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ORIGINAL ARTICLE

Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines – comparison with traditional herbal medicines (Kampo)

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Abstract

“LEOPIN ROYAL®” (LER), a non-prescription health-promoting medication in Japan, is a preparation containing six natural medicines, namely, aged garlic extract, ginseng, oriental bezoar, velvet antler, cuscute seed and epimedium herb. To determine the effect of LER on symptoms of aging in males, we conducted an open-labeled, randomized clinical trial using Kampo (mainly kamishoyosan) as a control. Forty-nine male patients (age, 62.7 (SD 11.8) years) with mild or more pronounced symptoms of aging were enrolled and randomly assigned to the LER ($n = 24$) or Kampo group ($n = 25$) for 6 months. The Aging Males’ Symptoms (AMS) scale and the International Index of Erectile Function with 5 questions (IIEF-5) were tested at baseline, and after 3 and 6 months of administration of the medications. In the AMS scale, the somatic and psychological sub-scores and total score decreased depending on the time course in both groups. However, the decrease in the slope of the LER group was greater than that of the Kampo group. There was a significant difference between the groups and the group and month interaction ($G \times M$), as revealed by a linear mixed model analysis ($p < 0.05$). The IIEF-5 score increased in the LER group ($p = 0.02$ with regard to $G \times M$). In conclusion, the present results indicate that LER is possibly superior to mainly kamishoyosan on the rate of improvement of symptoms of aging, including erectile dysfunction, in males.

Keywords

Andropause, erectile dysfunction, garlic, geriatrics

History

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Introduction

With the increasing aging population in Japan, the health-related quality of life (HRQoL) in elderly men has become an important issue. Age-related changes in somatic, psychological and sexual function in men are partially explained by the decline in androgen level, which is known as “Androgen Deficiency in the Aging Male” (ADAM) or “Late-onset Hypogonadism” (LOH). For treatment of the ADAM or LOH, androgen replacement therapy (ART), antidepressants and erectile dysfunction (ED) treatments are used. However, Kampo are often used because of patients’ preference to “natural” or “safe” medications. Kampo is based on traditional Chinese medicine (TCM) but adapted to Japanese culture. Currently, 148 Kampo medications are approved for reimbursement in Japan. Kampo and other

herbal medicines are different depending on whether or not it is based on TCM theory.

“LEOPIN ROYAL®” (LER) is a unique liquid formula, non-prescription health-promoting medication in Japan, but is not a Kampo. This preparation contains concentrated aged garlic extract (AGE), ginseng extract, oriental bezoar tincture, velvet antler fluid extract, cuscute seed extract and epimedium herb extract. AGE and ginseng have been reported to be effective against ED in male animal and human [1,2]. Velvet antler, cuscute seed and epimedium herb have been traditionally used as an aphrodisiac in East Asia [3].

In this study, we determined whether LER could improve the symptoms of aging in males in an open-label, Kampo-treatment controlled, randomized clinical trial.

Materials and methods

Participants

Men visiting our hospital with symptoms of aging were invited to enroll into the study. Selection criterion was a score of 27 or more (mild or more) on the Aging Males’ Symptoms

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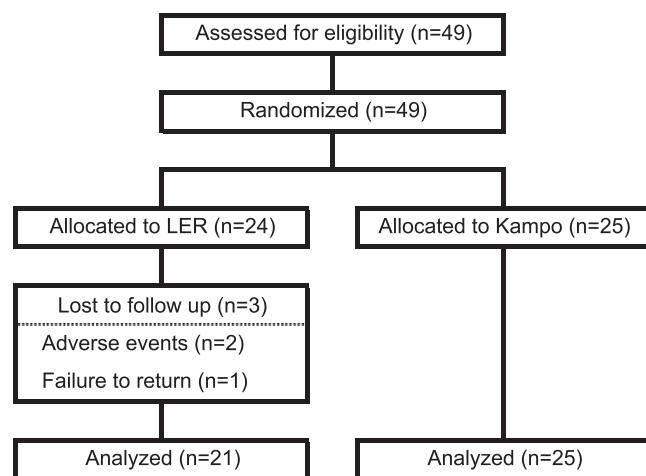


Figure 1. Flow chart for enrollment of patients and follow-up data.

scale (AMS scale). Traditional pattern for Kampo medicine was not diagnosed. All patients provided informed written consent, and the Institutional Review Board of the University of Tokyo Hospital approved this study.

Eligible participants ($n=49$, age 62.7 (SD 11.8) years) were enrolled and randomly assigned to the LER ($n=24$) or Kampo ($n=25$) group. Participants of each group were treated with LER or Kampo for 6 months according to the approved dosage of each regimen. Three participants in the LER group were lost to follow-up because of adverse events ($n=2$) and failure to return ($n=1$). As a result, 46 participants (21 in the LER group and 25 in the Kampo group) completed the study protocol (Figure 1).

Treatments

The LER (manufactured by Wakunaga Pharmaceutical Co., Ltd., Osaka, Japan, Lot no. EA0, F0G, GAB, H0F, etc) was purchased at a pharmacy. The package insert of LER has been described as follows: Ingredient: 2 mL of LER contains 1.8 mL of concentrated AGE, 273 mg of ginseng extract, 0.15 mL of oriental bezoar tincture, 0.03 mL of velvet antler fluid extract, 30 mg of cuscutea seed extract and 5 mg of epimedium herb extract. Dosage: adults 15 years and above; 1 mL (one capsule full), with normal or warm water, twice daily.

AGE contained in the LER is a unique garlic extract manufactured by soaking sliced garlic (*Allium sativum*) cloves in an aqueous ethanol and naturally extracted/aged [4]. Ginseng extract, cuscutea seed extract and epimedium herb extract are extracts of *Panax ginseng* root, *Cuscuta* sp. seed and *Epimedium* sp. herb, respectively, which are extracted with 30% aqueous ethanol and concentrated. Oriental bezoar tincture and velvet antler fluid extracts are alcoholic liquid extracts of *Bos taurus* gallstone and *Cervus* sp. antler in a pre-calcified stage, respectively.

Since the preparation of indistinguishable placebo against LER is difficult, we designed an open-labeled, mainly kamishoyosan (Kampo group) controlled, randomized trial. We decided to prescribe kamishoyosan ($n=20$, *Jia Wei Xiao Yao San* in Chinese), which is used for somatic symptoms of LOH, to patients assigned to the Kampo group. However, the following Kampo medications were prescribed according

to patient's symptoms or needs; hangekoubokuto ($n=1$, *Ban Xia Hou Pu Tang*), saikokaryukotsuboreito ($n=1$, *Cai Hu Jia Long Gu Mu Li Tang*), hochuekkito ($n=1$, *Bu Zhong Yi Qi Tang*), goshajinkigan ($n=1$, *Niu Che Shen Qi Wan*) and hachimijogan ($n=1$, *Ba Wei Di Huang Wan*).

Evaluation of symptoms of aging in males

Participants were evaluated using the AMS scale, the International Index of Erectile Function with 5 questions (IIEF-5), the ADAM questionnaire and the Self-Rating Questionnaire for Depression (SRQ-D) at the time of enrollment (baseline), and after 3 and 6 months of treatment. The AMS scale is a HRQoL scale for aging male and was developed by Heinemann et al. in Germany [5,6]. The scale consists of 17 items to obtain the degree of each symptom on a scale of 1–5, and is able to measure for three-dimension sub-scores (somatic, psychological and sexual) and total score (the sum of three sub-scores). Severity of symptoms in the total score is defined in the following four categories; severe (score 50+), moderate (37–49), mild (27–36) and no (≤ 26). The IIEF-5 developed by Rosen et al. [7] is a diagnostic tool for ED, and consists of five items of five degrees. ED severity is classified in the following five categories; severe (score ≤ 7), moderate (8–11), mild to moderate (12–16), mild (17–21) and no ED (22–25). The ADAM questionnaire developed by Morley et al. [8] is a screening test for ADAM, and consists 10 items to obtain yes/no answers. A positive result on the questionnaire is defined as an affirmative answer (“yes”) to questions 1 or 7 or any 3 other questions. The SRQ-D is a screening test for masked depression, and developed by Abe et al. [9] in Japan. The questionnaire consists of 18 items of four degrees, and the total score is calculated as the sum of each question score except questions 2, 4, 6, 8, 10 and 12. Depression severity is classified in the following three categories; masked depression (score 16+), borderline depression (11–15) and no depression (≤ 10).

Endocrinologic tests

Some of the subjects underwent endocrinologic tests at baseline and after 6 months of treatment for serum testosterone, free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and estradiol (E2). Serum testosterone and free testosterone levels were measured by coated tube radioimmunoassay (Mitsubishi Chemical Medience Corp., Tokyo, Japan), FSH, LH and PRL were measured by fluorescent enzyme immunoassay (Tosoh Corp., Tokyo, Japan), and E2 was measured by chemiluminescent enzyme immunoassay (Fjirebio Inc., Tokyo, Japan).

Statistical analysis

To compare the differences of time courses between the two treatment groups, we used a linear mixed model analysis adjusted for the baseline and age, with group and month interaction ($G \times M$). Difference from the baseline in each group was compared by paired *t*-tests with the Bonferroni correction. The baseline characteristics of the subjects were compared between the two groups by the Mann–Whitney

U-test and *t*-test. All tests were performed with a two-sided α level of 0.05 and analyzed using the Statistical Package for the Social Sciences (SPSS) 16.0J (SPSS Japan Inc., Tokyo, Japan).

Results

The baseline characteristics of the subjects are shown in Table 1. Age, interval of administration, categories of the AMS scale (total score), IIEF-5, SRQ-D and ADAM questionnaire were comparable between the LER and Kampo

groups. However, the mean psychological sub-score in AMS scale of the LER group was significantly lower than that of the Kampo group (Table 2).

Table 2 shows scores of the AMS, IIEF-5, SRQ-D and ADAM questionnaire after 3 and 6 months of treatment. The somatic sub-score in the AMS scale significantly decreased after 3 and 6 months in both the treatment groups. However, the decrease slope for the LER group was greater than that in the Kampo group, and there was a significant difference between the treatment groups (G) and the group and month interaction ($G \times M$), as revealed by the linear mixed model

Table 1. Baseline characteristics of subjects.

	LER (<i>n</i> = 21)	Kampo (<i>n</i> = 25)	<i>p</i> Value
Age – years, mean (SD)	61.9 (11.4)	63.7 (12.5)	0.61†
Range	37–85	40–84	
Interval of administration – day, mean (SD)	181 (15.5)	184 (35.7)	0.68†
AMS scale (total score) categories – no. (%)			
Severe (score 50+)	7 (33%)	12 (48%)	0.38‡
Moderate (score 37–49)	10 (48%)	9 (36%)	
Mild (score 27–36)	4 (19%)	4 (16%)	
No (score ≤26)	0 (0%)	0 (0%)	
IIEF-5 categories – no. (%)			
Severe (score ≤7)	16 (76%)	16 (64%)	0.26‡
Moderate (score 8–11)	4 (19%)	4 (16%)	
Mild to moderate (score 12–16)	1 (5%)	3 (12%)	
Mild (score 17–21)	0 (0%)	2 (8%)	
No ED (score 22–25)	0 (0%)	0 (0%)	
SRQ-D categories – no. (%)			
Masked depression (score 16+)	3 (14%)	5 (20%)	0.80‡
Borderline depression (score 11–15)	7 (33%)	5 (20%)	
No (score ≤10)	11 (52%)	15 (60%)	
ADAM questionnaire			
Positive (“yes” to question 1 or 7 or any 3 other questions) – no. (%)	21 (100%)	25 (100%)	

The *p* values were calculated by *t*-test† or Mann–Whitney *U*-test‡ to compare between the groups. LER, LEOPIN ROYAL®; AMS, Aging Males’ Symptoms; IIEF-5, International Index of Erectile Function with 5 questions; SRQ-D, Self-Rating Questionnaire for Depression; ADAM, Androgen Deficiency in Aging Males; ED, erectile dysfunction.

Table 2. Time courses of scores related symptoms of aging in males.

	Treatment group	Score – mean (SD)			<i>p</i> Value	
		Baseline	3 months	6 months	G	G × M
AMS scale						
Somatic sub-score	LER	20.4 (5.1)	15.2 (4.1)*	13.8 (4.1)*	<0.01	<0.01
	Kampo	22.4 (5.1)	21.3 (5.5)*	20.0 (5.2)*		
Psychological sub-score	LER	10.6 (3.9)†	8.5 (3.1)	8.0 (2.8)*	<0.01	0.047
	Kampo	13.2 (4.4)	13.0 (3.9)	12.7 (3.4)		
Sexual sub-score	LER	15.5 (5.0)	15.2 (4.0)	14.5 (3.9)	0.47	0.79
	Kampo	15.6 (3.5)	14.8 (4.0)*	14.4 (3.7)*		
Total score	LER	46.5 (11.4)	38.9 (8.9)*	36.2 (8.5)*	<0.01	0.048
	Kampo	51.2 (12.1)	49.0 (12.4)*	47.0 (11.4)*		
IIEF-5 score	LER	5.6 (3.3)	8.4 (6.1)*	7.5 (5.7)	0.041	0.019
	Kampo	6.5 (5.1)	6.7 (4.6)	6.4 (5.0)		
SRQ-D score	LER	10.3 (5.4)	8.8 (4.5)	9.0 (5.2)	0.50	0.55
	Kampo	9.9 (5.9)	9.3 (5.5)	9.0 (5.2)		
ADAM questionnaire	LER	21 (100%)	19 (90%)	20 (95%)		
Positive – no. (%)	Kampo	25 (100%)	24 (96%)	24 (96%)		

The *p* values were calculated by the linear mixed model analysis adjusted for the baseline and age to compare between the treatment groups (G) and the group and month interaction ($G \times M$).

† $p < 0.05$ compared between the two groups at the baseline by *t*-test.

* $p < 0.05$ compared with the baseline in each group by paired *t*-tests with the Bonferroni correction.

LER, LEOPIN ROYAL®; AMS, Aging Males’ Symptoms; IIEF-5, International Index of Erectile Function with 5 questions; SRQ-D, Self-Rating Questionnaire for Depression; ADAM, Androgen Deficiency in Aging Males.

Table 3. Endocrinologic values before and after treatments of LER and Kampo.

	Treatment Group	Serum level – mean (SD)			<i>p</i> Value
		<i>n</i>	Baseline	6 months	
Testosterone (ng/mL)	LER	18	3.28 (2.03)	3.44 (2.08)	0.51
	Kampo	14	3.60 (0.82)	3.80 (0.75)	0.17
Free testosterone (pg/mL)	LER	18	7.89 (3.73)	9.32 (6.08)	0.24
	Kampo	11	7.67 (3.28)	6.99 (3.38)	0.10
FSH (mIU/mL)	LER	17	13.0 (12.7)	12.8 (10.8)	0.66
	Kampo	15	11.0 (5.1)	10.9 (4.6)	0.77
LH (mIU/mL)	LER	16	5.41 (5.06)	5.31 (4.45)	0.85
	Kampo	11	6.70 (4.24)	6.28 (3.59)	0.48
PRL (ng/mL)	LER	13	7.56 (3.62)	8.10 (7.49)	0.83
	Kampo	12	4.85 (1.52)	4.93 (0.76)	0.89
E2 (pg/mL)	LER	5	36.0 (32.4)	32.8 (28.6)	0.18
	Kampo	10	15.8 (3.4)	16.4 (3.0)	0.44

The *p* values were calculated by paired *t*-test.

LER, LEOPIN ROYAL®; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; E2, estradiol.

analysis. The declines in the psychological sub-score and the total score in the AMS scale of the LER group were greater than those in the Kampo group, and the *p* values of G and G × M were less than 0.05. The IIEF-5 score increased in the LER group, and G and G × M showed significant differences. There was no inter-group difference in sexual sub-score in the AMS scale, SRQ-D and ADAM questionnaire. The serum levels of hormones showed no significant change in either group (Table 3).

Adverse events were noted in two cases of the LER group (epigastric discomfort and skin rash); no causal relationship of epigastric discomfort with LER was established, and that of skin rash with LER remains unclear.

Discussion

In the present study, somatic and psychological symptoms of aging in males showed greater improvement in the LER group than in the Kampo group. Further, only those subjects who were treated with LER reported an improvement in ED, as measured by the IIEF-5.

Kampo medications have been often used in male patients with LOH-related symptoms. Saikokaryukotsuboreito has been reported to be effective for eugonadal patients with LOH-related symptoms [10]. In the cases of severe nervousness, anxiety or irritation, Yokkansan (*Yi Gan San*) and keishikaryukotsuboreito (*Gui Zhi Jia Long Gu Mu Li Tang*) are used. Hachimijiogan, goshajinkigan and hochuekkito are used for ED. Kamishoyosan and hangekoubokuto are known to be medications for females, but these medicines are also used for males with somatic symptoms such as hot flashes and sweating abnormalities [11].

The LER formulation used in this study contains six crude extracts. AGE is one of the extracts that has several pharmacological actions. Kasuga et al. [1] have reported that AGE significantly enhanced sexual behaviors (mounting and intromission) and spermatogenesis in mice with testicular hypogonadism induced by warm water treatment. Nitric oxide (NO) is a trigger to increase blood flow into the corpus cavernous at erection. Morihara et al. [12] indicated that AGE temporarily increased NO production in the plasma of mice, and that the amelioration of NO induced by AGE was due

to constitutive activation of NO synthases. Flow-mediated dilation (FMD) is known to reflect NO-mediated endothelial function. AGE was reported to increase the FMD in patients with coronary artery disease [13] and acute hyperhomocysteinemia induced by an oral methionine challenge in healthy subjects [14]. AGE also has effects on psychological stress. Kyo et al. [15] found a protective effect of AGE on damaged immune function caused by psychological stress induced by a communication box. Psychologically stressed mice showed decreased immune functions, which was restored by AGE. In addition, AGE has been reported to have anti-aging effects on the Senescence-accelerated mice (SAM); AGE extended survival and improved the learning and memory impairment of the SAM [16].

Panax ginseng is an important herbal medicine and is frequently blended in Kampo medications considered tonics. Jang et al. [2] performed a systematic review based on randomized clinical studies of red ginseng and provided evidence suggestive of the effectiveness of red ginseng in the treatment of ED. Ginseng has several pharmacological actions. Gillis [17] reported that the antioxidant and organ-protective actions of ginseng are linked to enhanced NO synthesis in the endothelium of the lung, heart, and kidney and in the corpus cavernosum, and that the enhanced NO synthesis could contribute to ginseng-associated vasodilation and perhaps also to an aphrodisiac action of the root.

Traditionally, the epimedium herb (Ikariso in Japanese, *Yinyanghuo* in Chinese), cuscutea seed (Toshishi, *Tusizi*) and velvet antler (Rokujo, *Lurong*) have been used as an aphrodisiac in East Asia [3]. Makarova et al. [18] reported that oral administration of a lipid-based suspension of *Epimedium koreanum* extract improved erectile function (intromissions and ejaculation) in aged rats. It is well known that icariin is an active ingredient in *Epimedium* sp. The pharmacological actions of icariin on erectile function have been reported to be mediated by the inhibition of cGMP-specific phosphodiesterase 5 (PDE5) *in vitro* [19], expression of NO synthase in castrated rats [20] and increment of serum testosterone levels in cyclophosphamide-treated rats [21].

The flavonoids extracted from the Semen Cuscutae have been reported to increase the weight of testis, epididymis, pituitary gland, stimulated testosterone and LH secretion in

male rats [22], and reversed the reduction of testosterone level and expression of androgen receptor gene in kidney-yang deficient mice [23]. Velvet antler has been reported to increase the weight of testis and prostate in castrated rats [24]. Oriental Bezoar (Goo, *Niu Huang*) is a dried gallstone of *Bos taurus domesticus* Gmelin, and is widely used in cardioactive over-the-counter (OTC) drugs in Japan [25].

There are two reports on the effect of LER, containing crude extracts of these natural products, on ED. Ushijima et al. [26] indicate a spermatogenesis-enhancing effect of LER on mice with testicular hypogonadism induced by warm water treatment, and Yaguchi et al. [27] reported that, of the 16 patients with unidentified complaints, one with ED showed a complete response to LER administration for 4 weeks.

In this study, even though the symptoms of aging in male were improved by LER administration, there was no change in the serum androgen level. As described above, the active ingredients in epimedium herb and cuscutea seed have been reported to have a serum testosterone increasing action in animal experiments. However, there is no report on the optimal doses of the action in human. As the dosage of the herbal medicines was not enough, a significant increase in serum testosterone may have not been observed during LER treatment. It has been reported that serum testosterone level does not correlate with erectile function and hypogonadism symptoms [28–31]. The effect of LER may be due to mechanisms other than androgen, for example, peripheral vasodilation by promoting NO synthesis.

Conclusion

Although this study is an open-labeled trial, our data indicate that LER is a safe medication and possibly superior to mainly kamishoyosan on the improvement of somatic and psychological symptoms of aging including ED for elderly male patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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