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·*Complementary Medicine*·

Effect of an extract of *Ganoderma lucidum* in men with lower urinary tract symptoms: a double-blind, placebo-controlled randomized and dose-ranging study

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Abstract

Aim: To conduct a double-blind, placebo-controlled randomized and dose-ranging study to evaluate the safety and efficacy of the extract of *Ganoderma lucidum* (*G. lucidum*) in men with lower urinary tract symptoms (LUTS). **Methods:** We enrolled male volunteers (≥ 50 years) with an International Prostate Symptom Score (IPSS; questions 1–7) ≥ 5 and a prostate-specific antigen (PSA) value < 4 ng/mL. Volunteers were randomized into groups of placebo (n = 12), *G. lucidum* of 0.6 mg (n = 12), 6 mg (n = 12) or 60 mg (n = 14), administered once daily. Efficacy was measured as a change from baseline in IPSS and the peak urine flow rate (Q_{max}). Prostate volume and residual urine were estimated by ultrasonography, and blood tests, including PSA levels, were measured at baseline and at the end of the treatment. **Results:** The overall administration was well tolerated, with no major adverse effects. Statistical significances in the magnitude of changes between the experimental groups were observed at weeks 4 and 8. No changes were observed with respect to Q_{max}, residual urine, prostate volume or PSA levels. **Conclusion:** The extract of *G. lucidum* was well tolerated and an improvement in IPSS was observed. The recommended dose of the extract of *G. lucidum* is 6 mg in men with LUTS. *(Asian J Androl 2008 Jul; 10: 651–658)*

Keywords: lower urinary tract symptoms; phytotherapy; outcome; randomized trial

1 Introduction

Phytotherapeutic agents have gained widespread usage in the treatment of lower urinary tract symptoms (LUTS), including urinary incontinence, overactive bladder and benign prostatic hyperplasia (BPH) [1]. These agents have been popular in some Asian and European countries. The use of these agents in Japan has also escalated. The clinical profile of patients presenting with LUTS and BPH is not the same in all countries. Many factors, including differences in health services, treatment culture and degree of urbanization, influence the point at which a patient first consults with either their general practitioner

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or an office-based urologist. Defining the clinical profile and initial treatment selection of the LUTS and BPH population is important for health-care systems, impacting on medical manpower requirements and pharmacologic demands and expenses, as well as providing information for the cost–benefit analysis of treatment strategies [2]. When strict criteria of evidence-based medicine have been applied, the available data have not yet provided clear evidence of efficacy for most phytotherapeutic preparations [2]. As a result, the role of phytotherapeutic agents in treating LUTS secondary to BPH is continuously debated.

In Japan, the Minister for Health, Labor and Welfare introduced a unique law in 1991 for food companies that label foods claming to have specific health benefits. Those companies are required to present relevant scientific data to obtain permission or approval from the Minister to label their products as having specific health benefits. We reported recently that an ethanol extract of *Ganoderma lucidum* (*G. lucidum*) shows the strongest 5α-reductase inhibitory activity among the extracts of 19 edible and medicinal mushrooms, and the treatment of the fruit body of *G. lucidum* or the extract prepared from it significantly inhibits the testosterone-induced growth of the ventral prostate in castrated rats [3]. The fungi *G. lucidum* has been used for centuries in East Asia. Its fruiting body is called "Reishi" in Japan and "Lingzhi" in China. In these areas, *G. lucidum* is a popular folk or oriental medicine used to cure various human diseases, such as hepatitis, hypertension, hypercholesterolemia and gastric cancer [4, 5]. However, the role of *G. lucidum* in treating LUTS has never been reported.

The symptoms experienced by the 17 men with LUTS included in our clinical pilot study were alleviated after administration of *G. lucidum* (data not shown). A clinical trial was conducted to evaluate the safety and feasibility of the use of *G. lucidum*, and to determine an effective dose of the extract of *G. lucidum* for men with LUTS.

2 Materials and methods

2.1 Study design

This double-blind, placebo-controlled randomized and dose-ranging study was carried out at the Kurume Research Park at the Kurume University School of Medicine, Kurume, Japan, from November 2004 to April 2005. The aim of this trial was to evaluate the safety and feasibility of the use of *G. lucidum*, and to determine an effective dose of the extract of *G. lucidum* for men with LUTS. Participants were screened for eligibility using an interview on the first visit, and randomized on the second. The study included an 8-week double-blind dose-ranging treatment, during which participants were randomized to receive each extract of *G. lucidum* of 0.6, 6 or 60 mg, or the placebo, once daily. Written informed consent was provided by each participant before enrollment in the study. The study protocol was approved by the Kurume University School of Medicine Ethics Committee, and the study was conducted in accordance with the declaration of Helsinki.

2.2 Eligibility criteria

Eligibility criteria for enrollment in the study included: men aged ≥ 50 years with an International Prostate Symptom Score (IPSS; questions 1–7) ≥ 5 and a prostate-specific antigen (PSA) value < 4 ng/mL on the first interview [6]. Exclusion criteria included: men with concomitant urological disease; diagnosed or suspected carcinoma of the prostate; previous radiation therapy of the pelvic region; previous prostate surgery or invasive BPH treatments; men using androgens, α-blockers or herbal preparations for urinary problems in the previous 4 weeks; men with insulin-dependent diabetes, severe cardiopulmonary disease, active liver disease or significant central nerve system (CNS) disease.

2.3 Randomization

The men were randomized off-site using a blocked stratified procedure, where each block consisted of four treatment assignments with two strata, two age groups (< 65 years, ≥ 65 years) and two groups with different baseline IPSS scores (< 12, ≥ 12). Randomization codes were concealed in sealed envelopes and opened only after the last man had completed treatment. Power analysis was carried out based on the results from the previous pilot study, which furnished estimates of mean IPSS change from baseline to 12 weeks on 6 mg/day, 60 mg/day and placebo groups. They are 10.333 ± 7.506 (mean ± SD), 4.571 ± 4.504 and 2.143 ± 2.854, respectively. To determine the adequate sample size for the present study, mean changes and associated SD on the placebo group and the 6 mg/day group were used with a paired *t*-test with a power of 0.8 and a significance level of 0.05. This power analysis yielded 10 subjects for each group. Allowing for dropout, a final sample size of 12 subjects

for each experimental group was decided upon.

2.4 Intervention

Eligible participants were randomized to receive each extract of *G. lucidum* of 0.6 mg, 6 mg and 60 mg, or a placebo. Tablets providing different doses and placebo were manufactured by Chlorella Industry (Tokyo, Japan), using a method involving a sugar coating to produce the same taste and no smell. The weight of each tablet is 250 mg, and eight tablets were put together into a pack to be taken once daily. Each package for the four treatment groups was labeled using four different colors, and administered by study nurses in a double-blinded manner. In brief, dried and chipped *G. lucidum* was extracted with 30% EtDH at room temperature for 24 h using a blender. The extracts were filtered through ADVANTEC No. 2 filter paper, concentrated under a vacuum, and then freeze-dried. The basic contents of each tablet are 83.65% maltitol (Towa Chemical Industry, Tokyo, Japan), 10% cornstarch (San-ei Sucrochemical, Chita, Japan), 3% vitamin C (BASF Japan, Kawasaki, Japan), 0.2% gardenia yellow (Hodogaya Chemical, Tokyo, Japan) and 3% sucrose fatty acid ester (Dai-ichi kogyo seiyaku, Kyoto, Japan). The tablet for the *G. lucidum* groups of 0.6 mg, 6 mg and 60 mg included 0.075 mg, 0.75 mg and 7.5 mg of the extract of *G. lucidum* (Chlorella Industry, Tokyo, Japan), respectively, and the tablet for the placebo was adjusted by naringin (Inabata Koryo, Osaka, Japan) for the same taste. Participants were advised to take the study medication once a day with meals and to bring all unused tablets to each study visit.

2.5 Evaluation procedure

Participants were assessed on day –14, day 0, 4 weeks and 8 weeks into the double-blind treatment period, and followed up on the 10th week. Efficacy assessments included the seven-item IPSS and one quality-of-life (QoL) question, for which the answers ranged from 'delighted' (0) to 'terrible' (6) (on day –14, day 0, 4 weeks, 8 weeks and 10 weeks). The peak urinary flow rate was assessed using an uroflowmeter (W.O.M. World Medicine, UROPOWER201, Berlin, Germany), for which a voided volume of ≥ 150 mL is required for an accurate reading [7] (on day –14, day 0, 4 weeks and 8 weeks). Prostate volume and residual urine volume were also measured on day 0 and after 8 weeks using an ultrasonography (Aloka, SSD-900, Japan). Vital signs (heart rate and blood pressure) were assessed in the afternoon on day –14, day 0, 4 weeks, 8 weeks and 10 weeks. Treatment-emergent adverse effects, adverse effects leading to discontinuation of treatment, and serious adverse effects were monitored and recorded throughout the double-blind treatment period. Laboratory tests, including PSA, were conducted on blood samples taken on day –14 and at 8 weeks.

2.6 Statistical analyses

Data were entered into an online database with a security system by two research nurses using the electric data capturing system (System Lab, Kurume, Japan) and then analyzed using commercial software (SAS V9.1 for Windows; SAS Institute, Cary, NC, USA). To control the effects on the baseline measure, treatment efficacies were tested by analysis of covariance (ANCOVA), where the baseline measure was used as a covariate. The results from ANCOVA were conformed using linear mixed models, where all repeated measures were utilized while accounting for their serial correlations as well as baseline effects. Although no adjustment was made for multiple comparisons, significant treatment efficacy was reported only when the overall treatment group *F*-test was significant on ANCOVA.

3 Results

3.1 Study participants

Of the 63 men who were assessed for initial eligibility by the interview on the first visit, 50 qualified to be randomized to receive the placebo (12 men), *G. lucidum* of 0.6 mg (12 men), 6 mg (12 men) and 60 mg (14 men) (Figure 1). All of the 50 men completed the study. There were no statistically significant differences in baseline characteristics for age, PSA level, prostate volume, peak urinary flow rate, or symptom score among the *G. lucidum* groups and placebo. However, as a result of the entry criteria using only age and total-IPSS score, there is a wide range of variation between the groups for baseline prostate volume, baseline peak urinary flow rate, and PSA level (Table 1).

3.2 Serial changes of total IPSS and IPSS-QoL scores

The serial changes of total IPSS and IPSS-QoL scores in the four groups are shown in Figure 2. There was an escalating trend of dose-response among the placebo, *G. lucidum* of 0.6 mg, 6 mg and 60 mg groups, evident

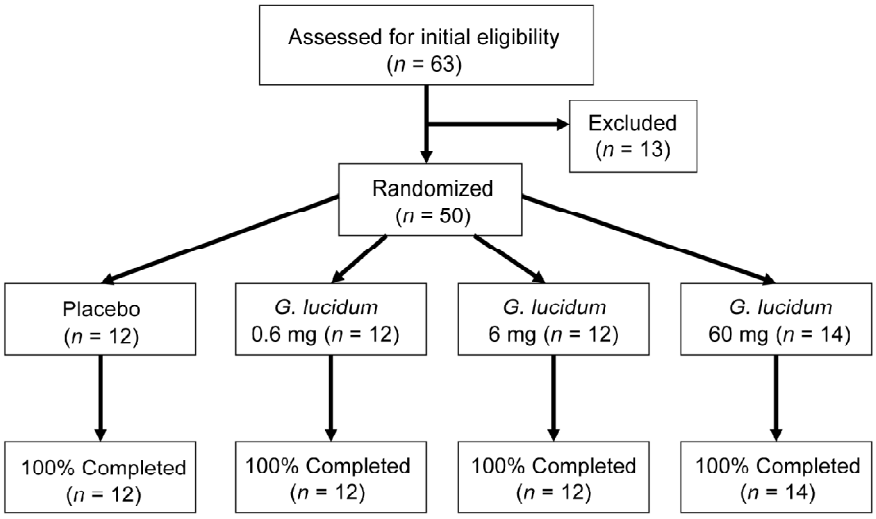

Figure 1. A flow diagram showing the distribution of participants at each stage.

Table 1. Baseline demographics and clinical characteristics of the participants. PSA, prostate specific antigen; QoL, quality-of-life; Q_{max}, peak urine flow rate.

Characteristics	Placebo	*G. lucidum*, once daily		
		0.6 mg	6 mg	60 mg
Number	12	12	12	14
Age (years)				
Mean	59.7	59.1	59.2	59.4
Median	60.5	59	59.5	60
Range	50–67	51–70	50–72	50–70
PSA (ng/mL)				
Mean	1.503	1.421	1.322	1.438
Median	1.315	1.110	1.190	1.315
Range	0.414 –3.700	0.286–2.810	0.515–3.260	0.243–3.010
Prostate volume (mL)				
Mean	23.3	29.7	22.8	23.9
Median	19.7	29.4	20.1	21.6
Range	9.1–67.3	12.3–55.3	9.3–59.6	12.3–38.3
IPSS (score)				
Mean	11.3	9.9	9.8	10
Median	9	10	9	10
Range	5–23	5–22	5–21	5–17
QOL (score)				
Mean	4	3.3	3.3	3.4
Median	4	3.5	3.5	4
Range	2–5	0–6	2–5	1–5
Uroflow (Q_{max}) (mL/s)				
Mean	17.9	13.8	19.2	15.4
Median	15.1	12.1	16.9	14.1
Range	8.0–34.3	6.4–26.0	4.9–42.6	7.5–29.8

in the mean change from baseline in total IPSS throughout the study. Significant overall treatment effects in total IPSS were observed at 4 weeks, F (3,45) = 7.08, P = 0.0005, and 8 weeks, F (3,45) = 3.38, P = 0.026, while there was a trend at 10 weeks, F (3,45) = 2.52, P = 0.07. Mean changes at 4 and 8 weeks adjusted for baseline measures and its 95% confidence intervals for each treatment group are shown in Table 2. At 4 weeks, the mean change in the *G. lucidum* 60 mg group was significantly larger than in the placebo group (P = 0.012) and in the *G. lucidum* 0.6 mg (P < 0.0001) group. The mean change in the *G. lucidum* 6 mg group was also larger than the *G. lucidum* 0.6 mg group (P = 0.004). At 8 weeks, the mean change in the *G. lucidum* 0.6 mg group was significantly smaller than that in the *G. lucidum* 60 mg group (P = 0.0049) and in the *G. lucidum* 6 mg group (P = 0.0155). For the QoL score, the *G. lucidum* 6 mg group had a baseline score of 3.3 (2–5), which decreased to 2.3 (1–4) after 8 weeks; the placebo baseline score was 4 (0–6), which decreased to 3.6 (2–5) after 8 weeks. The mean changes from baseline in the QoL after 8 weeks of treatment with *G. lucidum* 6 mg was significantly better than that for the placebo (P = 0.04).

3.3 Serial changes of the peak urine flow rate (Q_{max}), residual urine, prostate volume and PSA levels

The initial mean Q_{max} in the placebo, *G. lucidum* of 0.6 mg, 6 mg and 60 mg groups were 17.9, 13.8, 19.2 and 15.4 mL/s, respectively, which improved to 21.3 mL/s, 17.6 mL/s, 21.6 mL/s and 18.3 mL/s at 8 weeks after treatment, respectively. However, there was no statistical difference in the mean changes from baseline to 8 weeks among the four groups (Figure 3). No changes were observed with respect to residual urine, prostate volume or PSA levels (Figure 4).

3.4 Adverse events

All adverse events in each group are summarized in Table 3. The overall administration with *G. lucidum* of 0.6 mg, 6 mg and 60 mg was well tolerated with no

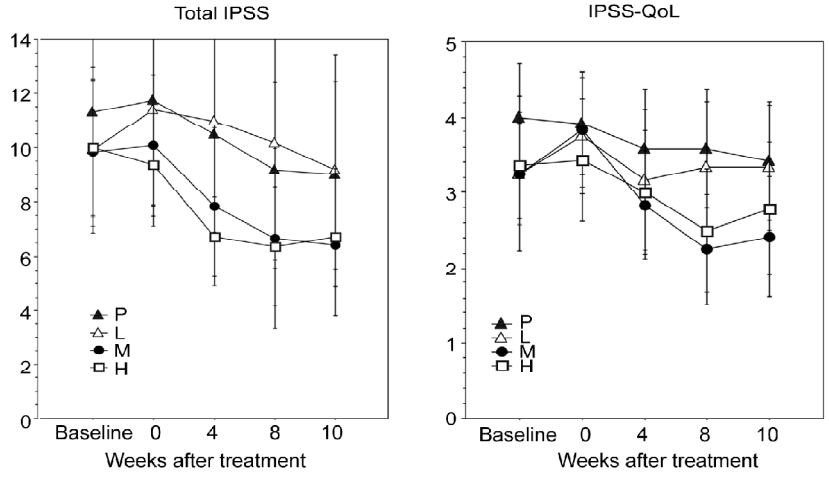

Figure 2. Serial changes (mean ± 95% confidence interval) of total International Prostate Symptom Score (IPSS) and IPSS quality-of-life (QoL) scores in the four groups. P: placebo; L: low dose (0.6 mg); M: medium dose (6 mg); H: high dose (60 mg).

Table 2. Mean changes of total International Prostate Symptom Score (IPSS) at 4 and 8 weeks.

Treatment group	4 weeks		8 weeks	
	Adjusted mean change	95% confidence interval	Adjusted mean change	95% confidence interval
60 mg	3.31	1.96–4.66	3.67	1.88–5.47
6 mg	2.05	0.59–3.5	3.22	1.28–5.16
0.6 mg	–1.05	–2.51–0.41	–0.21	–2.15–1.73
Placebo	0.72	–0.75–2.19	2.04	0.09–3.99

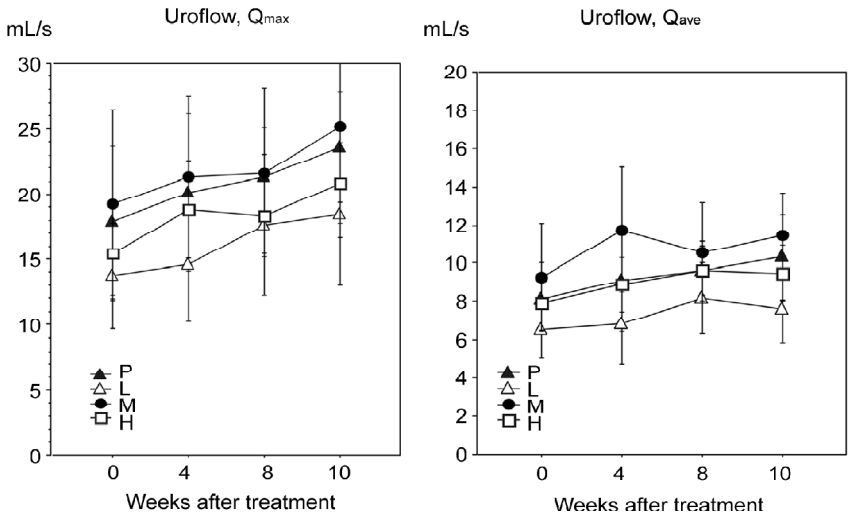

Figure 3. Serial changes (mean ± 95% confidence interval) of total peak urine flow rate (Q_{max}) and average flow rate (Q_{ave}) in the four groups. P: placebo; L: low dose (0.6 mg); M: medium dose (6 mg); H: high dose (60 mg).

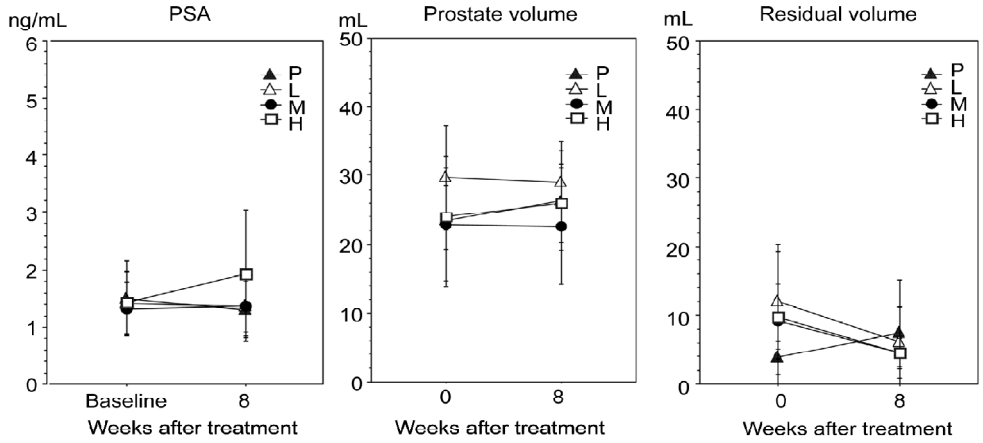

Figure 4. Serial changes (mean ± 95% confidence interval) of prostate-specific antigen (PSA) levels, prostate volume and residual urine in the four groups. P: placebo; L: low dose (0.6 mg); M: medium dose (6 mg); H: high dose (60 mg).

Table 3. Adverse events in each group.

Variable	Placebo (n = 12)	*G. lucidum* (0.6 mg) (n = 12)	*G. lucidum* (6 mg) (n = 12)	*G. lucidum* (60 mg) (n = 14)
Nonserious adverse events				
Constipation	2	0	0	0
Diarrhea	1	0	0	0
Nausea	0	1	0	1
Rash	0	1	0	0
High blood pressure	0	1	0	1
Fatigue	0	0	1	0
Serious adverse events	0	0	0	0
Total	3	3	1	2

major adverse effects. Mean changes from baseline in heart rate and blood pressure were small and similar among the four treatment groups. There was no treatment related hematologic, hepatic or renal toxicity.

4 Discussion

Although there is a relatively high total IPSS at baseline in the placebo group, the baseline demographics and clinical characteristics of the participants were comparable between the four treatment groups. The results of the present study showed that the extracts of *G. lucidum* 6 mg and 60 mg significantly improved the total IPSS scores, with mean changes of 3.2 and 3.6 from the baseline in men with LUTS. Statistically significant overall treatment efficacy in IPSS total scores was observed at 4 and 8 weeks. Specifically, these significant differences revealed a dose response among the *G. lucidum* treated groups, whereas there was a significant difference between the 60 mg of *G. lucidum* group and the placebo group at week 4. The 6 mg dose was more effective in improving the disease-specific QoL in those men than was the 60 mg dose. However, there were no significant changes in the PSA levels and prostate volume, and no significant improvement was noted in peak urinary flow rate and post void residual urine volume among the four groups.

In our recent study, we found a new facet of the biological activities of the *G. lucidum*, anti-androgenic activities on *in vitro* 5α-reductase inhibitory activity and *in vivo* growth suppression of the rat prostate, and that the extracts of *G. lucidum* have the strongest 5α-reductase inhibitory activity among the extracts of 19 edible and medicinal mushrooms [3]. In addition, the treatment of *G. lucidum* itself or the ethanol extract prepared from it significantly inhibited the growth of the ventral prostate induced by testosterone in rats. The inhibitory concentration leading to 50% activity loss (IC_{50}) of the ethanol extract of *G. lucidum* was estimated to be 93.6 μg/mL. Finasteride, which is known as a potent steroidal inhibitor, showed an IC_{50} of 0.73 μmol/L in our assay system [8]. These results indicated that the fruiting body of *G. lucidum* contained some triterpenoids with 5α-reductase inhibitory activit, although their inhibitory activity is lower than that of finasteride. Finasteride is an inhibitor of human 5α-reductase, which causes in a decrease in plasma and intraprostatic dihydrotestosterone (DHT) levels. In clinical studies involving men with BPH, finasteride has been shown to reduce the volume of the prostate and to reduce urinary symptoms [9, 10]. Our observations that prostate volume and PSA did not decrease in men might be explained by the assumption that the effects of 5α-reductase inhibitors are limited in small-sized prostates [11]. In the present study, the mean prostate volume was only 25.4 mL. Hamdy [12] also postulates that the prostate volume does not correlate with the efficacy of treatment using either finasteride or phytotherapy. In addition, a short period of treatment time, such as 8 weeks in the present study might result in no significant change in prostate volume. Treatment with the extracts of *G.lucidum* had no effect on serum PSA levels in the present study. The absence of any effects of *G. lucidum* on serum PSA suggests that this agent has little or no effect on other androgen-dependent processes, which rely on the binding of androgens to their receptor [13]. This is in contrast with other 5α-reductase inhibitors, such as finasteride, which in addition to their enzyme-inhibitory activities, appear to alter the level of PSA expression by inhibiting the complex formed between androgen receptors and the steroid receptor binding consensus in the promoter region of the PSA gene [14]. The residual volume is known to be an unreliable measurement, with poor reproducibility [15]. The lack of any effect on prostate volume and PSA for *G. lucidum* is similar to the effect seen with other phytotherapeutic agents, such as Permixon or a Saw Plametto extract. Perhaps the mechanism of action of all plant extracts with 5α-reductase activity is both similar and different from that of the synthesized pharmaceuticals.

Phytotherapy for men with LUTS is very popular in France and Germany, with a market share up to 50% of all drugs used to treat symptomatic BPH [16]. In these countries, phytotherapeutic agents are prescription drugs, whereas they are neither approved nor reimbursed in the UK [17]. In the USA, up to 90% of newly referred patients with LUTS secondary to BPH have already tried or are using some form of alternative or complementary medication at the time of their presentation [1, 18]. A recent US survey conducted by National Family Opinion determined that the widespread use of these agents was a result of the philosophical congruence with people's own values, beliefs and orientation toward health and life [19]. However, this widespread and increasing patient preference has to be balanced against the call for an increased awareness of the need to submit to medical

evaluations and decisions according to the evidence-based approach [20].

This is the first randomized, double-blind, placebo-controlled study in Japan assessing the usefulness of phytotherapy for men with LUTS. In Japan, phytotherapeutic agents can be obtained in health food stores as non-reimbursable and non-prescription "dietary supplements", and are being used by an increasing number of patients without medical evaluation. However, the Japanese medical insurance system is the most comprehensive in the world, and their costs are increasing. Therefore, the Minister for Health, Labor and Welfare in Japan introduced the new law for labeling food.

The results of the present study encourage us to perform further evaluations to obtain approval from the Minister of Health, Labor and Welfare for the use of LUTS in healthy food products.

The extracts of *G. lucidum* in 6 mg and 60 mg doses were tested and found to be safe and effective in relieving urinary symptoms in men with symptoms of bladder outlet obstruction. The 6 mg dose was more effective in improving the disease-specific QoL in men than was the 60 mg dose. Therefore, the 6 mg dose is going to be selected for further evaluation in a placebo-controlled trial.

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