Angelica keiskei (ashitaba) as adjuvant therapy in the maintenance of blood glucose levels among patients with type II diabetes mellitus

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Abstract

Introduction This study aimed to determine if using *Angelica keiskei* (ashitaba) tablets as adjuvant therapy to the usual medications for patients with type II diabetes mellitus would result in significant lowering of blood sugar.

Methods The antidiabetic effect of *Angelica keiskei* was evaluated in diabetic Filipino patients as an adjuvant treatment to antidiabetic medications through a randomized single-blind placebo-controlled clinical trial. Patients recruited from select barangays in Quezon City and San Juan City were randomly assigned to either ashitaba or placebo group. The effect was measured by obtaining and comparing fasting blood sugar pre- and post-treatment.

Results There was no significant change in FBS from the baseline in the ashitaba ($p = 0.174$) and placebo ($p = 0.128$) groups after two weeks. There was a significant increase in the systolic BP of the ashitaba group ($p= 0.014$) but not in the placebo group. There were no significant changes in the diastolic BP of either group.

Conclusion Dietary supplementation of 500 mg ashitaba capsules thrice daily for two weeks did not exhibit any glucose-lowering effects among type II diabetic patients maintained on oral anti-diabetic medications.

Keywords: Ashitaba, pharmaceutic adjuvant, diabetes mellitus type II, blood glucose

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Diabetes remains a healthcare problem worldwide resulting in increasing numbers of newly diagnosed patients per year and deaths throughout the globe. According to the World Health Organization (WHO), between 2000 and 2030, the number of individuals diagnosed with diabetes will increase up to 114% globally as a consequence of urbanization and population aging.[1] Presently, the prevalence of type II diabetes is rapidly increasing in Asian countries and is becoming a major site of a diabetes epidemic

particularly in the Philippines. The country ranked 15th out of 21 countries under the International Diabetes Foundation (IDF) for diabetes prevalence.[2] Statistics showed a prevalence of 5.5% among men and 6.1% in women in 2016, and it was the 6th most common cause of death among Filipinos in 2013.[3,4] Ashitaba (*Angelica keiskei*), a Japanese herb, is known to possess many biological activities. Its medicinal use has been centered on the prevention of diabetes and its associated complications. Its bioactive components, which include chalcones, coumarins and flavanone, have cytotoxic, antidiabetic, antioxidative, anti-inflammatory, antihypertensive, and antimicrobial properties.[5] Two major chalcones from ashitaba have an insulin-like behavior, which ameliorated hyperglycemia in mice.[6] Another study also noted that long-term ingestion of ashitaba juice reduced HbA1c levels in mice with borderline and mild hyperglycemia.[7] A study also discovered that *A. keiskei* chalcones increased the expression of insulin receptors in liver cells as well as in erythrocytes while decreasing the fasting blood glucose in diabetic mice.[7] While studies have supported the effects of *A. keiskei* in vivo as anti-diabetic medicine, clinical testing is required to confirm its efficacy as an antidiabetic in humans. Only few human studies were conducted regarding ashitaba's effectiveness in lowering blood glucose levels.

In this study, the researchers determined the effect of ashitaba as an adjuvant to regular diabetes maintenance medications among type II diabetic Filipino patients. This study also tried to identify adverse events reported by the participants up to 8 to 10 weeks post-treatment.

Methods

A randomized single-blind placebo-controlled clinical trial was carried out to determine the effect of ashitaba, compared with placebo, as an adjunct in the maintenance of blood glucose levels among Filipino patients with type II diabetes. Patients recruited from selected barangays in Quezon City and San Juan were randomly assigned to receive ashitaba or placebo capsules for two weeks. Fasting blood sugar levels were compared within and between groups. The study was approved and conducted in compliance with the PHREB 2017 National Ethical Guidelines for Health and Health-Related Research and was approved for implementation by the UERMMMCI Research Institute for Health Science Ethics Review Committee.[8]

Patients were recruited from selected barangays in Quezon City and San Juan City. Informed consent was obtained from those who fulfilled the following inclusion criteria (based on the history) and agreed to join the study: adult Filipino males or females aged 18 to 59 years, fasting blood glucose ≥ 110 mg/dL, previously diagnosed with type II diabetes mellitus, and taking one or two oral antidiabetic agents as maintenance. Those with any of the following based on the history were excluded: hypersensitivity to any of the active phytochemical substances contained in *A. keiskei* determined through thorough history taking; maintenance with sulfonylureas and/or insulin; severe diseases, complications and comorbidities such as but not limited to cancer, tuberculosis and anemia; current intake of medications for the previously mentioned diseases; possible liver and/or kidney problems; recurrent/severe infections; intake of other herbal supplements; pregnancy or breastfeeding; and alcohol or drug abuse. The minimum sample size was calculated at four per group based on the pilot study conducted to determine the efficacy and safety of ashitaba on patients with metabolic syndrome.[9] The sample size was calculated, wherein the level of significance was set at $p = 0.05$, power of 80%, the standard deviation of 4.9 and a difference to be detected of 10.

Participants were randomly assigned to either ashitaba or placebo group through block randomization. Both simple random sampling and block randomization were computer-generated using Research Randomizer (www.randomizer.org). The participants were asked to attend two sessions. During the first session, the participants' fasting blood sugar (FBS) levels were measured as a baseline laboratory evaluation at the UERM Hospital, as well as their demographic and baseline data. Participants in the experimental group received 500 mg ashitaba capsules while participants in the control group received 500 mg starch capsules as placebo. Both treatments provided were placed in sealed, opaque bottles when handed out to the patients. The participants were instructed to take three capsules, with meals, per day for two consecutive weeks.

The participants were reminded daily through SMS to take both their maintenance and treatment medications. A monitoring sheet was provided per patient to track their compliance. Adverse effects were monitored to a period eight to ten weeks after the

completion of the study. In the second session after the two-week intake of the assigned intervention, the participants were asked to have their fasting blood sugar levels measured for evaluation. During the study, the participants were advised not to switch to different anti-hyperglycemic agents nor to take other herbal medications.

Data were gathered and analyzed per protocol and with intention to treat. The investigators determined the change in blood sugar level at the end of the second week as the primary outcome. Statistical analysis of the data was conducted using IBM SPSS Version 20. Each parameter was expressed as a mean ± standard deviation. A paired t-test was used to determine if there was a statistically significant difference in the changes of means of the measured FBS and BP, pre- and post-intervention among the ashitaba and placebo groups. An independent t-test was also used to analyze the significant difference between groups. $P < 0.05$ was considered to be significant for both tests. Fisher's exact test for the nominal variables, and an independent t-test for numerical variables, were used to determine the comparability of the ashitaba and placebo groups.

Results

Table 1 shows that there were more men in the ashitaba group, that those in the ashitaba group were younger, had a higher BMI, larger waist circumference, and weighed more. The differences in BMI ($p = 0.005$), waist circumference ($p = 0.019$), and weight ($p = 0.029$) were significant. There was no significant change in FBS from the baseline in the ashitaba ($p = 0.174$) and placebo ($p = 0.128$) groups after two weeks, as seen in Table 2.

The adverse effects were monitored as reported by the patients and are shown in Table 3. There was a significant increase in the systolic BP of the ashitaba group ($p= 0.014$) but not in the placebo group. There were no significant changes in the diastolic BP of either group. For every 10 patients given ashitaba at 500 mg thrice daily, two patients would develop elevations of their systolic BP (number needed to harm).

Discussion

The efficacy of ashitaba, a traditional Japanese herb, was evaluated as an adjunct to standard therapy in patients with type II diabetes mellitus. Based on the results of the study, the ingestion of 500 mg ashitaba capsules thrice daily for two weeks did not lead to any significant changes in the FBS levels of the study participants.

The significant differences in BMI, waist circumference and weight may have affected the outcome of the study. The dose of ashitaba given to the study participants and the total duration may have been insufficient to produce significant effects.

Table 1. Baseline characteristics of study participants

Demographics	Ashitaba (n = 5)	Placebo (n = 5)	p-value
Number of males	3	1	0.429
Age (yr ± SD)	44.2 ± 11.30	50.2 ± 7.09	0.344
Body mass index (kg/m^2)	32.8 ± 5.24	21.5 ± 3.94	0.005
Waist circumference (cm)	42.1 ± 5.57	34.0 ± 2.67	0.019
Weight (kg)	79.8 ± 23.82	49.4 ± 9.56	0.029
Height (cm)	157.4 ± 9.10	152.2 ± 5.50	0.306

Table 2. Comparison of fasting blood sugar in ashitaba and placebo groups

	Ashitaba (n = 4)			Placebo (n = 4)		
	Week 0	Week 2	Change	Week 0	Week 2	Change
FBS (mmol/L)	12.6 ± 5.14	13.0 ± 5.27	-0.42 ±0.56	11.8 ±4.01	10.7 ± 3.38	1.16 ±1.09

Note: All values are shown as mean ± standard deviation
*Significant at $p < 0.05$ (paired t-test)

Table 3. Comparison of blood pressure in ashitaba and placebo groups

Blood pressure (mm Hg)	Ashitaba (n = 4)			Placebo (n = 4)		
	Week 0	Week 2	Change	Week 0	Week 2	Change
Systolic	127.5 ± 18.93	142.5 ± 17.08	-15.0 ± 5.77 *	134.0 ± 27.93	128.0 ± 8.37	6.0 ± 27.02
Diastolic	87.5 ± 9.57	100.0 ± 11.55	-12.5 ± 12.58	88.0 ± 8.37	92.0 ± 8.37	-4.0 ± 5.48

Note: All values are shown as mean ± standard deviation
*Significant at $p < 0.05$ (paired t-test)

The pilot study conducted by Ohnogi used a daily dose of 6.2 g of ashitaba on patients diagnosed with metabolic syndrome, with results being significant after four weeks.[9] However, ashitaba administration was given thrice daily since a study recommended that oral administration of ashitaba should be at least three times per day to achieve and maintain its desired plasma levels, due to C16, a bioactive metabolite found in ashitaba.[10]

Numerous studies have been able to prove that ashitaba exerts a significant effect on blood sugar levels. The current study only administered a daily dose of 1.5 g ashitaba for a two-week period as recommended by the pharmaceutical company producing the capsules. It was also done due to limitations on time and resources. Ideally, the study should have been conducted for four weeks based on literature.

There have been studies that investigated the safety of ashitaba as a drug and have concluded that ashitaba was generally safe with little to no adverse effects reported.[11] Ohnogi reported that ashitaba is a safe foodstuff for human consumption, as adverse effects were not observed among patients diagnosed with metabolic syndrome.[9] However, this study noted a significant increase in the systolic blood pressure of the patients in the treatment group, which is in contrast to the purported antihypertensive effects of ashitaba as seen in previous studies. There is a need to investigate this apparent adverse effect in future studies.

There was no significant change in the FBS values within the treatment and control groups during the two-week period. These results suggest that daily administration of 1.5 g ashitaba for two weeks does not exhibit any glucose-lowering effects among type II diabetic patients maintained on oral antidiabetic medications.

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