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Research Article

Safety Assessment of Oral *Lysiphyllum strychnifolium* Aqueous Extract in Healthy Volunteers

Piracha Jumpa-ngern[1], Parunkul Tungsukruthai[1], Chuntida Kamalashiran[1], Somboon Kietinun[1], Kesara Na-Bangchang[2,3], Kusuma Sriyakul[1,*]

ABSTRACT

Background: *Lysiphyllum strychnifolium* (LS), widely known as Ya nang daeng in Thailand, is a traditional herbal remedy that has long been used to promote health and treat diverse health conditions, especially detoxification, by alleviating the severity of symptoms and lowering the risks associated with toxic exposures. Although it is extensively used in Thailand, human safety studies have been lacking. Thus, this study aimed to examine the safety of using LS capsules in healthy participants through a Phase I clinical trial. **Objective:** This study aimed to investigate the safety of aqueous extract of LS in twenty–four healthy Thai participants. **Method:** The participants were received 1,000 mg of LS aqueous extract each morning before their meals for seven days. All participants were examined safety assessment including history taking, physical examination, and laboratory tests at day 0, 8 and 14 (follow–up). **Results:** The findings showed that there were no significant side effects or abnormalities found during the history taking, physical examination, or laboratory evaluation. Particularly, when compared to baseline, participants who received LS experienced statistically significant reductions in blood sugar, triglyceride, LDL cholesterol, and creatinine ($P < 0.05$), but still within normal ranges. **Conclusions:** Dietary supplementation with 1,000 mg of LS aqueous extract per day may have a beneficial effect on blood sugar and cholesterol management while remaining safe for healthy people.

Keywords: *Lysiphyllum strychnifolium*, Yanang Daeng, Safety, Healthy volunteers, Clinical study.

Piracha Jumpa-ngern[1], Parunkul Tungsukruthai[1], Chuntida Kamalashiran[1], Somboon Kietinun[1], Kesara Na-Bangchang[2,3], Kusuma Sriyakul[1,*]

[1]Department of Integrative Medicine, Chulabhorn International College of Medicine, Thammasat University, Pathumthani 12120, THAILAND.

[2]Graduate Program in Bioclinical Sciences, Chulabhorn International College of Medicine, Thammasat. University, Pathum Thani 12120, THAILAND.

[3]Drug Discovery and Development Center, Office of Advanced Science and Technology, Thammasat University, Pathumthani 12120, THAILAND.

Correspondence

Kusuma Sriyakul

Department of Integrative Medicine, Chulabhorn International College of Medicine, Thammasat University, Pathumthani 12120, THAILAND.

E-mail: kusuma-s@tu.ac.th

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INTRODUCTION

Herbal medicines are the integration of traditional medical practices and therapeutic experiences from previous generations and have been utilized for more than 100 years worldwide.[1] Numerous studies have proven the safety and potentially beneficial effects of herbal remedies.[2, 3] Moreover, several phytoconstituents found in herbal remedies are well-known for their pharmacological effects on the body.[4] Many diseases including cancer, diabetes, hypertension, and skin diseases have reportedly been successfully treated with herbal.[5]

In Thailand, the Thai government strongly encourages the use of herbal and traditional medicine as a supplementary to conventional therapy as part of the National Economic and Social Development Plan. Since 1999, the public health insurance system has reimbursed herbal medications that are listed on the National List of Essential medications.[6] In addition, many Thai herbal medicinal products can be purchased over the counter and self-prescribed. However, when used incorrectly, certain Thai herbal medicines have been discovered to be potentially hazardous.[7] To avoid toxicity, it is vital to use herbal medicine appropriately.

Lysiphyllum strychnifolium (Craib) A.Schmitz (LS); or *Bauhinia strychnifolia* Craib, commonly known as "Ya-Nang-Daeng" or "Kha-Yan" and mostly found in northern and northeastern regions of Thailand[8,9], is one of traditional Thai medicinal herb. It has traditionally been used to promoting health and treating various health conditions, especially detoxification, to alleviate the severity of symptoms and reduce the risks associated with toxic exposures such as toxic mushrooms, poison shellfish, alcohol intoxication and act as a neutralizing pesticide poisoning in animals and humans. [9-12] The dried stems and leaves are prepared as herbal tea and prescribed by Traditional Thai doctors.[11, 12]

Previous studies have demonstrated that LS is potentially effective for providing anti-inflammatory, anti-hyperuricemia, antiproliferative, antibacterial, and antioxidant activities.[13, 14] Moreover, the ethanol extract of LS has been used for anti-HIV-1 integrase and showed anti-allergy properties[15, 16] anti-cancer activity[17] antidiabetic properties[18-20] antidote effects,[9] inhibitor of H5N1 Influenza A, and antibacterial activities.[21] Three major bioactive compounds discovered from the leaves of LS include gallic acid, trilobatin and yanangdaengin[14, 22] while its stems have been reported several chemical constituents such as quercetin, 3,5,7,3′,5′-pentahydroxy-flavanonol-3-O-α-Lrhamnopyranoside, 3,5,7-trihydroxychromone-3-O-α-L-rhamnopyranoside, β-sitosterol, stigmasterol[16] and astilbin.[23, 24] To date, few reports on toxicity testing. The ethanolic extract of LS leaves at the doses up to 3,000 mg/kg did not show any signs of toxicity effects in all animals during acute toxicity test.[25] In clinical study, there have been limit research of safety and efficacy in humans and mostly used in tea form. The daily consumption of tea for fourteen days revealed no adverse effects and a significant increase in cholinesterase levels after taken twice daily for two weeks.[26] Another study showed that LS was both safe and effective in increasing breastmilk volume when consumed three times a day for seven days.[27] Even though this plant has a wide range of medicinal applications and has been used for a long time, there

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have been no comprehensive studies on LS aqueous extract in the form of capsules in healthy Thai participants. Therefore, the purpose of this study was to examine the safety of LS aqueous extract in the form of capsule in twenty-four healthy Thai participants.

MATERIALS AND METHODS

Chemicals

The standardized LS capsules were prepared by Pharmaceutical Chemistry and Natural Products, Faculty of Pharmacy, Mahasarakham University, Thailand. Methanol (HPLC grade) and acetic acid were obtained from Labscan Asia Co. Ltd. (Bangkok, Thailand). Deionized water was purified by Ultra Clear system (Siemen Water Technologies Corp., USA). The standard powder of gallic acid was purchased from Tokyo Chemical Industry Co., Ltd. (Japan). Trilobatin were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemical reagents used in this study were of analytical grade.

Preparation of the Standardized LS capsules

Plant materials, fresh leaf of LS was collected from the Khud Chum district of Yasothorn province in Thailand. The voucher specimens of LS (TTM No.0003601) was deposited at Department of Thai Traditional and Alternative Medicine, Ministry of Public Health. Thailand. The leaf of LS was rinsed thoroughly with tap water to remove extraneous contaminants and hot air oven-dried at 60 °C for 48 hours. LS was ground into powder using a blender and sieved through mesh no.14. The powdered LS was extracted by boiling in 1,000 ml of distilled water for 1 hour. The extracted solvent was separated and filtered through Whatman no. 1 filter paper. The extracts were evaporated using the freeze-drying technique and irradiated with gamma-ray for the elimination of microbial contamination.

The quality control using high-performance liquid chromatography (HPLC) analysis of LS were measured according to the methods of Kongkiatpaiboon et al with modifications. The HPLC analyze was performed on an Agilent 1260 Series (Agilent Technologies) equipped with a 1260 Quat pump VL quaternary pump, 1260 ALS autosampler, 1260 TCC column thermostat, 1260 DAD VL diode array detector and a Hypersil BDS C18 column (4.6x 100 mm; 3.5 mm particle size). The mobile phases were a mixture of (A) 0.5% acetic acid in water and (B) methanol, gradient elution: 0% B in A for 5 min, linear increasing from 0% B in A to 30% B in A for 3 min, linear increasing from 30% B in A to 60% B in A for 22 min and 100% B for 5 min at flow rate of 1 mL/min. The wavelength of UV detector was operated at 280 nm. The HPLC analysis revealed that the aqueous extract of LS had Gallic acid, Trilobatin, and Yanangdaengin.The concentrations were calculated to be 0.60, 7.04, and 2.62 %w/w, respectively as shown in the figure 1.

The LS capsules were prepared by Pharmaceutical Chemistry and Natural Products Research Units, Faculty of Pharmacy, Mahasarakham University, Thailand, and characterized according to the USP Standard (weight variation, content uniformity, disintegration, and dissolution). Each capsule contained 500 mg of aqueous extract of LS.

Study design

This study was designed as a single-arm, open-label, prospective clinical trial to evaluate the safety of LS in healthy Thai participants. The study was conducted at Chulabhorn International College of Medicine, Thammasat University, Pathum Thani, Thailand.

Ethical considerations

The study protocol was reviewed and approved by the Human Research Ethics Committee of the Faculty of Medicine Thammasat University, Thailand (MTU-EC-00-4-17/64) and it was registered in the Thai Clinical Trials Registry (TCTR20220110008). Before study participation, written informed consent was obtained from the participants after being provided adequate information relating to the study rationale, objectives, and procedures.

Study Subjects

The study included Twenty-four healthy Thai participants (12 males and 12 females), aged 20 to 45 years with a body mass index (BMI) of 20 to 25 kg per m^2. Inclusion criteria were as follows:(i) absence of underlying or history of significant clinical conditions or diseases, particularly liver, kidney, and cardiovascular diseases, peripheral

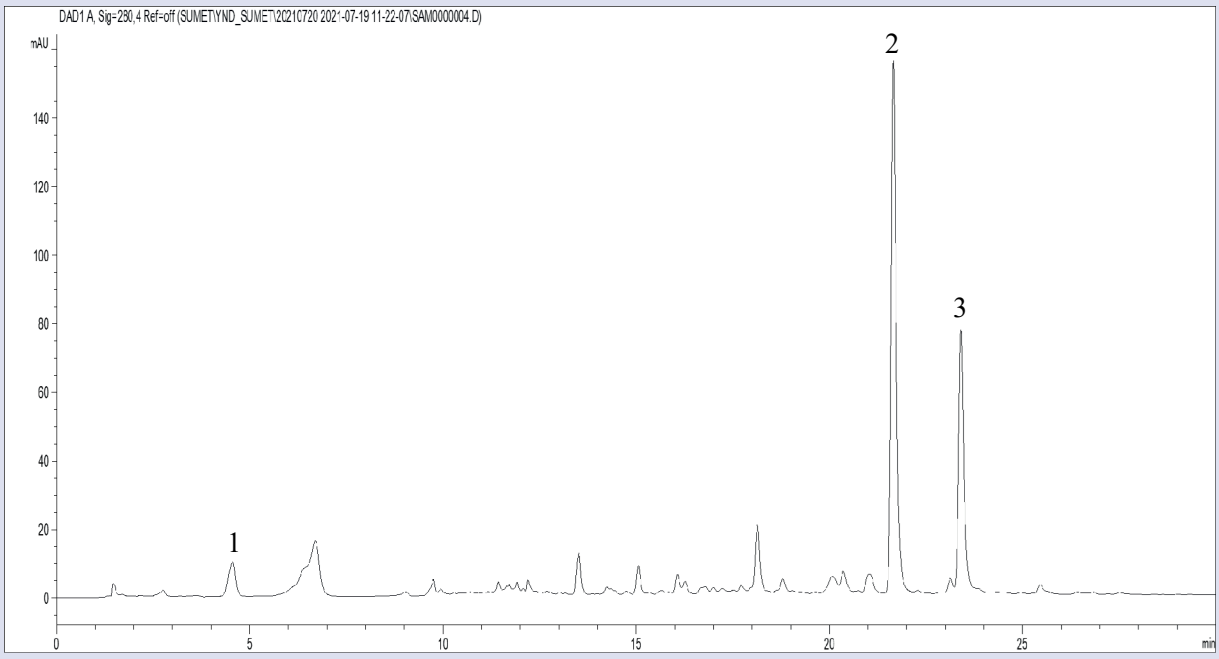

Figure 1: HPLC chromatogram of LS extract (gallic acid (1), trilobatin (2) and yanangdaengin (3).

neuropathy or allergic conditions, (ii) non-lactating and non-pregnant (females), (iii) no current use of medicines including herbal medicines, within two weeks, and (v) no history of alcoholism, cigarette smoking or unlikely to refrain from excessive alcohol consumption, smoking during the study period. A participant was excluded from the study if he or she had three significant abnormal routine laboratory tests (blood chemistry, hematology, and urinalysis) during screening. Written informed consent for participation was obtained from each participant before study initiation.

Interventions and Safety measurement

The participants were instructed to take two capsules of LS water extract (1,000 mg/day) once a day before breakfast for seven consecutive days. The safety evaluation of LS was assessed by the clinically significant changes before starting the medicine (baseline), after finishing the medicine (Day 8), and 1 week after the final consumption of LS (Day14) for the evaluation of laboratory parameters (the liver function, renal function tests, fasting blood sugar, complete blood count, and lipid profile), physical examination results, vital signs, and any incidence of adverse events (AEs).

Clinical laboratory tests were collected blood samples at the fasting stage to evaluate liver function, which included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. Renal function tests assessed serum creatinine and blood urea nitrogen (BUN). Additionally, analyses included fasting blood sugar (FBS) and lipid profile, including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). Hematology parameter analysis included the assessment of white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), and platelet count. Physical examinations were performed by a physician and included the examination of the general appearance, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological/psychiatric systems. Vital signs, including systolic and diastolic blood pressure, pulse rate, and body temperature, were monitored at the beginning and end of the treatment. Any adverse events (AEs) or serious adverse events (SAEs) were recorded in the medical history.

Statistical analysis

Data were expressed as mean ± standard deviation. Paired t-test was used to analyses parameters of interest at a statistical significance level of $\alpha = 0.05$. Statistical analysis was performed using SPSS Statistics for Windows, version 16 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic characteristics of participants

Twenty-four healthy Thai participants (12 males and 12 females) met the inclusion criteria and were enrolled in the study (Figure 2). The mean age of all participants was 27.9 years, a mean BMI of 21.7 kg/m^2. There was no considerable change in the demographic characteristics (height, weight, and BMI) and vital signs measured (systolic and diastolic blood pressure, heart rate, and respiration rate) at baseline and the end of study (Table 1).

Safety assessments and clinical blood parameters

All of the participants were healthy before, during, and after taking the LS extract at the dose levels of 1,000 mg, as verified by results of medical histories, signs and symptoms, physical examination, vital signs, and laboratory assessments.

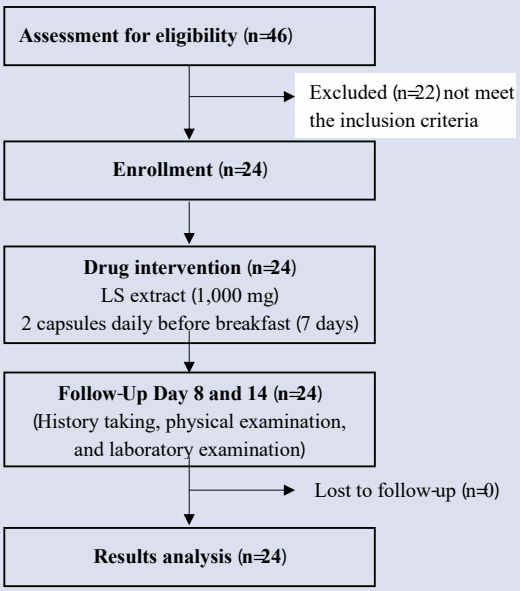

Figure 2: Flowchart of the study procedures.

The primary end point analysis included the assessment of liver and renal function parameters. There were no any statistically significant differences observed in the levels of AST, ALT, ALP, total protein, albumin, globulin, and total bilirubin from baseline to the end of treatment. The kidney function parameters, significant decrease in creatinine level was observed on day 8 and day 14 compared to baseline ($p<0.05$), but still within the normal range. There were no statistical differences in BUN. The FBS was used to measure blood sugar levels in this experiment. The FBS levels decreased significantly on Days 8 and 14 ($p<0.05$) when compared to the baseline, all levels were within the normal range without clinical signs and symptoms. The lipid profile, especially the mean of total cholesterol and HDL-cholesterol levels showed no significant changes. In contrast, the TG and LDL-cholesterol levels on days 14 were significantly lower than at baseline ($p<0.05$), but there were still within the normal range (Table 2).

The comparison of mean WBC, neutrophil, lymphocyte, eosinophil, basophil, RBC, Hb, Hct, and platelet count before and after oral administration of LS extract showed no significant differences in results. However, there was a slight change in hematological values was observed (within the normal range) after the participants took 1,000 mg of LS extract for 7 consecutive days when compared to the values following oral administration of LS extract, as shown in Table 3.

DISCUSSION

According to the World Health Organization (WHO), herbal and traditional medicines had been utilized as the primary method around 80% of the population in underdeveloped countries.[1] Especially, in Thailand, herbs were frequently prescribed as a traditional therapy. Prior study had discovered that Thai herbs have potent efficacy in a variety of disorders, including cancer, inflammation, and diabetes.[28] However, little empirical information on the pharmacological aspects of Thai herbal medicines has been documented. In addition, there is lack of scientific evidence to evaluate safety of Thai herbal medicines.

Being aware of the safety of drugs is an essential responsibility for medical professionals. As a result, it was necessary to investigate the safety of each herb. To the best of our knowledge, no studies have reported the safety of LS aqueous extract in capsules in healthy people. Thus, this was the first report that examine the safety of LS capsule on liver function, renal function, complete blood count, fasting blood sugar and cholesterol. According to the data, 1,000 mg of LS extract for

Table 1: Demographics and baseline vital signs of 24 healthy Thai study participants.

Variables (Unit)	baseline (D0)	After medication (D8)	Follow-up (D14)
Age(years)	30.46 ± 5.64	-	-
Weight (kg)	58.79±8.19	-	-
Height (cm)	163.25±7.32	-	-
BMI (kg/m^2)	22.01± 2.33	-	-
Systolic blood pressure (mmHg)	116.66 ± 13.88	117.96±9.63	116.96±10.07
Diastolic blood pressure (mmHg)	78.29 ± 9.81	77.58±7.65	77.96±9.53
Heart rate (bpm)	74.29 ± 11.00	77.13±9.83	76.37±10.03
Respiration rate (bpm)	19.66 ± 1.12	19.92±1.38	19.58±1.17

All data assessment was presented as mean ± standard deviation

Table 2: Blood chemistry of healthy participants taking aqueous extract of LS extract at a dose of 1,000 mg per day, once a day, before breakfast for 7 days. (N=24).

Variables (normal values)	baseline (D0)	After medication (D8)	Follow-up (D14)
Fasting blood sugar (74-106 mg/dl)	86.50±11.42	80.04±7.13*	81.75±6.73*
Blood urea nitrogen (7-18.0 mg/dl)	12.40±3.60	12.00±2.85	12.37±2.95
Creatinine (0.67-1.17 mg/dl)	0.89±0.18	0.84±0.17*	0.85±0.18*
Total Cholesterol (0-220 mg/dl)	208.54±31.59	200.41±32.67	201.33±30.47
Triglyceride (0-150 mg/dl)	100.70±44.52	87.70±36.89	82.87±39.13*
HDL-Cholesterol (40-60 mg/dl)	61.50±14.16	61.79±14.16	62.29±16.15
LDL-Cholesterol (0-130 mg/dl)	124.29±25.43	119.04±26.83	113.70±21.54*
Total protein (6.4-8.2 mg/dl)	8.15±0.36	7.76±1.10	7.99±0.51
Albumin (3.5-5.0 mg/dl)	4.27±0.25	4.17±0.28	4.20±0.30
Globulin (1.5-4.2 mg/dl)	3.73±0.39	3.73±0.41	3.68±0.40
Total bilirubin (0.2-1.0 mg/dl)	0.62±.18	0.56±0.33	0.54±0.25
Aspartate aminotransferase (15-37 U/L)	18.75±6.66	20.75±9.60	21.16±6.78
Alanine aminotransferase (16-63 U/L)	30.54±13.17	33.25±21.35	29.70±17.25
Alkaline phosphatase (46-116 U/L)	64.45±15.42	65.08±12.07	64.37±15.47

All data assessment were presented as mean ± standard deviation and analyzed using Analyze Descriptive statistics, p-value is within group analyzed by paired t-test compared baseline, *The mean difference is significant ($p < 0.05$)

Table: 3 Hematology results of healthy participants taking aqueous extract of LS at 1,000 mg per day, for 7 days and follow-up day14. (N=24).

Variables (normal values)	baseline (D0)	After medication (D8)	Follow-up (D14)
White blood cells (4.0-11.0 K/mm^3)	6.20±1.17	6.02±1.44	8.62±13.20
Neutrophil (45-75%)	50.92±9.97	52.79±9.65	53.61±10.73
Lymphocyte (20-45%)	40.85±8.68	39.62±8.12	38.50±9.73
Monocyte (2-10%)	3.97±8.73	3.46±1.12	3.78±1.32
Eosinophil (4-6%)	2.63±1.32	2.63±1.46	2.54±1.21
Basophil (0-1%)	0.54±0.27	0.63±0.29	0.58±0.20
RBC (4.50-6.00x10^6/mm^3)	4.95±0.97	5.11±0.75	4.95±0.97
Hemoglobin (14.0-18.0 gm/dL)	13.86±1.52	13.81±1.46	13.69±1.85
Hematocrit (41.0-51.0%)	42.08±4.39	41.75±4.20	41.47±5.40
Platelet count (150-400 K/mm^3)	311.87±70.59	313.75±68.11	298.12±62.40

All data assessment were presented as mean ± standard deviation and analyzed using Analyze Descriptive statistics, p-value is within group analyzed by paired t-test compared baseline, *The mean difference is significant ($p < 0.05$)

7 consecutive days had no clinically significant adverse effects on liver or renal function while improving blood sugar, LDL, and Triglyceride levels (Table 2-3).

This is consistent with previous animal studies that LS doses of 500, 1,500, and 3,000 mg/kg showed the absence of toxic signs and symptoms in all animals.[25, 29] Furthermore, a clinical trial investigation found that 2,300 mg aqueous extract of LS or LS tea was safe in healthy participants for 28 days.[26, 30] Traditionally, the Thai folk healers used tea derived from the stem and leaves of LS to assist in body detoxification and promoting health. For instance, within an hour, LS extract significantly decreased blood alcohol levels in healthy volunteers with no adverse effects documented.[26, 30] Furthermore, LS has been demonstrated to raise acetylcholine esterase levels and decrease pesticide-induced damage to the liver and kidney tissues in animal models.[9] As a results, LS could be used as a novel antidote agent for treating organophosphate insecticide poisoning.

According to the blood chemistry results, LS capsules significantly decreased fasting blood sugar levels on Days 8 and 14, while TG and LDL levels decreased statistically on Day 14, but all these results were within the normal range. This study did not explain the mechanism of action of LS extract, particularly identifying the specific substance responsible for reducing blood sugar, TG, and LDL levels. However, a prior investigation discovered that LS extracts achieved a reduction in glucose uptake in Caco-2 cells by downregulating the expression of glucose transporter genes and inhibiting the binding sites of SGLT1 and GLUT2.[31] Furthermore, gallic acid, one of the main constituents of

LS, has been reported to possess antihyperglycemic potential through its antioxidant and anti-inflammatory properties.[24, 32] According to research data in rats induced obesity and given gallic acid 10 mg/kg/day for 2 weeks, triglyceride concentrations were significantly improved in the gallic acid group compared to those measured in the control group, and most importantly, blood glucose concentrations in the gallic acid group were significantly improved.[33] However, contrary to previous studies, rats fed LS ethanol extract at a dose of 125 mg/bw for 21 days cholesterol, TG statistically increased ($p<0.05$).[34] Altogether, LS capsule was safe and might be utilized as an alternate herb in detoxifying, blood sugar control, and lipid profile management. Moreover, LS also reduced creatinine levels which are beneficial to the kidneys. Anyway, we recommended avoiding LS usage by patients with diabetes taking hypoglycemic medications since it can result in dangerously low blood sugar levels.

For future study, signs, symptoms, and blood sugar levels must all be recorded in future Phase II clinical trials and larger sample sizes. In addition, the decreased creatinine level was inconclusive about the mechanism of action of LS affecting creatinine. This topic needed to be investigated further.

CONCLUSION

In conclusion, LS capsule at daily dose of 1,000 mg was mostly safe dose in healthy participants that could be further investigated in diverse disease in the future.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no conflicts of interest related to this study.

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