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Efficacy Assessment of *Kaempferia parviflora* for the Management of Erectile Dysfunction

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ABSTRACT

Age-related decline in erectile function is a noted phenomenon worldwide. A variety of medicinal plants have been identified as having strong aphrodisiac properties along with the ability to improve erectile functioning. *Kaempferia Parviflora* (KP) has famous as a Thai Viagra and use it to increase male impotency. However, there is limited scientific evidence regarding the efficacy of this herb on this issue in aging healthy men. This study therefore investigated the effect of KP extract administration on erectile response of male elderly volunteers. Total 45 male healthy elderly volunteers will be divided into 3 separated groups including placebo and the different doses of ethanolic extracts of KP (25 and 90 mg) once daily at a period of 2 months. The erectile function tests including the response latency time to visual erotic stimuli, size and length of penis both in flaccid and erection states were assessed after single administration, 1 and 2 months of treatment. In order to investigate the possible underlying mechanism, we also determined the alteration of testosterone, FSH and LH concentrations. KP at a dose of 90 mg day^{-1} treated group exhibited a significant enhanced all parameters after 1 and 2 months of treatment. Moreover, the penile length at erection states and the response latency to sexual erotic stimuli appeared to be the parameters that showed significant changes during the delay period. Unfortunately, our study failed to show the significant changes on hormones concentration. Our study clearly demonstrates that KP is a potential resource for the development of nutraceutical compound against aged related male erectile dysfunction.

Keywords: *Kaempferia Parviflora* (KP), Erectile Dysfunction (ED), Nitric Oxide (NO), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH)

1. INTRODUCTION

Sexual relationships are some of the most important social and biological relationship in human life. Male impotence also called Erectile Dysfunction (ED) is a common medical condition that affects the sexual life of millions of aging men worldwide (Montorsi *et al*., 2003). ED is a sexual dysfunction characterized by the inability to develop or maintain penile erection sufficiently while engaging in sexual intercourse (Monga, 1999). Several type of treatment is claimed in the modern medicine but due to serious side effects and higher cost, search of natural supplement from medicinal plants as an aphrodisiac substance is significantly increased (Yakubu *et al*., 2007).

Kaempferia Parviflora Wall. Ex. Baker (KP), which commonly referred to Thai name, Kra-Chai-Dum, belongs to Family Zingiberaceae. Thai folk use the rhizome of this plant as a traditional medicine to increase male libido, alleviate male impotency, induce an

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energizer, balance blood pressure and also reduce stomach pain by boiling or soaking KP with alcohol (Yenjai *et al*., 2004). Previously, we provided evidence that oral administration of KP extract, a Thai medicinal plant reputed for aphrodisiac activity and enhanced the expression of male sexual behaviors in aging rats (Wattanathorn *et al*., 2012). Recently, KP products are widely available in market as aphrodisiac booster. However, supported document with valid biological data is still very limited. Therefore, the present study is carried out to determine the effect of KP extract on the erectile function in the male elderly volunteers.

2. MATERIALS AND METHODS

2.1. Subjects

Forty-five male healthy elderly volunteers (mean age 65.05±3.56 years) were recruited to participate in this study. Prior to participation, each volunteer signed an informed consent form and completed a medical health questionnaire. All subjects were also undergone extensive medical evaluation in order to ascertain subject suitability for entering the double-blind phase of trial. Individuals on medication, abusing drugs/alcohol, or exhibiting endocrinological, psychological, or sexual dysfunction/disorders, were excluded from the study. All participants reported that they had an exclusively heterosexual orientation and a relaxed attitude toward pornography. The protocol for this study was approved by the Ethics Committee of Faculty of Medicine, Khon Kaen University, Thailand. Additionally, most of the subjects did not use dietary supplements that interfered on the sexual function for at least 6 months before study.

All volunteers were randomly placed in one of three groups. No significant difference about mean age, height and body mass index among groups were observed. Two groups received active treatment whereas the other group received placebo. For 8 weeks, one group (n =15) received one capsule of KP extract at a dose of 25 mg day^{-1}. The second group (n = 15) received one daily capsule of KP extract at a dose of 90 mg day^{-1}. The third group received capsule of placebo daily for the 8-week span in the same schedule. During the study, all men maintained their usual eating regimen.

2.2. Kaempferia Parviflora Preparation

A standardized extract of KP rhizomes was prepared by the Center for Research and Development of Herbal Health Product, Faculty of Pharmaceutical Sciences, Khon Kaen University. All KP used in this study was obtained from Amphoe Na Hear, Loei Province, Thailand. The plant was authenticated and kept as voucher specimen at Faculty of Pharmaceutical Sciences, Khon Kaen University. Standardization and conformity of the extract is assured by strict in-process controls during manufacture and complete analytical control of the resulting dry extract. A-day capsule contained total flavonoids content approximate 40.37 mg g^{-1} dried powder consisting 2 main constituents 5, 7-dimethoxyflavone (8.789 mg g^{-1}) and 3,5,7,3',4'-pentamethoxy flavone (9.858 mg g^{-1}).

2.3. Procedures and Treatments

This study was a pilot study conducted as 8-week, double-blind, placebo-controlled, randomized trial. A random list of numbers was generated by computer. After being randomly assigned to various treatment groups, each participant received one capsule of placebo or KP extract at dose of 25 and 90 mg once daily. Placebo and KP capsules had the same color, texture, size and smell.

All participants were assessed baseline data about the response latency time to visual erotic stimuli, size and length of penis both in flaccid and erection state and then they were assessed all parameter as mention previously, after the single administration, 1 and 2 months of treatment and 1 month after the cessation of KP administration (the delay period).

The code for study allocation was only broken when the last participant completed the entire follow up. Staff involved in the collection of the study's endpoints was instructed to follow a rigorous protocol and not to discuss any issues related to the use of medication.

2.4. Penile Circumference and Length Measurements

All subjects were fitted with the Rigiscan device (UroHealth Systems, Laguna Niguel, California) and seated in a room on their own with a video screen in front of them. After 15 min of adaptation, the Rigiscan was as turn on to record the erectile response to visual erotic stimuli.

In addition, the flaccid and fully stretched penile lengths were measured after watching erotic films involved heterosexual activity for 12 min.

A measuring tape was used to measure the length and the midshaft circumference of the penis. The starting point was on the dorsal aspect of the penis at its base at the pubic-penile skin junction, pushing the prepubic fat pad against the pubic bone as described by Wessells *et al*. (1996) while the tip of the penis was the other reference point.

2.5. Erectile Response to Visual Erotic Stimuli Measurement

The duration of erectile response to visual erotic stimuli was measured with real-time Rigiscan

monitoring. Subjects recorded the duration of erectile events (resting state until fully erect state).

2.6. Hormones Measurement

Venous blood samples were drawn for the determination of the levels of the following hormones: LH, FSH and testosterone after a single administration, 1 and 2 months of treatment. Analyses for hormone concentrations were conducted at the laboratory of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand.

2.7. Statistical Analysis

All data are expressed as mean ± S.E.M. Comparisons between placebo and various doses of KP at different time points were made using analysis of variance (ANOVA). The differences between frequencies before and during treatment were assessed by the chi-squared test. A $p<0.05$ was considered statistically significant.

3. RESULTS

3.1. Characteristics of subjects

The baseline data about characteristic of subjects in all groups were shown in **Table 1**. No significant differences of all parameters among various groups were observed.

3.2. Penile Circumference and Length

The effects of KP extract on penile circumference and length both in flaccid and erection states were shown in **Fig. 1-4** respectively. The baseline data of penile circumference and length both in flaccid and erection states of placebo, KP 25 and KP 90 day^{-1} treated groups showed no significant difference. After 1 and 2 months of treatment with KP at a dose of 90 mg day^{-1} experienced a statistically significant increase in the length and width of their penis both in flaccid and erection states when compared with the placebo treated group ($p<0.05$). Interestingly, the length of penis at erection states appeared to be the parameter that showed significant change during the delay period ($p<0.05$).

However, no significant difference was seen in these parameters in either the KP at a dose of 25 mg day^{-1} or the placebo treated groups.

3.3. Latency of Erectile Response to Visual Erotic Stimuli

Again, KP at a dose of 90 mg day^{-1} significantly decreased the response latency to sexual erotic stimuli and still showed the significant changes during the delay period ($p<0.05$) as shown in the **Fig. 5**. No major adverse events were reported during the clinical trial.

3.4. Hormonal Status

Prior to the determination of KP effect on testosterone, FSH and LH concentrations, baseline data for all treated groups were subjected to a one-way ANOVA. There were no significant differences on any measure. Unfortunately, no statistical differences in testosterone, FSH and LH levels after treatment in any of the subject groups (**Table 2**).

Table 1. Characteristics of subjects

Baseline data	Placebo	KP 25	KP 90
Age (y)	65.88±5.11	67.25±1.39	64.75±2.71
BMI (kg/m^2)	22.29±3.32	21.25±2.61	22.75±1.13
Height (cm)	170.25±6.39	171.50±5.47	169.25±5.09

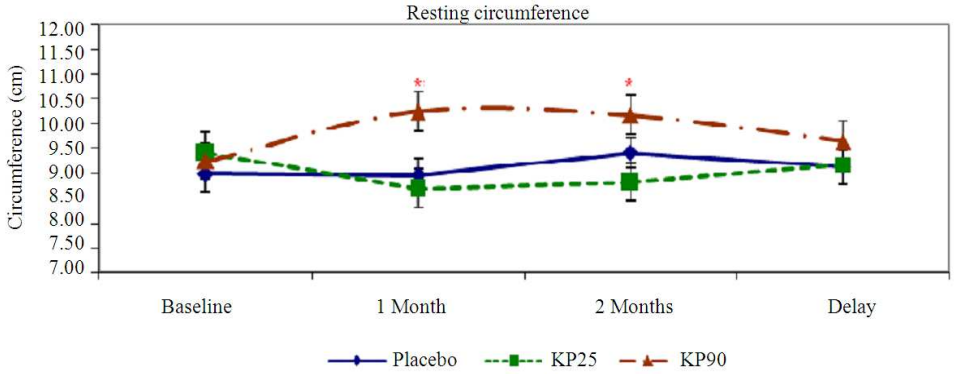

Fig. 1. Effect of KP (25 and 90 mg day-1) on penile circumference in resting state. Values given are the mean ± S.D (n =15). *$p<0.05$ as compared to placebo treated group

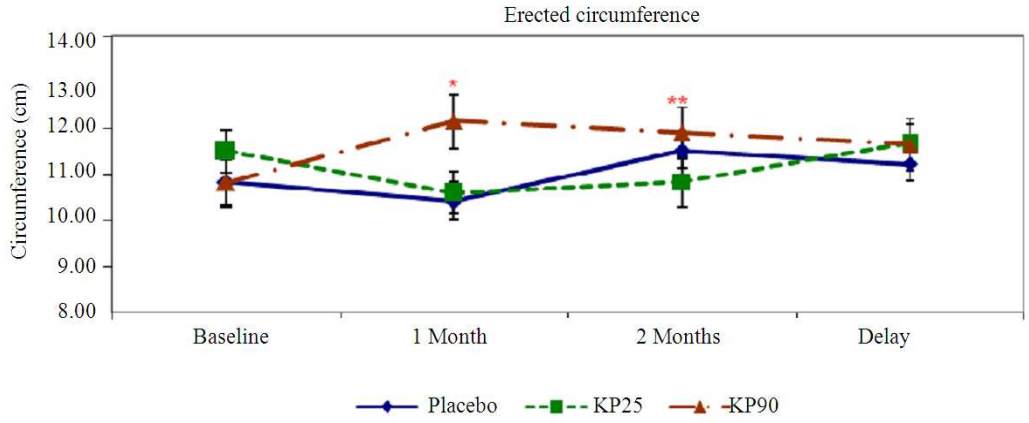

Fig. 2. Effect of KP (25 and 90 mg day^{-1}) on penile circumference in erection state. Values given are the mean ± S.D (n = 15). *p<0.05 as compared to placebo treated group, **p<0.01 as compared to placebo treated group

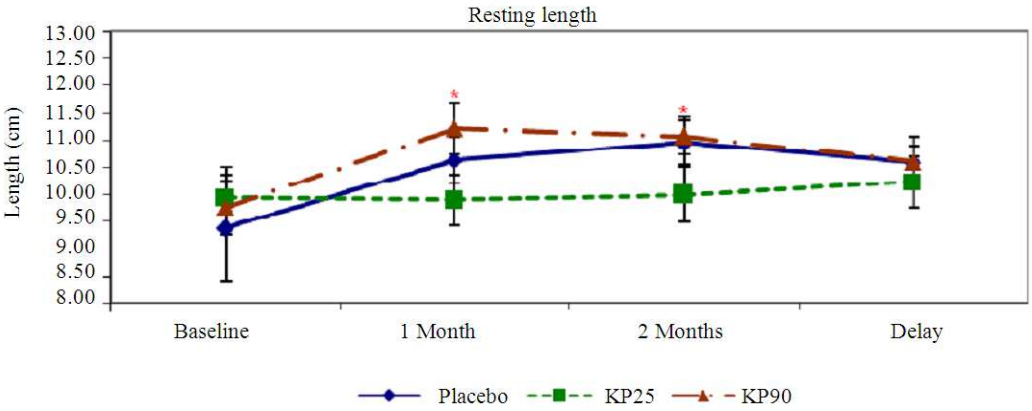

Fig. 3. Effect of KP (25 and 90 mg day^{-1}) on penile length in resting state. Values given are the mean ± S.D (n=15). *p<0.05 as compared to placebo treated group

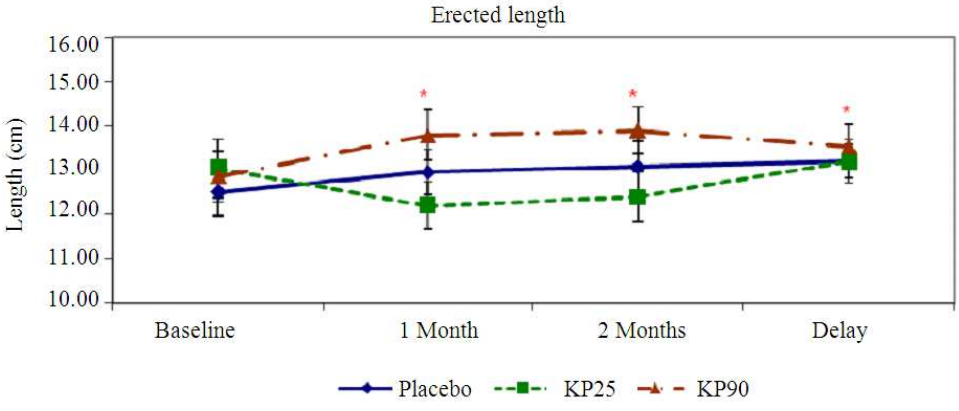

Fig. 4. Effect of KP (25 and 90 mg day^{-1}) on penile length in erection state. Values given are the mean ± S.D (n=15). *p<0.05 as compared to placebo treated group

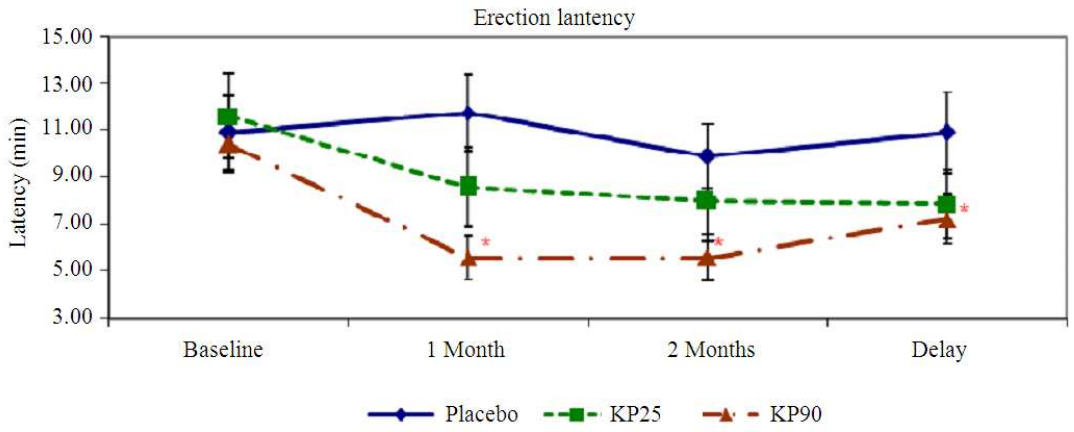

Fig. 5. Effect of KP (25 and 90 mg day^{-1}) on response latency to sexual erotic stimuli. Values given are the mean ± S.D (n = 15). *p<0.05 as compared to placebo treated group

Table 2. Effect of KP extract administration on serum hormones concentrations

			Pre-dose (baseline)			
Blood test	Group	Pre-dose (baseline)	Single dose	1 month	2 month	Delay
Testosterone	Placebo	4.14±0.92	5.28±2.76	5.92±5.49	5.65±1.23	5.14±0.92
	KP 25	4.11±1.56	4.79±4.63	5.11±3.13	4.64±1.22	5.71±2.38
	KP 90	4.11±1.30	4.89±2.63	4.26±0.83	5.74±2.60	6.06±3.19
FSH	Placebo	7.88±4.34	6.73±2.54	6.52±5.51	5.95±2.34	5.88±3.34
	KP 25	8.80±4.29	7.35±4.23	7.23±5.37	7.96±3.32	8.81±5.12
	KP 90	7.53±2.92	6.14±2.26	6.29±2.25	6.01±2.79	7.03±2.35
LH	Placebo	7.14±5.62	7.59±3.21	7.30±4.24	7.82±2.34	8.14±3.23
	KP 25	7.25+5.90	8.12±2.72	7.04+5.34	8.48+4.64	8.72+4.67
	KP 90	6.99±4.37	7.65±1.88	8.55±3.64	7.41±4.67	8.82±4.44

4. DISCUSSION

There is a growing worldwide trend in use of alternative medicine especially herbal medicine. For centuries among the herbal experts, *Kaempferia Parviflora* (KP) has been known to have aphrodisiac like properties.

However, the validity and efficacy of such a claim had remained uninvestigated. In this study we evaluated and confirmed its effect on ED of male elderly volunteers.

The penile erection index is important for evaluating the effect of drug or substance administration on erectile function (Thakur and Dixit, 2007). The results of the present study demonstrate that the ethanolic extract of KP at a dose of 90 mg day^{-1} administered orally in a capsule during 8 weeks significantly increased the penile circumference, length and rigidity compared with the placebo treated group. In addition, the plant extract also decreased the response latency to sexual erotic stimuli. Moreover, the penile length at erection states and the response latency to sexual erotic stimuli appeared to be the parameters that showed significant changes during the delay period. This indicates that the KP extract also increases erectile activity. These data confirm our results obtained in aging rats (Wattanathorn *et al*., 2012). Recent findings showed that effect of KP at a dose of 90 mg day^{-1} in aging healthy men is noticeable since 1 week of treatment. Certainly, data at single administration of treatment did not show differences between KP treated men and placebo treated men. Unfortunately, low dose of KP extract do not affect erectile function in aging healthy men. One possible explanation for this phenomenon might be related to the insufficient concentrations of active ingredients of KP to reach the therapeutic level.

It has been reported that hormonal control system is recognized as one key factor to regulate sexual behavior and ED including Follicle Stimulating Hormone (FSH),

Luteinizing Hormone (LH) and testosterone concentrations (Finkelstein *et al*., 1991; Luboshitzky *et al*., 1996). However, the current study has demonstrated that the improvement in ED by KP administration did not correlated with the change of serum hormones as mention earlier. This finding is in accordance with the previous report of serum testosterone levels were not associated to the improvement in sexual desire or ED by treatment with KP (Trisomboon *et al*., 2007; Sudwan *et al*., 2006). Since there was no any change in testosterone or gonadotropin concentrations after KP administration, it is clearly indicate that KP does not have testosterone-like effect and then does not disrupt the hypothalamic-pituitary-testicular axis in aging healthy men.

A normal erection occurs as a resulted of a coordinated vascular event in the penis. This is usually triggered neutrally and consists of vasodilation and smooth muscle relaxation in the penis and its supplying arterials vessels (Shabsigh and Anastasiadis, 2003). Arterial inflow causes enlargement of the substance of the corpora cavernosa. Venous outflow is trapped by this enlargement, permitting sustained high blood pressures in the penis sufficient to cause rigidity.

Previous studies have been found that the rats treated with the alcohol extract of KP could induce a significant increase in testicular blood flow without affecting heart rate and mean arterial blood pressure (Chaturapanich *et al*., 2008).

Accumulating lines of evidence reported that the increasing of penile size, length and rigidity indicated the involvement of Nitric Oxide (NO) (Du and Hull, 1999). Experimental studies have demonstrated that KP extracted with alcohol could also induce an increasing of endothelial Nitric Oxide Synthase (eNOS) and protein expression in human umbilical vein endothelial cells (Hu *et al*., 2009). eNOS, abundantly presented in the endothelium of penile vasculature and sinusoidal endothelium within the corpora carvernosa, is a mediator of penile erection. eNOS inhibitor can block penile erection. Then, the penile erection is depended on the nitric oxide via eNOS action (Yakubu and Afolayan, 2009; Tajuddin *et al*., 2004). Hence, we assume that KP may affect the increasing penile circumference, length and rigidity of the aging healthy volunteers via the increasing blood flow.

Many studies have reported that many bioactive components of plant extracts especially the flavonoids also exhibit aphrodisiac activities by acting directly on the central nervous system to modulate the action of neurotransmitters are involved in the regulation of erectile activity including the dopamine, the serotonin and the GABA systems (Hull *et al*., 2004; Michelson *et al*., 2001).

From the study of chemical components by gas chromatographic technique, the contents of KP rhizome were kinds of flavonoid substances, including 5-hydroxy-3, 7-dimethoxyflavone, 5-hydroxy-7-methoxyflavone, 5-hydroxy-3, 7, 4'-trimethoxyflavone, 5-hydroxy-7, 4'-dimethoxyflavone, 5-hydroxy-3, 7, 3'4' tetramethoxyflavone, 3, 5, 7-trimethoxyflavone, 3, 5, 7, 4'-tetramethoxyflavone, 5, 7, 4'-trimethoxyflavone and 5, 7, 3'4'-tetramethoxyflavone (Sutthanut *et al*., 2007; Yenjai *et al*., 2004). Therefore, the effects of KP extract on modulation the several neurotransmitter systems still could not be omitted. Further studies are required to identify the active constituent(s) responsible for the male impotence improvement activities and the mechanisms whereby these activities are implemented.

The results of the current study suggest that ethanolic extract of KP rhizomes may be a promising novel nutraceutical compound for the clinical treatment of ED.

5. CONCLUSION

Male impotence was studied in aging healthy men to further understand the role of KP extract as an aphrodisiac. There was an overall increase in the erectile function in the KP extract at a dose of 90 mg treated groups of volunteers as reflected in penile size and length both in flaccid and erection states and the response latency time to visual erotic stimuli. These results were statistically significant. It is concluded that the ethanolic of KP rhizomes appears to possess aphrodisiac activity.

6. ACKNOWLEDGMENT

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