RESEARCH ARTICLE

Efficacy and safety of freeze-dried form of *Tragia involucrata* L. decoction in treating diabetes: a randomized controlled clinical trial

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Abstract

Background and objectives: *Tragia involucrata* L. (Family: Euphorbiaceae, S. *Wel Kahambiliya*) is a highly used medicinal plant in both systems of Sri Lankan traditional medicine and Ayurveda medicine. This plant is used for the treatment of diseases such as diabetes, wounds, dysuria, and epilepsy. The aim of this study was to evaluate the efficacy and safety of the freeze-dried form of *Tragia involucrata* L. decoction in the treatment of diabetes.
Subjects and methods: This randomized, two-arm, open-label, controlled clinical trial was conducted in type 2 diabetes patients at National Ayurveda Teaching Hospital in Colombo, Sri Lanka during the year 2016–2017. Thirty-six type 2 diabetes patients aged 18–70 years were included in each group. Patients received treatment with 120 mL of *Tragia involucrata* L. decoction and 500 mg of metformin, twice a day, for 14 days used as the test drug and positive control drug groups. Fasting blood glucose level was measured on days 0, 8, and 15. Lipid profile and liver and kidney functions were measured on days 0 and 15. This study was approved by the Ethics Review Committee, Institute of Indigenous Medicine (ERCIIM), University of Colombo, Rajagiriya, Sri Lanka (approval No. ERC 16/61) on October 27, 2016.
Results: Fasting blood glucose levels in the test group were significantly decreased on days 8 and 15 compared to day 0 ($P < 0.05$). There was no significant change in the lipid profile values before and after treatment ($P > 0.05$). Also the decoction did not cause changes in the function of the liver and kidneys. Further no other adverse reactions were recorded in the patients.
Conclusion: *Tragia involucrata* L. can reduce fasting blood glucose level and has antidiabetic effects in diabetes.

Key words: biological activities; randomized controlled trial; toxicity; *Tragia involucrata*

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Introduction

Type 2 diabetes is a progressive disease with major complications and also a leading cause of morbidity and mortality worldwide. An estimated 80% of the world's diabetic population comes from the lower and middle income countries such as Sri Lanka.[1] The well-defined risk factors of diabetes, such as obesity, less physical activity, improper diet and smoking, are prevalently perceived in people having a low socio-economic status.

People living in South Asian countries are known to have an increased predisposition for type 2 diabetes due to the increased genetic, biological and lifestyle factors.[2] According to International Diabetic Federation (IDF), out of the 425 million people with diabetes in the world, 82 million people are affected in the Southeast Asian Region. In Sri Lanka, 1.1 million cases of diabetes have been reported for the year 2017, with a prevalence of 8.6%. Diabetes can be managed by lifestyle management such as healthy diet, physical exercise, weight control, medical nutritional therapy and oral glucose-lowering drugs and insulin injection.[3]

These conventional therapies have adverse side effects, need for long-term use, and are expensive and require expertise. While medicines are less expensive, more readily available to people and are assumed to be less toxic due to their long term clinical exposure.

Tragia involucrata L. (*T. involucrata*), known as Wel Kahambiliya in Sinhala and Indian stinging nettle in English is one such medicinal plant much used in Sri Lankan indigenous medicine and in Ayurveda for several centuries. As described by Dassanayake and Clayton in 1997,[4] and Jayaweera in 2006,[5] *T. involucrata* belonging to family Euphorbiaceae, is a perennial, densely hispid-pubescent vine, with scattered, stinging hairs throughout the stem and leaves. The stem twines on a support, specifically on another tree. Leaves and the stems cause injurious itching and stinging which limits the tangibility. *T. involucrata* is found largely in India, Sri Lanka, Burma, and China. In Sri Lanka the plant is commonly found in Jaffna, Anuradhapura, Galle, and Matara districts. *T. involucrata* appears as a weed, and it is frequently found in waste grounds and as a weed of cultivation. Ethno-medicinal uses of *T. involucrata* include biological activities pertaining to multiple systems of the body. In the gastro-intestinal tract,

T. involucrata is applied in gastropathy[6] and hemorrhoids[7] and as an anthelmintic.[8] In the respiratory system, it is used for treating cough and asthma.[5,9] It is also used for skin diseases,[10] inflammation,[9] allergies[11] and mainly for fever.[12]

Our previous studies demonstrated that freeze-dried form of hot water extract of *T. involucrata* contains total flavonoid and total phenol content in great amount and presence of these potent antioxidants in the plant may be the reason for its health benefits.[13-15] Furthermore, our studies confirmed that freeze-dried form of the hot water extract of *T. involucrata* at the therapeutic dose of 550 mg/kg significantly reduced the blood glucose level and glucose tolerance effect when challenged with a glucose load, in high fat diet fed streptozotocin induced diabetic rats.[13-15]

Results of *T. involucrata* sub-acute toxicity study (5000 mg/kg dose) and the *T. involucrata* subchronic toxicity study (550 mg/kg dose) showed that the oral administration of the freeze-dried extract did not produce any sign of toxicity in terms of (a) hepatotoxicity (b) renotoxicity (c) hemototoxicity (d) gross morphology and weights of organs, (e) stress and aversive behaviors or death.[13-15]

Although there are few scientifically validated studies on the antidiabetic activity of *T. involucrata*, there have been no published data on the anti-diabetic effect on the decoction made using the whole plant of *T. involucrata*, which is the dosage form used in Sri Lankan traditional medicine for diabetes.[16]

The objective of the present study was to assess the anti-diabetic effects of *T. involucrata* (*Wel kahamabiliya*) decoction in patients with type 2 diabetes. The study also focuses on the lipid lowering effect of *T. involucrata* in type 2 diabetes patients and explored whether the decoction exerted any effects on kidney and liver functions of diabetes patients.

Subjects and Methods

Study design

This open-label, two-arm parallel group non-inferiority randomized controlled trial was conducted at the National Ayurveda Teaching Hospital in Colombo, Sri Lanka during 2016–2017. The freeze-dried form of *T. involucrata* was the test products. The efficacy and safety of the *T. involucrata* dosage forms were tested compared with the metformin. Patients with type 2 diabetes were included according to the inclusion criteria and randomized into 2 groups (test and control groups with 36 patients in each group), who were attending the clinic at the Ayurvedic Teaching Hospital, Borella after a 1-week run-in period and the drugs were administered orally for 14 days (**Figure 1**).

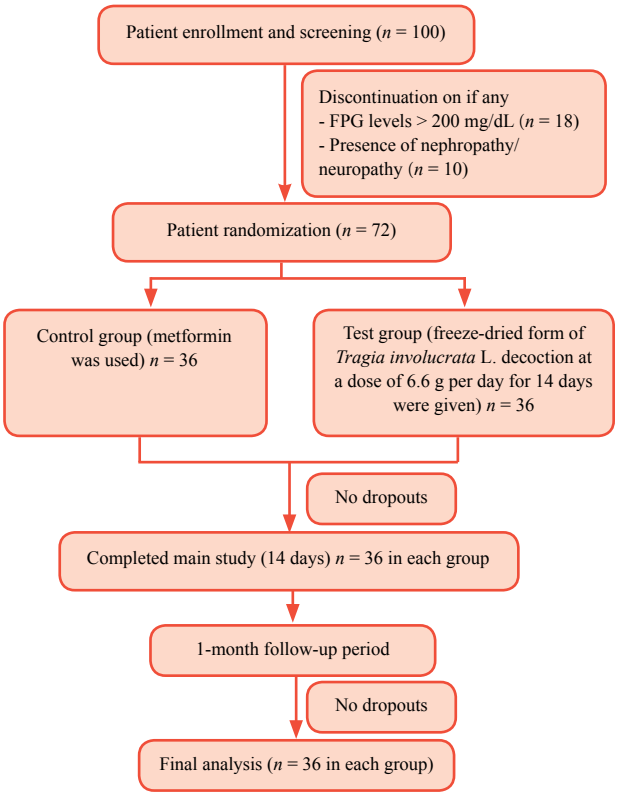

Figure 1: Flow diagram of study design showing the randomization of participants.
FPG: Fasting plasma glucose.

Patients

Inclusion criteria

- Age 18–70 years, of either sex
- Patients who have[17]
  Fasting plasma glucose (FPG) > 126 mg/dL (7.0 mM; fasting is defined as no caloric intake for at least 8 hours)
  OR
  2-hour plasma glucose > 200 mg/dL (11.1mM) during an oral glucose tolerance test
  OR
  Hemoglobin A1c (HbA1c) > 6.5% (48 mmol/mol)
  OR
  In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose > 200 mg/dL (11.1 mM).
- Those who have no known systemic disorders
- Newly diagnosed diabetes patients or diabetic patients who are receiving Ayurvedic treatment
- Those who have no any history of drug allergy
- Those who have no history of intolerance to *T. involucrata*
- Provision of written informed consent

Exclusion criteria

- Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy
- Patients with impaired liver and kidney functions, anaemia, and unstable cardiovascular conditions or cerebrovascular conditions
- History of motor weakness or peripheral sensory neuropathy
- Any evidence of organ dysfunction or any clinically significant deviation from the normal, in physical or clinical determinations
- Pregnant or lactating women

Ethical approval

This study was approved by the Ethics Review Committee, Institute of Indigenous Medicine (ERCIIM), University of Colombo, Rajagiriya, Sri Lanka (approval No. ERC 16/61)

on October 27, 2016 and performed in accordance with the *Declaration of Helsinki*. The study conformed to the reporting guidelines of the CONsolidated Standards Of Reporting Trials (CONSORT) statement (**Additional file 1**). All patients' records were kept safely and securely. Identification data of patients were encrypted using a participant code.

Informed consent

A detailed information sheet was provided in all three languages (Sinhala/English/Tamil) to the patients and informed written consent was acquired from the patients before enrollment (**Additional file 2**).

Randomization

Randomization sequence was generated using an online randomization website (http://www.randomization.com/). Block randomization was done using blocks of 2 to generate the randomization schedule for 72 patients. The patients were allocated to treatments based on the randomization sequence generated. Each group was assigned with an allocation ratio 1:1. The allocation for each randomization number was put in to individually sealed opaque envelopes. The envelopes and allocation sequence were kept under lock and key by one investigator not involved in recruiting patients. The patients meeting inclusion exclusion criteria and recruited into the study were assigned a randomization number sequentially according to the date and time of recruitment. The allocated treatments indicated in the sealed envelope for each randomization number was supplied to each patient.

Drugs

The plant materials *T. involucrata* was identified by the curator of National Herbarium, Department of National Botanic Gardens, Peradeniya, Sri Lanka. A voucher specimen of the plant was deposited at the National Herbarium of Department of National Botanic Gardens, Peradeniya and at the herbarium at Institute of Indigenous Medicine, University of Colombo, Rajagirya, Sri Lanka for future references.

The drug was prepared according to Good Manufacturing Practices and the World Health Organization guidelines. The whole plant of *T. involucrata* (*Wel Kahambiliya*) was cut into small pieces, washed and air dried. The dried herb was made into a decoction according to Sri Lankan Ayurveda Pharmacopoeia.[18] For one part of the dried plant material, 32 parts of distilled water was added and the water was reduced to one eighth of the total volume. Then the decoction was filtered and freeze dried and then stored in sachets. One sachet contained decoction enough for one day. The required number of sachets was provided for the patients.

Storage, packaging and dispensing of investigational drugs

All two investigational products (freeze-dried powder and metformin) were packed for 14 days and labeled which would indicate the batch number, dose, time of administration, and mode of administration. These were stored and provided to randomized patients according to the predetermined allocation sequence. Supply of drugs for 14 days will be dispensed to the study participants at beginning with instructions.

Treatment

The patients in the control group were administered orally metformin at a standard therapeutic dose and the test group was administered orally 1 sachet of freeze-dried decoction which is equivalent to 240 mL of the *T. involucrata* (*Wel Kahambiliya*) decoction twice daily. The patients were advised to prepare the decoction by adding 240 mL warm water and consumed half the volume before breakfast and the remaining half before dinner, around 6 a.m. in the morning and 6 p.m. in the evening for 14 days. A follow-up period of 1 month was carried out after the main study.

Criteria for assessment

On day 0, following a clinical assessment, 5 mL of blood was drawn by a phlebotomist to check the FPG level, HbA1c, lipid profile, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and serum creatinine, and blood urea levels. All the tests of all the patients were carried out by the Accredited Asiri Hospital Diagnostic Laboratory.

All the patients were asked to re-visit the clinic on days 8 and 15. FPG was measured on days 8 and 15, a volume of 5 mL blood were drawn for the analysis of FPG, lipid profile, AST and ALT values, serum creatinine, and blood urea values. At the end of 1-month follow-up period blood was taken again from the patients to check FPG level. A patient diary was given to the patients to write down their experience regarding the decoction during the study period (any physical or mental feelings the patient encounters) and they were requested to note down the time at which they consumed the decoction. On days 0 and 15, a questionnaire was administered by the investigators to collect data on the patients' views regarding their new therapy. The core study was carried out for 2 weeks and the follow-up period was carried out for 1 month.

Termination of the clinical trial

The patient had the right to withdraw consent to participate in this study at any time, with no penalty or effect on his/her medical care or loss of benefits. Patients were requested to notify investigator as soon as they decide to withdraw their consent.

Adverse event management

All adverse events experienced by patients planned to record weekly by the investigators at every visit to the clinic. The patients were further advised to record any adverse reactions in their patient diaries and be advised to inform the investigators using the given contact numbers. They were also advised to come to the clinic for assessment when they experienced any unexpected symptoms or complaints.

Data collection and management

Data was collected by the main investigator under supervision by the consultants. Data will be kept for 5 years from the date of analysis. The results of the study used for scientific reporting in conferences and planned to be published in peer-reviewed journals. Further results of the study and the grouping information of the participants planned to provide to the individual after completion of the trial.

Data analysis

Data were expressed as the mean ± SD and analyzed using SPSS 22.0 software (IBM, Armonk, NY, USA). Independent-samples *t*-test and paired sample *t*-test were used for comparisons between the two groups. A value of $P < 0.05$ was considered statistically significant.

Sample size

Sample size was estimated that would be sufficient to detect statistical significance in assessment between groups. A total of 72 patients were allocated randomly to the test and control groups with 36 in each group.

Results

Participation of patients for the clinical study

Overall 100 patients were screened and 72 patients were randomized to positive control group and study drug group. All the selected patients were completed the trial (**Figure 1**). The number of female patients was greater in comparison to male patients, and most of the patients in both groups had been suffering from diabetes mellitus for 2–10 years (**Table 1**).

Baseline demographic and clinical characteristics of the patients

There were no significant differences in age, sex and FPG at onset between both groups ($P > 0.05$; **Table 1**).

Effect of *T. involucrata* on FPG level in patients with type 2 diabetes

FPG levels on days 0, 8, and 15 are shown in **Table 2**. FPG levels of patients in both control and test groups were decreased significantly on days 8 and 15 compared with day 0 ($P < 0.05$).

Table 1: Characteristic of patients for the clinical study performed for the antidiabetic effect of *Tragia involucrata* L. freeze-dried decoction on type 2 diabetic patients

Item	Control group	Test group
n	36	36
Age[a] (yr)	51±18	50±22.5
Sex (M/F, *n*)	14/22	13/23
FPG at onset[a] (mg/dL)	169.9±34.8	162.6±20.4

Note: "a" Data are expressed as the mean ± SD. F: Female; M: male; FPG: fasting plasma glucose.

Effect of *T. involucrata* decoction on the lipid profile in patients with type 2 diabetes

There was no significant difference in the lipid profile values between the control and test groups on days 0 and 15 ($P > 0.05$). Also there was no significant difference in the lipid profile values between days 0 and 15 in the test group ($P > 0.05$; **Table 3**).

Effect of *T. involucrata* decoction on liver function in patients with type 2 diabetes

There was no significant difference in the ALT, AST, and alkaline phosphatase values between the control and test groups on days 0 and 15 ($P > 0.05$). Also there was no significant difference in the enzyme levels between days 0 and 15 in the test group (**Table 4**).

Effect of *T. involucrata* decoction on the kidney functions of patients with type 2 diabetes

There was no significant ($P > 0.05$) change in the blood urea and serum creatinine values between the control and test groups on both occasions on days 0 and 15. Also there was no significant ($P > 0.05$) difference in the blood urea and serum creatinine levels compared to days 0 and 15 within the test group (**Table 5**).

Discussion

A majority of people suffering from type 2 diabetes still rely on traditional medical systems and plant material for their treatment. *T. involucrata* is one such plant used in the management of diabetes mellitus in Sri Lankan indigenous medicine as well as in Ayurveda medicine. Although there are few scientifically validated studies on the antidiabetic activity of *T. involucrata* conducted in animal models, there have been no published data regarding the anti-diabetic effect of the decoction prepared from the whole plant of *T. involucrata*, which is the dosage form used in Sri Lankan traditional medicine for diabetes mellitus.[16] There have been no published data found in hu-

Table 2: Fasting blood glucose levels (mg/dL) of patients on days 0, 8, and 15

Group	Day 0	Day 8	Day 15
Control	135.6±27.0	127.1±22.2*	124.0±21.6*
Test	164.4±20.4	136.6±19.8*	130.9±16.2*

Note: *$P < 0.05$, *vs.* day 0 (paired sample *t*-test). Data are expressed as the mean ± SD.

Table 3: Effect of *Tragia nvolucrata* L. decoction on lipid profile of patients with type 2 diabetes on days 0 and 15

	TC	TG	HDL	LDL	VLDL	CHO/HDL
Control group						
Day 0	192.4±30.0	121.8±43.2	50.8±5.4	116.4±22.2	24.6±8.4	3.8± 0.6
Day 15	195.0±31.2	125.1±44.4	52.0±6.0	120.3±26.4	23.9±7.8	3.9±0.6
Test group						
Day 0	195.6±35.4	127.7±38.4	49.1±6.0	120.1±30.0	25.4±7.8	4.0±0.6
Day 15	192.4±34.2	120.2±37.8	50.1±6.0	117.4±31.8	23.9±7.8	3.8±0.6

Note: Data are expressed as the mean ± SD. CHO: Cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol; TG: triglycerides; VLDL: very-low-density lipoprotein.

Table 4: Effect of *Tragia involucrata* L. decoction on liver enzymes of patients with type 2 diabetes on days 0 and 15

	ALT	AST	ALP
Control group			
Day 0	26.5±13.8	28.2±10.2	165.6±32.4
Day 15	28.8±19.2	28.9±10.8	167.0±33.6
Test group			
Day 0	27.9±9.6	27.5±7.2	162.9±57.0
Day 15	27.6±10.8	27.6±6.6	156.4±40.2

Note: Data are depicted as the mean ± SD. ALP: Alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 5: Effect of *Tragia involucrata* L. decoction on kidney functions of patients with type 2 diabetes mellitus on days 0 and 15

	Blood urea (mg/dL)	Serum creatinine (mg/dL)
Control group		
Day 0	19.8±5.4	0.73±0.24
Day 15	19.8±5.4	0.72±0.30
Test group		
Day 0	21.3±7.8	0.72±0.40
Day 15	21.0±7.2	0.72±0.40

Note: Data are depicted as the mean ± SD.

man studies using the decoction or extracts of *T. involucrata*.

The control and test groups showed significant reduction of FPG on days 8 and 15 compared to day 0. Although these patients were already administered metformin tablets as they were prescribed, most of the patients confessed to neglecting drug therapy. After the oral advice and handing over of the leaflet and constant reminding for them to use the medication at the proper dose and timing, the FPG levels of most patients improved and became stable. Both control and test groups received oral advice as well as a leaflet containing information about type 2 diabetes and the food and life style changes they should adapt to.

In the present study, the *T. involucrata* decoction did not show any significant changes to the values of lipid profile as they were in the normal range. Even in the pre-clinical study the decoction did not make changes in the triglyceride and high-density lipoprotein levels in rats that had normal values. Therefore, the *T. involucrata* decoction did not result in significant changes in the lipid profile of the test group patients since their values were in the normal range.

It is well-known that certain plant materials used without proper knowledge and proper purification and preparation methods can cause liver toxicity causing mortality and morbidity.[19] Therefore, the levels of the liver enzymes were measured to evaluate whether the test drug has an influence on the liver enzymes. The study showed that there was no significant change in the ALT, AST, and alkaline phosphatase levels between the control and test groups on days 0 and 5. Also there was no significant difference in the enzyme levels between days 0 and 15 in the test group.

Similar to hepatotoxicity, most plants cause toxicity in kidneys[20] if not used appropriately. Therefore, levels of blood urea and serum creatinine were measured to evaluate whether the test drug has an influence on the kidney functions. The present study showed that there was no significant change in the blood urea and serum creatinine values between the control and test groups on days 0 and 15. Also there was no significant difference in the blood urea and serum creatinine levels between days 0 and 15 in the test group.

Strengths and limitations

To our knowledge, this is the first randomized controlled clinical trial to investigate the efficacy of the freeze-dried form of *T. involucrata* decoction in Sri Lanka for type 2 diabetes. Results of this study will provide evidence regarding the use of this herbal preparation for the treatment of diabetes.

Conclusion

T. involucrata decoction at a dose of 240 mL/d for 14 days significantly reduced the FPG levels of type 2 diabetes patients. The decoction did not show a significant change in the lipid profile since the triglyceride and high-density lipoprotein levels were in the normal range in the diabetic patients. The decoction also did not significantly change the levels of liver enzymes and blood urea and serum creatinine. Hence, it can be concluded that the *T. involucrata* decoction did not imply any significant effect on liver or kidney functions of type 2 diabetes patients while significantly lowered the FPG levels.

Additional files

Additional file 1: CONSORT checklist.
Additional file 2: Model consent form.

Author contributions

The study was conceptualized by MP, PKP and NK. The protocol was developed by MP, PKP, NK, CLG and MA. Clinical trial conducted by MP, PKP and NK collectively. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Financial support

This project was funded by the University Grant Commission in Sri Lanka.

Institutional review board statement

This study protocol was approved by the Ethics Review Committee, Institute of Indigenous Medicine (ERCIIM), University of Colombo, Rajagiriya, Sri Lanka (approval No. ERC 16/61) on October 27, 2016, and performed in accordance with the *Declaration of Helsinki.*

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Reporting statement

This study follows the CONsolidated Standards Of Reporting Trials (CONSORT) statement.

Biostatistics statement

The statistical methods of this study were reviewed by the biostatistician of General Sir John Kotelawala Defence University, Rathmalana in Sri Lanka.

Copyright license agreement

Data sharing statement
The data used to support the findings of this study are available from the corresponding author upon request.
Plagiarism check
Checked twice by iThenticate.
Peer review
Externally peer reviewed.

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