BMI of 25.9 kg/m^2. Two (15.4%) of the 13 subjects who completed the study were current smokers.

3.2. Primary efficacy analyses

Changes in IIEF parameters and total score from baseline to day 30 are shown in Table 1.

For the total score (questions 1–15), the mean IIEF score increased by 6.3%, from 58.8 ± 8.5 at baseline to 62.5 ± 9.1 on day 30 (P = 0.0067). For question 3 related to erectile function ("Over the last month, when you attempted intercourse, how often were you able to penetrate your partner?"), the mean score increased by 12.5%, from 4.0 ± 1.2 at baseline to 4.5 ± 1.0 at day 30 (P = 0.0075). For the erectile function domain total (questions 1–5 and 15), the mean score increased by 4.1%, from 12.3 ± 2.5 at baseline to 12.8 ± 2.2 on day 30 (P = 0.0269). For the intercourse satisfaction domain (questions 6–8), the mean score increased by 13%, from 10.8 ± 1.9 at baseline to 12.2 ± 1.9 on day 30 (P = 0.0296).

3.3. Secondary efficacy analyses

For the GAQ (described under subsection 2.2.2), 61.5% (8/13) of the subjects who completed the study stated that the product they were taking over the previous 4 weeks improved their erections.

3.4. Safety assessment

All 14 participants enrolled in the study were included in the assessment of adverse effects and no serious adverse events were reported. Two subjects reported a total of two adverse events, both mild in severity. One adverse event, light headache, was considered unlikely to be related to the study product; the other one, shortness of breath, was also considered unrelated to the study product. Both had resolved by the end of the study.

No statistically significant changes were seen in blood pressure over the course of this 30-day investigation. A mean decrease of 5 bpm was seen in heart rate between baseline and day 30, a change that was statistically significant (P = 0.0317) but not clinically meaningful. Liver function tests, in subjects who completed the study, showed an insignificant mean increase of 2 IU/L in alanine aminotransferase (ALT) and 1 IU/L in aspartate aminotransferase (AST) from baseline to day 30 (P = 0.3755 and 0.4000, respectively). No significant changes were observed in the values for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), blood glucose, total testosterone, free testosterone, estradiol, DHEA-S, PSA, body weight or BMI (Table 2).

4. Discussion

Concerns with erectile function and dysfunction affect growing numbers of men at younger ages, and they are therefore emerging as an increasingly important issue in society. PDE5 inhibitors are currently the first-line therapy for ED [35,36]. However, these medications cause several types of adverse effects and not all men are candidates. A review and meta-analysis reported that the rate of discontinuation of PDE5 inhibitors was high, with a mean discontinuation rate of 4% per month and almost 50% after one year [36]. Therefore, additional or alternative options to support erectile function are essential. Even more importantly,

Table 1
IIEF changes from baseline to day 30 for participants who completed the study.

IIEF parameter	Score (mean ± SD, n = 13)			P-value
	Baseline	Day 30	Change	
Erectile function (Q3 only)	4.0 ± 1.2	4.5 ± 1.0	0.5 ± 0.5	0.0075*
Erectile function (Q4 only)	4.1 ± 1.2	4.3 ± 1.0	0.2 ± 0.4	0.0821
Erectile function domain total (Q1–5 and 15)	12.3 ± 2.5	12.8 ± 2.2	0.5 ± 0.7	0.0269*
Intercourse satisfaction (Q6–8)	10.8 ± 1.9	12.2 ± 1.9	1.4 ± 2.0	0.0296*
Orgasmic function (Q9 and 10)	8.8 ± 1.6	9.0 ± 1.5	0.2 ± 0.7	0.4363
Sexual desire (Q11 and 12)	6.8 ± 2.0	7.3 ± 1.8	0.5 ± 1.6	0.3073
Overall satisfaction (Q13 and 14)	11.8 ± 2.2	12.1 ± 2.1	0.3 ± 2.0	0.5345
Total score (Q1–15)	58.8 ± 8.5	62.5 ± 9.1	3.6 ± 4.0	0.0067*

* Statistical significance: P < 0.05; IIEF: International Index of Erectile Function; SD: standard deviation.

Table 2
Changes from baseline to day 30 in laboratory and anthropomorphic parameters for the 13 completing participants.

Parameter	Data (mean ± SD, n = 13)			P-value
	Baseline	Day 30	Change	
Body weight (kg)	81.1 ± 13.9	81.0 ± 13.8	−0.3 ± 1.8	0.5935
Body mass index (kg/m^2)	25.9 ± 3.6	26.0 ± 3.6	0.1 ± 0.2	0.0511
Systolic blood pressure (mm Hg)	116.8 ± 12.4	117.8 ± 11.5	0.9 ± 12.2	0.7903
Diastolic blood pressure (mm Hg)	76.5 ± 5.9	78.1 ± 4.9	1.5 ± 6.5	0.4112
Heart rate (beats/min)	68.5 ± 4.7	63.5 ± 5.9	−5.0 ± 7.2	0.0317*
Total cholesterol (mg/dL)	191.3 ± 49.3	188.1 ± 53.5	−3.2 ± 20.9	0.5866
Triglycerides (mg/dL)	92.3 ± 29.8	84.5 ± 29.9	−7.9 ± 17.8	0.1381
HDL-c (mg/dL)	54.7 ± 11.9	53.2 ± 12.6	−1.5 ± 4.0	0.2159
LDL-c (mg/dL)	118.2 ± 44.0	118.0 ± 47.7	−0.2 ± 17.5	0.9628
AST (IU/L)	22.0 ± 6.0	23.0 ± 7.0	1.2 ± 5.1	0.4000
ALT (IU/L)	25.0 ± 12.0	27.0 ± 14.0	2.2 ± 8.7	0.3755
Glucose (mg/dL)	94.3 ± 7.9	94.4 ± 8.3	0.1 ± 9.9	0.9780
Total testosterone (ng/dL)	529.0 ± 156.0	515 ± 166	−14.6 ± 72.3	0.4802
Free testosterone (pg/mL)	8.6 ± 3.3	8.9 ± 3.9	0.3 ± 1.8	0.5512
Estradiol (pg/mL)	21.9 ± 8.8	21.5 ± 8.7	−0.4 ± 5.3	0.7996
DHEA-S (mcg/mL)	151.1 ± 80.9	153.0 ± 84.7	1.9 ± 17.9	0.7070
PSA (ng/mL)	1.1 ± 0.7	1.2 ± 0.5	0.1 ± 0.3	0.2442

* Statistical significance: $P < 0.05$; SD: standard deviation; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; DHEA-S: dehydroepiandrosterone sulfate; PSA: prostate-specific antigen.

interventions to prevent the deterioration of vascular function, erectile function and sexual health are critically needed.

Irrespective of a person's age, the most common cause of ED is a problem with the vascular system of the penis. While in the past it was widely viewed as a psychological condition, ED is currently recognized as predominantly a disease of vascular origin [20,37]. ED and cardiovascular disease share some of the main risk factors, and vascular ED is a powerful marker of an increased risk of cardiovascular diseases [38,39].

In vitro studies reported that *K. parviflora* improves several aspects of vascular dysfunction that were found to be dysregulated in patients with ED, and animal and human studies confirmed that it improves various parameters related to sexual activity. Several lines of scientific evidence support the mechanistic bases of these beneficial effects. In human umbilical vein endothelial cells, a *K. parviflora* ethanol extract improved the production of NO [12], which is considered the main chemical responsible for the relaxation of the smooth muscle in the penis [40] and increased blood flow to the penis [41]. In rats, a *K. parviflora* ethanol extract significantly improved blood flow to the testes and increased the animals' sexual motivation and mating behaviors, as observed on video recordings [29]. In addition, *K. parviflora* extracts showed inhibitory activities against PDE5 [28], which is the predominant phosphodiesterase found in the corpus cavernosum and represents an important pharmacological target for ED [42]. PDE5 selectively cleaves cGMP into 5′-GMP and initiates a cascade of signaling events that relax the smooth muscle of the corpus cavernosum, increasing blood flow to the penis [43]. PDE5 inhibitors are structurally similar to cGMP and competitively bind PDE5 and inhibit cGMP hydrolysis, which accumulates in the corpus cavernosum and enhances the effects of NO [43,44]. In another study [45], which involved male rats with streptozotocin-induced diabetes, a water extract of *K. parviflora* rhizomes significantly increased sperm density and serum testosterone and led to the recovery of sexual behavior. The mechanistic bases of *K. parviflora*-mediated erectile function benefits are also illustrated by a study that found that an ethanol extract of *K. parviflora* caused vasorelaxation in isolated rat hearts, and this beneficial effect was partly inhibited by removal of the endothelium or by chemically inhibiting NO synthesis. The extract also inhibited the contractile response to exogenous Ca^{2+} in a dose-dependent manner [13].

This open-label pilot study investigated the effects of 30 days of supplementation with 100 mg/d of KaempMax™, a *K. parviflora* rhizome ethanol extract standardized to 5% DMF, on erectile function in generally healthy male volunteers aged 50–68 years. Changes were quantified using the established IIEF questionnaire, which reflected a 6.3% improvement in the total score. In addition, as mentioned under subsection 3.3, the response to the GAQ revealed that most participants (61.5%) reported that the tested study product improved their erections.

While the changes that we found were quantitatively smaller than the changes reported with prescription medication available for ED, the benefits that we observed are promising. In comparison, a placebo-controlled study that administered sildenafil citrate (Viagra®) for six weeks to patients with ED reported increases of 7–8 points were seen for the erectile function domain [46]. Another study of men with ED [47] found statistically significant mean improvements of seven points on the erectile function domain of the IIEF. It is noteworthy that in our study, the test product was administered for a shorter time than sildenafil citrate was administered in these other studies that found benefits [46–48]. Moreover, our study population was comprised of healthy men, with mild self-reported erectile function concerns, as compared to many studies that examined the effect of sildenafil citrate in men with more pronounced ED and/or co-morbidities. This may also explain the moderate improvements reported here.

This study found no statistically significant changes from the baseline in the levels of free testosterone, total testosterone, estradiol, DHEA-S, PSA, total cholesterol, LDL-c, HDL-c, triglyceride, ALT, AST, body weight or BMI. The fact that these values remained stable during the investigation is an indication that KaempMax™ did not cause any overt metabolic effects. KaempMax™ was well tolerated, and mild adverse events, observed in two subjects (as reported under subsection 3.4), were unrelated or unlikely to be related to the study product.

In conclusion, men taking 100 mg/d of KaempMax™ for 30 days reported improvements in their overall sexual health. These generally healthy 50–68 year old men felt they had mild ED, yet reported statistically significant increases in mean IIEF scores in erectile function, intercourse satisfaction and total scores. While prescription drugs are available for more impaired men suffering from ED, these can have undesirable side effects and not all men are

candidates. The effects reported here are not as pronounced as what might be expected from a prescription medication, but they appeared to be satisfying to most of the study participants. Additional research is warranted to assess effects with more prolonged use and against placebo to confirm and build on these findings.

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Conflict of interests

All the authors were, at the time of preparing this manuscript, employed by Life Extension, which sells dietary supplements.

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