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Original Research

Evaluating the safety of *Clausena harmandiana* root-bark powder (Song Fa) capsules in healthy volunteers: A phase 1 clinical trial

Pornthip Waiwut, Chantana Boonyarat, Patsaporn Siowthong, Ploylada Phanitsetthaphon , Pongput Pimsa , Nawinda Vanichakulthada , Wiwan Worakunphanich , Manit Saeteaw, Peerawat Jinatongthai, Rawiwun Kaewamatawong, Sureewan Duangjit, Teeraporn Sadira Supapaan

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Abstract

Background: Cancer is the leading cause of death worldwide. Chemotherapy is an important clinical treatment for cancer. However, the limitation of chemotherapy is its adverse effects on normal cells. Currently, the research focus is on the development of drugs and chemical compounds that have fewer side effects on normal cells. Extracts of *Clausena harmandiana* (*C. harmandiana*; Song Fa) root-bark have anticancer effects and is non-toxic to normal cells. Moreover, 7-methoxyheptaphylline, found in the root-bark of Song Fa, has been shown to inhibit the metastasis of breast cancer to the lungs in BALB/c mice. In this Phase I clinical trial, we aimed to investigate the safety of Song Fa in healthy volunteers. **Objectives:** To evaluate the safety and determine the adverse effects of *C. harmandiana* root-bark powder (Song Fa) capsules in healthy volunteers. **Methods:** An open-label, single-arm trial was conducted at the Ubon Ratchathani University Hospital, Thailand, between December 2022 and February 2023. The study enrolled 10 healthy male and 10 healthy female volunteers. Each volunteer orally ingested capsules of *C. harmandiana* root-bark extract (450 mg per capsule) once daily before breakfast for 14 days, and attended follow-up appointments after 1, 7, and 14 days. Physical examinations, signs and symptoms, hematology, and blood chemistry (e.g., liver function test, lipid profile, renal function test, and electrolytes) were assessed for screening (Day 0), at the beginning of the trial (Day 1), and on Days 7 and 14. After finishing the trial on Day 14, all volunteers were invited to participate in a follow-up session. To evaluate the safety of the *C. harmandiana* root-bark powder (Song Fa) capsules, each volunteer engaged in a phone interview on Day 30. The results were assessed against the normal range and baseline using repeated-measures ANOVA statistics. **Results:** At an oral dose of 450 mg/day, *C. harmandiana* root-bark powder (Song Fa) capsules did not result in serious adverse effects among the healthy volunteers. Participant physical examination results were all within normal ranges. All laboratory tests including hematology, liver and renal functions, lipid profiles, blood sugar levels, and serum electrolytes remained within normal limits. Measurements were taken the day before drug administration and at 1, 7, and 14 days post-dosing. Using repeated measures ANOVA to compare pre-treatment values at a 95% confidence interval, no significant differences were noted, except in fasting blood sugar levels, which showed a deviation from baseline ($p < 0.001$). However, these levels were within the normal ranges. **Conclusion:** The study results confirmed that *C. harmandiana* root-bark powder (Song Fa) capsules are safe in healthy volunteers. Physical health assessment and laboratory results did not differ from normal values.

Keywords: safety; *Clausena harmandiana*; Song Fa; healthy volunteers; phase I clinical trial; 7-methoxyheptaphylline

Pornthip WAIWUT. Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand. porntip.w@ubu.ac.th
Chantana BOONYARAT. Faculty of Pharmaceutical Science, Khon Kaen University, Khon Kaen, 40002, Thailand. chaboo@kku.ac.th
Patsaporn SIOWTHONG. Pharmacy student, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand. patsaporn.si.61@ubu.ac.th
Ploylada PHANITSETTHAPHON. Pharmacy student, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand. ploylada.ph.61@ubu.ac.th
Pongput PIMSA. Department of Internal Medicine, Sunpasitthiprasong Hospital, Ubon Ratchathani, 34000, Thailand. bebeerzpb@gmail.com
Nawinda VANICHAKULTHADA. Ubon Ratchathani Hospital, Ubon Ratchathani University, Ubon Ratchathani, 34190, Thailand. nawinda.j@ubu.ac.th
Wiwan WORAKUNPHANICH. Institute of Thai Traditional Medicine, Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, Nonthaburi, 11000, Thailand. wiwan.worak@gmail.com
Manit SAETEAW. Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, 40002, Thailand. Manitsa@kku.ac.th
Peerawat JINATONGTHAI. Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand. peerawat.j@ubu.ac.th
Rawiwun KAEWAMATAWONG. Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand. rawiwun.k@ubu.ac.th
Sureewan DUANGJIT. Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand. sureewan.d@ubu.ac.th
Teeraporn Sadira SUPAPAAN*. Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand. teeraporn.s@ubu.ac.th

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INTRODUCTION

Cancer is a significant global health issue that accounted for nearly 10 million deaths in 2020. The most common types are lung, colon, rectal, liver, stomach, and breast cancers.[1] Cancer is a leading cause of premature death. Three out of every ten premature noncommunicable disease deaths are caused by cancer.[2] Cancer occurs when normal cells transform into tumor cells, which is influenced by genetics and external risk factors.[1] Cancer is characterized by uncontrolled cell growth, suppression of apoptosis, and programmed cell death. This unchecked cell proliferation often stems from the loss of the regulatory mechanisms governing cell proliferation and apoptosis.[3,4] Difficulty in controlling abnormal growth often leads to unsuccessful cancer treatment outcomes. Hence, the development of novel and effective chemotherapeutic agents capable of targeting various signaling pathways to interrupt cell growth and promote cancer cell death is critically important.[4]

The plant, ***Clausena harmandiana*** (*C. harmandiana)*, known as "Song Fa" (Figure 1) in Thai, belongs to the Rutaceae family and is prevalent in Southeast Asia, especially in northeastern Thailand.[5,6] Young leaves of this plant are used in traditional Thai cuisine and as feed for ruminants. It is known for its medicinal properties and is used to treat headaches, stomach aches, and other illnesses [6-8]. The roots of this plant contain significant quantities of carbazole alkaloids and coumarins, which have shown to have antimalarial, antifungal, and antituberculosis effects. Carbazole alkaloids, found extensively in the *Clausena* species, have been shown a wide range of pharmacological effects, including being anticancer, antiplatelet aggregation, vasorelaxation, antimycobacterial, anti-HIV-1, antiplasmodial, and anti-inflammatory. *C. harmandiana* is also associated with cognitive impairment and cytotoxic properties.[5,6,9]

Our previous research found that the primary components of the medicinal plant *C. harmandiana*, namely, heptaphylline and 7-methoxyheptaphylline (7-MH), exhibit anticancer properties against the human small cell lung cancer (NCI-H187) and human epithelial carcinoma cells (KB) cell lines. Furthermore, 7-MH exhibited a neuroprotective effect in NG108-15 cells against H_2O_2-induced cell death.[10]

To elucidate its action in both cancer and Alzheimer's disease models, we examined 7-MH's antiapoptotic impact on SH-SY5Y neuroblastoma cells under H_2O_2-induced oxidation and its apoptotic effects on both neuroblastoma cells and LNCaP prostate cancer cells. We also explored 7-MH's effect on various signaling proteins, including glycogen synthase kinase-3 (GSK-3), mitogen-activated protein kinase 13 (MAPK13), and pro- and anti-apoptotic proteins. Previous findings demonstrated that 7-MH can inhibit the proliferation and metastasis of 4T1 cancer cells, significantly reducing their viability compared to the resveratrol control group. A closer examination of the effect of 7-MH on Nuclear factor kappa B (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3) signaling proteins in these mouse mammary gland tumor (4T1) cells revealed its inhibitory role. An *in vivo* assay further confirmed that 7-MH significantly inhibited 4T1 cancer cell migration and reduced the metastasis of these cells in a mouse model. These findings suggest that 7-MH may be a potential drug candidate for cancer treatment.[4,10,11]

In cancer research, a remarkable finding was observed when the carbazole derivative 7-MH was extracted from CH. It augmented tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in HT-29 colon adenocarcinoma cells by enhancing DR5 expression via the JNK pathway. Furthermore, in an in vivo anticancer activity assay, 7-MH inhibited 4T1-Lucifease (Luc2) cell metastasis in the lungs of female Bagg Albino (BALB)/c mice.[10,12]

Figure 1. The leaves and flowers of *Clausena harmandiana*

Previous studies have primarily focused on *in vitro* cell models. In 2021, an animal study on safety by the Song Fa Research Group 2021 involving 14-day oral ingestion of Song Fa capsules of 300 mg/kg and 2,000 mg/kg body weight in Sprague Dawley rats reported no signs of abnormalities or death. Moreover, all rats in the study showed increased growth rates. These results are promising. Pharmacotherapeutic investigations of *C. harmandiana* determined that the plant exhibits non-toxic effects on human colon cells, and cytotoxicity towards cancer cells. To date, no *in vivo* or clinical studies have verified the anticancer effects of fractions, alkaloids, and coumarins from Clausena plants.[10,11] To the best of our knowledge, this is the latest phase I clinical trial to investigate the safety profile of *C. harmandiana*. This study aimed to evaluate the safety and adverse effects of *C. harmandiana* root-bark powder (Song Fa) capsules in healthy volunteers. Notably, in a separate study, which investigated the acute toxicity of *C. harmandiana* extract in Wistar rats, was confirmed to be safe.[13] These findings lay the groundwork for future therapeutic applications of *C. harmandiana*.

METHODS

Drug preparation and dosage calculation

C. harmandiana root-bark powder (Song Fa) capsules were prepared by PharmCare Manufacturing, Faculty of Pharmacy, Mahasarakham University, Thailand, under good manufacturing practice-certified conditions. Quality control of the Song Fa capsules was conducted by the 10th Regional Medical Sciences Center in Ubon Ratchathani, which is a medical and public health laboratory approved by ISO/IEC 17025.

Song Fa capsules were made from the *C. harmandiana* root-bark powder (Song Fa) 450 mg/capsule with the controlled active substance 7-MH, which is the active ingredient that has been laboratory-tested *in vitro* and *in vivo,* both at a dosage of 3.35 ± 0.12 mg/capsule.

C. harmandiana root-bark powder (Song Fa) was enclosed within the green capsules and packaged in polyethylene bottles. Each bottle contained 60 capsules. These capsules have a shelf life of two years when stored in an airtight container at room temperature.

As mentioned earlier, the safety of Song Fa capsules was investigated in an animal study conducted by the Song Fa Research Group in 2021. Oral Song Fa capsules at doses of 300 and 2,000 mg/kg body weight were administered to Sprague-Dawley rats continuously for 14 days. Throughout the study period, no signs of abnormalities or death were observed, and the rats exhibited increased growth rates.[14] Additionally, an acute oral toxicity test was conducted with a maximum dose of 15,000 mg/kg of *C. harmandiana* during a 14-day observation period, and no toxic signs or deaths were observed, indicating that *C. harmandiana* was non-toxic. Assessing the "no observed adverse effect level (NOAEL)" is a crucial step in animal toxicity studies. This value represents the highest dose at which adverse effects were not observed in experimental animals.[15] According to the US FDA guidelines, the NOAEL value, along with the human equivalent dose (HED) and maximum recommended starting dose (MRSD), can be calculated. These calculations provide essential information regarding the safety ranges and potential toxicities of specific clinical doses of drugs, including herbal products.[16] Based on these calculations, the maximum recommended starting dose (MRSD) of *C. harmandiana* is 2,400 mg/day. However, considering the safety and volunteer compliance, a treatment dose of 450 mg/day Song Fa extract was used in this phase I clinical trial.

Study design

This study was a phase I clinical trial of healthy volunteers. The study aimed to determine the safety and adverse reactions of the drug. A phase I trial usually involves 10-20 volunteers.[17] Therefore, our study sample was set at 20 (10 males and 10 females). Between December 2022 and February 2023, a prospective, open-label, single-arm phase I trial was conducted at Ubon Ratchathani University Hospital in Thailand. This study aimed to evaluate the effects of *C. harmandiana* root-bark powder (Song Fa) capsules in 20 healthy volunteers (10 males and 10 females). Each participant received an oral capsule containing 450 mg of the extract once daily before breakfast for 14 days. Follow-up appointments were scheduled at 1, 7, and 14 days after the start of the trial.

Participants and sample size

Healthy volunteers were recruited using various channels, including printed advertisements, and social media. The screening process involved telephone interviews or on-site consultations to evaluate the suitability of the potential participants. Those who met the necessary criteria were invited to register for a study-specific screening visit.

The study-specific screening visit further assessed participation eligibility. The screening collected demographic data and medical history. The current health status of each volunteer and their body mass index (BMI) were determined health status was evaluated via a physical examination, measurement of vital signs (such as temperature, respiratory rate, heart rate, and blood pressure), electrocardiogram (ECG), and laboratory analyses (serum electrolyte levels, liver and kidney function, and safety parameters in blood and urine samples).

Detailed information about the study, including its purpose, procedures, potential risks and benefits, and the rights of the participants, was provided to the potential participants during the screening visit. The volunteers were given ample opportunities to ask questions and to fully comprehend the study before providing informed consent to participate.

Of those who completed the screening process, 20 participants met the inclusion criteria. The same inclusion criteria were applied to male and female individuals, except that participating females cannot be pregnant or breastfeeding. The age range of the participants was set between 18 and 45 years, and their BMI needed to fall within the range of 18.5 – 24.9 kg/m^2. Additionally, the participants were required to be in good health without any underlying medical conditions; not

take any medications or herbal formulations; and not engage in cigarette smoking, drug use, or alcohol consumption. Those with severe illness, medical conditions, smoking habits, and allergies to the Song Fa herbal extracts were excluded from the study. Additionally, female volunteers who were pregnant or breastfeeding were also excluded.

During each visit (on days 1, 7, and 14), the participants underwent a comprehensive assessment that included physical examination, vital sign measurements (temperature, respiratory rate, heart rate, and blood pressure), electrocardiogram (ECG), and laboratory blood and urine analyses. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was applied to evaluate all adverse events.

Interventions and outcomes

Each volunteer participant was instructed to ingest one capsule (450 mg Song Fa) once a day, before breakfast, for a total of 14 days. In this experiment, history taking, physical examination, and laboratory testing including hematology and chemistry profiles, were conducted on days 1, 7, and 14. Subsequently, the volunteers were interviewed via phone on day 30 to evaluate the safety of the *C. harmandiana* root-bark powder (Song Fa) capsules (Figure 2).

At each visit, adverse drug reactions were monitored and evaluated by a team of physicians, pharmacists, nurses, and medical technologists. The study protocol included that if adverse reactions relating to the medication arose during the study, the affected participants would be admitted to Ubon Ratchathani University Hospital and managed immediately according to standard practices. Any medical treatment costs incurred would be covered by the researchers. If adverse reactions that concern participants occur, participants can contact the research team at any time, as detailed in their illness logbooks.

Statistical analysis

Data were analyzed using descriptive statistics, which offered insights into baseline characteristics, physical examination results, and adverse drug reactions. The results were presented as frequency distributions. Additionally, differences were examined using repeated-measures analysis of variance. Statistical analysis was performed using SPSS Statistics for Windows (version 29.0; SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Ethical considerations

Ethical approval for this study was obtained from the Ubon Ratchathani University Ethics Committee for Research in Human Subjects (Approval No: UBU-REC-96/2565). All volunteers provided written informed consent before participating in the study.

RESULTS

Baseline and clinical characteristics of volunteers

Among the 23 individuals who volunteered for the prospective study, 20 participants (10 males and 10 females; average age 20.75 ± 0.894 years) fulfilled the inclusion criteria and were included in the study (Figure 3). Their mean body mass index was (20.96 ± 1.60) kg/m^2, indicating a normal or healthy weight status. Regarding their blood pressure, the average systolic pressure was (116.85 ± 10.12) mmHg, while the average diastolic pressure was (76.85 ± 6.80) mmHg. The mean pulse rate was (75.10 ± 8.52) beats/min, and the average respiratory rate was (20.03 ± 0.11) breaths/min. The normal baseline vital signs of all participants indicating that all participants were healthy and met the inclusion criteria (Table 1).

Hematological and blood chemistry parameters of the healthy volunteers taking C. harmandiana root-bark powder (Song Fa) capsules

The fasting blood sugar level (FBS in mg/dL) after intake *C. harmandiana root-bark powder* (Song Fa) *capsules* significant variate from baseline (p-value of < 0.001). FBS levels fluctuated notably over time, peaked on day 7, and then decreased by day 14. However, all FBS values were within the normal ranges

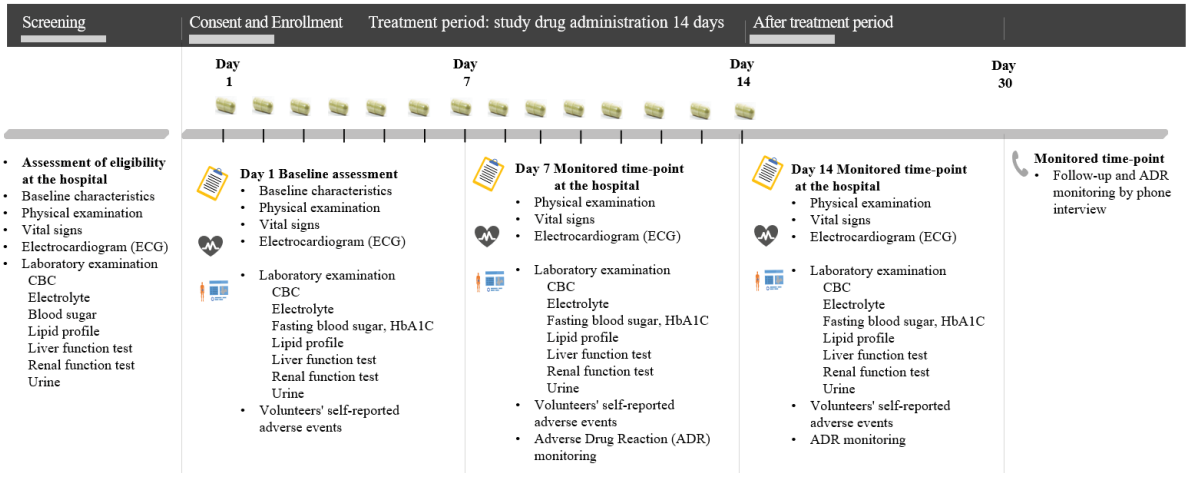

Figure 2. Timeline of participant study drug administration and data collection.

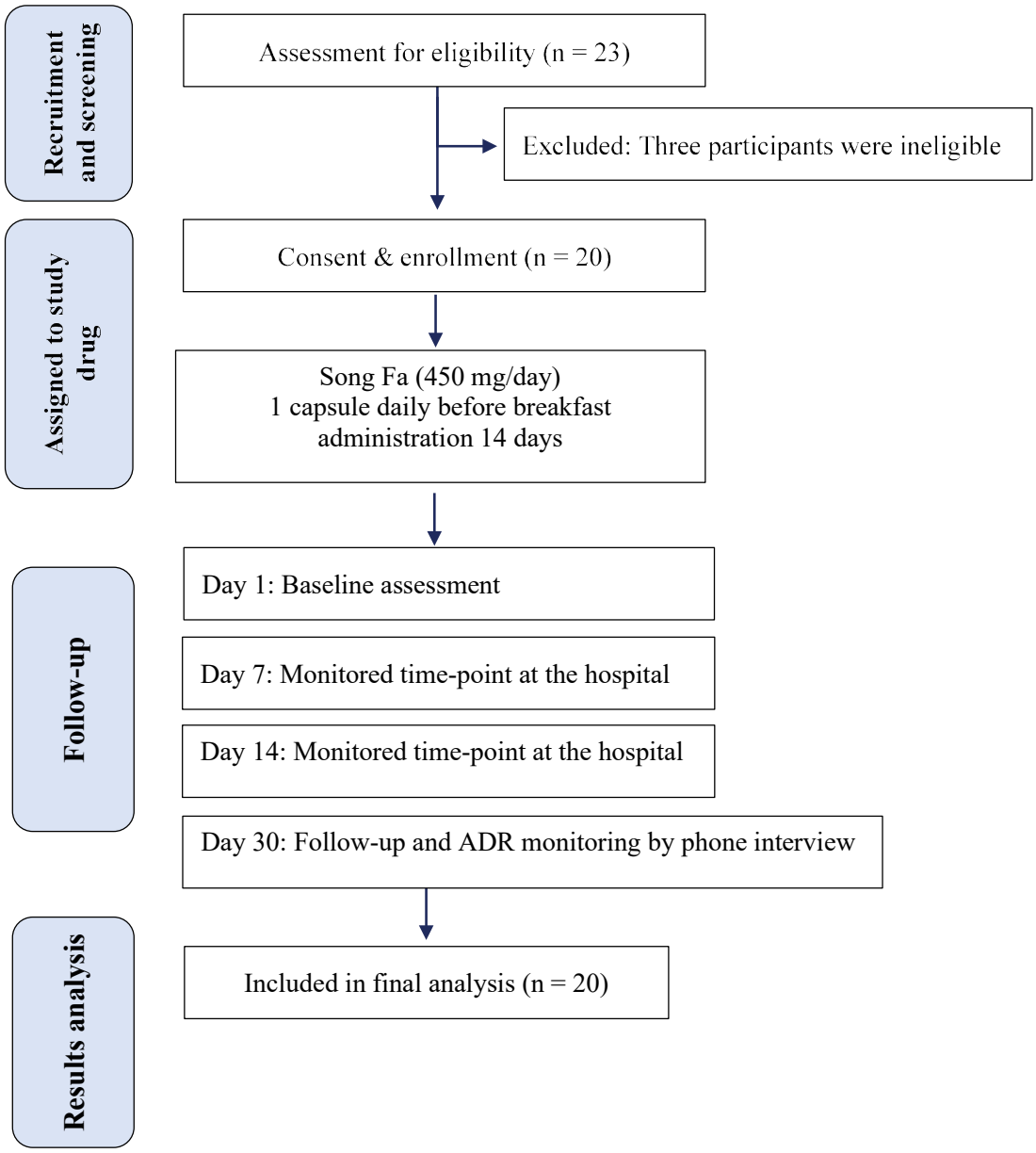

Figure 3. Trial flowchart

Table 1. Participant characteristics (N = 20)

	n (%)	Mean ± SD	Range
Gender			
Male	10 (50.0)		
Female	10 (50.0)		
Age, years		20.75 ± 0.89	19-23
BMI (Kg/m^2)		20.96 ± 1.60	18.5-25.0
PR (bpm)		75.10 ± 8.52	60-100
RR (bpm)		20.03 ± 0.11	16-22

throughout the study period. Parameters, such as HbA1c, hemoglobin, WBC, ANC, and platelet counts demonstrated no statistically significant alterations. Minor variations in total bilirubin, liver enzymes (AST and ALT), serum creatinine, and eGFR were observed, although not statistically significant. Lipid profiles and electrolytes, including Na^+, K^+, Ca^{2+}, HCO_3^-, Mg^{2+}, Cl^-, and P, maintained consistent levels throughout the study (Table 2).

Adverse events

As shown in Table 3, adverse events noted by participants were recorded in a diary of symptoms and side effects. Participants who experienced adverse events were followed up and assessed by the medical team. None of the volunteers experienced severe side effects. One female volunteer experienced grade 2 diarrhea which increased bowel movements (4 – 5 times per day) on the second day after taking the medicine. These symptoms persisting for 4 days. One male volunteer experienced nausea and reduced appetite, beginning on the second day after taking the medication. Two volunteers (one man and one woman) experienced muscle pain and fatigue on the first day of taking the medication.

DISCUSSION

This study explored the effects of *C. harmandiana* root-bark powder (Song Fa) capsules in 20 healthy volunteers. The demographic data indicated a balanced gender representation. The participants were all young adults as indicated by the average age. Moreover, all participants were of normal weight and their vital signs were within normal ranges. These baseline

Table 2. Laboratory results of the healthy volunteers

Parameter	Mean ± SD				P-value*
	Screening	Day 1	Day 7	Day 14	
Blood sugar test					
FBS (mg/dL)	86.63 ± 5.89	94.82 ± 4.90	95.59 ± 6.30	91.40 ± 6.80	< 0.001
HbA1c (%)	5.38 ± 0.27	5.11 ± 0.34	5.28 ± 0.36	5.22 ± 0.40	0.717
Hemoglobin (g/dL)	13.51 ± 1.30	13.55 ± 1.45	13.51 ± 1.42	13.63 ± 1.37	0.437
Complete blood count					
WBC (mm^3)	7047 ± 1755.47	7244.5 ± 1492.27	7334.5 ± 1510	7231.5 ± 2049.1	0.854
ANC (mm^3)	4063.65 ± 1503.05	4326.45 ± 1426.96	4302.05 ± 1280.30	4185.78 ± 1756.92	0.852
Platelet (mm^3)	282,450 ± 48,677	287,400 ± 57,143	295,050 ± 53,977	294,250 ± 59,167	0.272
Liver function test					
Total bilirubin (mg/dL)	0.73 ± 0.33	0.77 ± 0.27	0.71 ± 0.27	0.70 ± 0.23	0.427
AST (U/L)	19.66 ± 3.58	21.71 ± 4.29	22.59 ± 6.87	21.33 ± 6.68	0.152
ALT (U/L)	14.41 ± 6.32	18.28 ± 8.05	17.79 ± 12.98	15.82 ± 13.90	0.244
Renal function test					
Scr (mg/dL)	0.80 ± 0.18	0.89 ± 0.20	0.86 ± 0.18	0.87 ± 0.20	0.095
eGFR (mL/min/1.73m^2)	118.52 ± 12.40	108.61 ± 14.49	112.96 ± 15.35	112.41 ± 15.00	0.208
Lipid profile					
LDL (mg/dL)	110.7 ± 27.18	105.02 ± 26.03	110.73 ± 33.42	110.77 ± 29.29	0.626
Total cholesterol (mg/dL)	181.86 ± 32.05	189.57 ± 36.35	191.66 ± 45.26	192.13 ± 37.84	0.122
Triglyceride (mg/dL)	73.4 ± 33.69	73.8 ± 27.07	73.85 ± 28.94	73.9 ± 23.78	0.181
Electrolytes					
Na^+ (mmol/L)	141.25 ± 1.16	141.9 ± 1.59	140.5 ± 1.61	139.3 ± 1.49	0.836
K^+ (mmol/L)	3.93 ± 0.22	4.16 ± 0.33	4.17 ± 0.31	4.06 ± 0.32	0.785
Ca^{2+} (mg/dL)	9.58 ± 0.38	9.44 ± 0.30	9.51 ± 0.38	9.405 ± 0.36	0.582
HCO_3^- (mmol/L)	26.72 ± 2.52	24.96 ± 1.67	26.44 ± 2.43	25.96 ± 2.59	0.843
Mg^{2+} (mg/dL)	2.13 ± 0.22	2.12 ± 0.21	2.15 ± 0.22	2.20 ± 0.48	0.451
Cl^- (mmol/L)	102.85 ± 1.81	103.3 ± 1.63	102.25 ± 1.41	101.65 ± 1.93	0.188
P (mg/dL)	3.91 ± 0.40	3.82 ± 0.38	4.01 ± 0.41	3.75 ± 0.33	0.198

*P < 0.05, calculated using repeated measures analysis of variance (ANOVA) for overall parameter comparison.
Abbreviations: FBS: Fasting Blood Sugar; HbA1c: Hemoglobin A1C; WBC: White Blood Cell; ANC: Absolute Neutrophil Count; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; SCr: Serum Creatinine; eGFR: Estimated Glomerular Filtration Rate; LDL: Low-Density Lipoprotein Cholesterol; Na^+: Sodium; K^+: Potassium; Ca^{2+}: Calcium (mg/dL); HCO_3^-: Bicarbonate (mmol/L); Mg^{2+}: Magnesium (mg/dL); Cl^-: Chloride (mmol/L); P: Phosphorus (mg/dL)

Table 3. Adverse events or side-effects

	Adverse events reported				
	Day 1	**Day 7**	**Day 14**	**Day 30**	**Total**
1. Gastrointestinal system					
1.1 Nausea	1	0	0	0	**1**
1.2 Vomiting	0	0	0	0	0
1.3 Abdominal pain	0	0	0	0	0
1.4 Constipation	0	0	0	0	0
1.5 Flatulence	0	0	0	0	0
1.6 Diarrhea	1	0	0	0	**1**
2. Urinary system	0	0	0	0	0
2.1 Urinary tract disorders	0	0	0	0	0
3. Neurological system					
3.1 Headache	0	0	0	0	0
3.2 Dizziness	0	0	0	0	0
3.3 Insomnia	0	0	0	0	0
4. Metabolism and nutrition					
4.1 Loss of appetite	1	0	0	0	**1**
5. Skin					
5.1 Rash	0	0	0	0	0
5.2 Itching	0	0	0	0	0
5.3 Swelling	0	0	0	0	0
6. Blood system					
6.1 Pale	0	0	0	0	0
7. Eyes					
7.1 Blurred vision	0	0	0	0	0
8. Musculoskeletal system					
8.1 Muscle pain	2	0	0	0	**2**
8.2 Muscle spasm	0	0	0	0	0

characteristics are crucial for understanding the potential impact of the intervention on healthy young adults.

The most notable finding of our study was the significant variation in fasting blood sugar (FBS) levels, which fluctuated over time but remained within the normal range. This observation is particularly intriguing as it suggests a potential regulatory effect of *C. harmandiana* on blood glucose levels. Reports have indicated that Clausena essential oils exhibit α-glucosidase inhibitory activity, which is aimed at managing hyperglycemic effects by reducing glucose production from carbohydrates. This is achieved through the inhibition of digestive α-glucosidase enzymes.[18-20] Nevertheless, these findings underscore the importance of vigilant monitoring, particularly in populations experiencing glucose regulation issues.

In contrast, other hematological and blood chemistry parameters, such as HbA1c, hemoglobin, white blood cell count, absolute neutrophil count, and platelet count, remained stable throughout the study. This stability indicates that *C. harmandiana* does not adversely affect these aspects of systemic health. Additionally, minor variations in liver enzymes, serum creatinine, and eGFR were observed. However, none were of statistical significance, suggesting that s *C. harmandiana* did not significantly affect liver and kidney functions.

Lipid profiles and electrolyte levels, including sodium, potassium, calcium, bicarbonate, magnesium, chloride, and phosphorus, remained consistent. This lack of significant change is important, as it suggests that *C. harmandiana* does not disrupt lipid metabolism or electrolyte balance in healthy individuals.

There were low incidences of reported adverse events in this study. In addition, all adverse events were mild to moderate in severity., which is consistent with the findings of similar studies on medication tolerability. For example, gastrointestinal symptoms, such as diarrhea and nausea, have been previously reported. Traditionally the young leaves, roots, bark, and flowers of *C. harmandiana* were often combined with other herbs to ease intestinal gas and address food poisoning.[6,21] Two

of our participants reported muscle pain and fatigue on the first day. Interestingly, *C. harmandiana* has been traditionally used in for muscle pain treatment [19,22]. Overall, a low incidence and severity of adverse effects were observed in this study. In the future, large-scale studies on the safety profiles of this herbal medicine is warranted.[23] In summary, our study contributes to the growing body of evidence supporting the safety of natural supplements, specifically, *C. harmandiana.* Moreover, the transient fluctuations in FBS levels warrant further investigation but are not indicative of adverse effects. Overall, these findings suggest that *C. harmandiana* root-bark powder is well-tolerated in healthy young adults, with no significant alterations to hematological and biochemical parameters. Further research in a broader population is warranted for a comprehensive safety assessment.

CONCLUSION

This study significantly advances our understanding of the safety and tolerability of *C. harmandiana* root-bark powder (Song Fa) capsules at an oral dose of 450 mg/day. The results indicated that *C. harmandiana* was generally well-tolerated by healthy young adults, with no major changes in key hematological and biochemical markers. Although temporary variations in FBS were observed, the levels remained within the normal ranges. Only minor adverse effects were observed in this phase I clinical study, indicating the overall tolerability of *C. harmandiana* among human volunteers.

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AUTHORS' CONTRIBUTIONS

Pornthip Waiwut: Conceptualization, Methodology, Data collection, Formal analysis, Writing-original draft preparation; Chantana Boonyarat: Methodology, Writing-reviewing and editing; Patsaporn Siowthong: Data collection, Formal analysis; Ploylada Phanitsetthaphon: Data collection, Formal analysis; Pongput Pimsa: Methodology, Validation, Writing-reviewing and editing; Nawinda Vanichakulthada: Data collection, Validation, Writing-reviewing and editing; Wiwan Worakunphanich: Conceptualization, Methodology, Writing-reviewing and editing; Manit Saeteaw: Conceptualization, Methodology, Writing-reviewing and editing; Peerawat Jinatongthai: Formal analysis, Writing-reviewing and editing; Rawiwun Kaewamatawong: Validation, Writing-reviewing and editing; Sureewan Duangjit: Validation, Writing-reviewing and editing; Teeraporn Sadira Supapaan: Conceptualization, Methodology, Writing-original draft preparation.

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