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Original Research Article

A Single-Blind, Randomized, Controlled Trial Assessing the Efficacy and Safety Parameters of Traditional Thai Medicine, Aphayathikun, in Prediabetic Men with Lower Urinary Tract Symptoms

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ABSTRACT

Lower urinary tract symptoms (LUTS) are not only more common in the elderly, but various pathophysiological pathways suggest a link between hyperglycemia and LUTS. Due to the long-standing traditional use of medicinal plants in Thailand, the present work aims to establish the safety and efficacy of Aphayathikun (AP), a recorded Thai Traditional medicinal drug for LUTS. The standardized decoction of AP has been established, and phenolic and flavonoid content, antioxidant activity, and *in vivo* toxicity were assessed using previously published methods. A randomized, open-label, controlled study was conducted on 34 prediabetic men with mild to moderate uncomplicated LUTS. As a supplementary treatment for standard self-management, 30 mL of AP decoction was administered thrice daily before meals for 14 consecutive days. Baseline and endpoint (the 4th week) improvements in IPSS scores, blood glucose control, serum lipid profiles, and liver function testing of the subjects were determined. There was an improvement in the total IPSS score and a significant decrease in the IPSS voiding and storage subscores among the subjects in the AP group. Additionally, the quality-of-life index, as measured by the IPSS, and the number of nocturia episodes per night decreased significantly from baseline to the 4th week in the AP group. This traditional polyherbal preparation, AP decoction, appears to be a safe and effective therapy option for the alternative treatment of mild-to-moderate LUTS in prediabetic patients.

***Keywords*:** Aphayathikun; Prediabetes; Lower urinary tract symptoms; Traditional Thai Medicine

Introduction

The prevalence of prediabetes in adults is rising dramatically. The global diabetes burden was expected to reach around 400 million patients in 2019.[1] This condition is recognized as a key factor linked to the increased risk of developing diabetes and its complications, such as retinopathy, neuropathy, nephropathy, etc.[2] Globally, the prevalence of prediabetes, based on impaired glucose tolerance (IGT), is expected to rise from 352.1 million individuals in 2017 to 587 million in 2045.[3] Among these, 5-10 percent of prediabetic patients develop diabetes each year, with up to 70 percent progressing to diabetes.[2,4] Adequate treatment is required to prevent the development of diabetes. Diabetes patients are more likely to suffer from cardiovascular disease, chronic lower respiratory disorders, and chronic renal disease.[5]

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Despite these deadly complications, increasing evidence indicates that hyperglycemia is often associated with lower urinary tract symptoms (LUTS), including benign prostatic hyperplasia (BPH), which has significant adverse effects on health-related quality of life, particularly in terms of sleeping efficiency, mental health, and workforce productivity. [6,7]

Several pathophysiological mechanisms have been suggested to clarify the relationship between diabetes and LUTS.[8,9] Type 2 diabetes is strongly associated with hyperinsulinemia, which may contribute to LUTS and BPH/LUTS by increasing sympathetic nerve activity, leading to increased smooth muscle tone in the prostate, prostate size, and voiding symptoms. [10,11] Also, elevated insulin levels can influence the amount of sex hormones, subsequently affecting the prostatic hormone environment and prostatic cell development.[10,12] Elevated glucose and insulin levels can stimulate and proliferate prostate cell growth. Recent research indicates that both LUTS and BPH/LUTS are also caused by persistent systemic inflammation and oxidative stress resulting from hyperglycemia.[13-15]

Earlier studies in the United States have shown that up to 90 percent of newly diagnosed patients with LUTS secondary to BPH receive some form of alternative or complementary treatment.[16-19] Due to the long tradition of using plant extracts in Europe, more than 100 herbal medicines are widely available for treating LUTS and BPH/LUTS.[16,17] Research studies and clinical trials on popular phytotherapeutic agents such as *Serenoa repens* [19,20] and *Cucurbita pepo* [18,21] have established their efficacy. The number of publications focused on the biological activities of traditional herbal preparations used in Thailand has increased in recent years.[22,23] However, knowledge related to LUTS has yet to be explored.

Therefore, in this current investigation, we report for the first time the safety and effectiveness of Aphayathikun (AP), which has been described as a treatment for LUTS in an ancient national textbook called 'Manchu-Sara-Vichian.' [24] The decoction obtained from AP has been used as an adjunctive treatment in mild and moderate LUTS patients in traditional Thai medical units in several hospitals, including the Traditional Thai Medicine Hospital at Prince of Songkla University and Yala Regional Hospital. Based on the pathophysiologic association between hyperglycemia and LUTS, as well as the hypoglycemic properties of AP's components, which include *Terminalia chebula*,[25] *Phyllanthus emblica*,[26] *Vetiveria zizanioides*,[27] and *Cyperus rotundu*, [28] this study aims to determine the safety and effectiveness of the standardized AP decoction in prediabetic men with LUTS.

Materials and Methods

The decoction of Aphayathikun (AP)

Plant parts, including the rhizome of *Cyperus rotundus*, pre-dried fruits of *Phyllanthus emblica* and *Terminalia chebula*, and the root of *Vetiveria zizanioides*, were obtained from a local licensed medicinal plant store called Maha-Khun Pharmacy, located in Khuha Sawan city, Phatthalung province, Thailand. The medicinal plants were authenticated and identified against reference specimens by a botanist specializing in traditional Thai herbs and a traditional Thai medical doctor at the Materia Medica Museum of the Faculty of Traditional Thai Medicine (Prince of Songkla University, Songkhla, Thailand). Their voucher and batch numbers are provided in Table 1. The oven-dried plants were prepared in the VENTICELL® chamber (MMM Group, München, Germany) at 60°C for 72 hours. These samples were separately powdered using a multi-functional grinder (Yongkang Sufeng Industry and Trade Co., Ltd., China) to a fine grade, passed successively through a mesh No. 16 (980 µM), and stored at 4°C in a vacuum-sealed, light-protective bag. These plant materials were used throughout the entire study period to reduce batch-to-batch variability.

The AP decoction was manufactured by a licensed herbal pharmaceutical factory (Prachuab Pharmaceutical Factory; Mueang, Songkhla province, Thailand). In brief, the medicinal plants described in Table 1 were mixed in equal proportions and placed into a sterile cotton bag. An AP herbal bag (1000 g per pack) was soaked in 15 liters of water and boiled at 100±3°C for 45 minutes. The resulting solution was kept at room temperature (25±2°C) for three hours and filtered through mesh No. 60 and Whatman filter paper Number 1, respectively. This decoction was filled into sterile, light-protective glass containers (30 mL) and sealed.

The acute *in vivo* toxicity of AP decoction was examined based on OECD guidelines 425 conducted by the Thailand Institute of Scientific and Technological Research (Pathum Thani province, Thailand). Heavy metals and microbiological contaminations were assessed according to standard procedures provided by Central Laboratory (Thailand) Co., Ltd. (Hat Yai, Songkhla province, Thailand), respectively. The AP decoction was standardized by qualitatively identifying its active constituents using liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (LC-QTOF MS), provided by the Office of Scientific Instrument and Testing, Prince of Songkla University (Hat Yai, Songkhla province, Thailand). Additionally, its phenolic and flavonoid contents were measured, and antioxidant and anti-inflammatory activities were evaluated using standard procedures. [22]

Study setting and design

The study was a prospective, single-blind, open-label, randomized, parallel-group, add-on study conducted over four weeks at Yala Regional Hospital (Yala province, Thailand). The research protocol was designed in accordance with local laws and the Declaration of Helsinki's guidelines for medical research involving human subjects. Before patient recruitment, the Ethics Review Committee of the Faculty of Traditional Thai Medicine, Prince of Songkla University (EC.61/TTM-004), and the Ethics Review Committee of Yala Regional Hospital (YL.0032.102/1279) approved the study protocol. Potential participants were informed about the study details via email, and researchers then contacted individuals who expressed their willingness to participate in the clinical study. Each participant signed an informed consent form before undergoing screening and enrollment in the trial.

Inclusion and exclusion criteria

Eligible patients met the following criteria: (i) men aged between 30 and 60 years, (ii) with vital signs within the normal physiological range, and (iii) newly diagnosed with prediabetes based on the Thailand Diabetes Risk Score (>5) and fasting blood glucose level (100-125 mg/dL) and having moderate to low LUTS severity (an IPSS score between 1 and 19) at baseline. Exclusion criteria encompassed: (i) patients with a history of type-1 diabetes, type-2 diabetes, gestational diabetes, or benign prostatic hyperplasia (BPH) patients with a post-void residual (PVR) above 20 cm3, (ii) those currently taking medications or herbal supplements with hypoglycemic effects, muscarinic receptor antagonist, anti-cholinergic, beta-3 adrenergic antagonist, alpha1-blockers, and 5-alpha-reductase inhibitors, and (iii) patients with a history of allergies to the medicinal plants utilized in this study.

Study population and sample size calculation

All potential participants from the non-communicable diseases (NCDs) clinic at Yala Regional Hospital (Yala province, Thailand) were randomly assigned to either the control group (SMI group) or the experimental group (AP group) using a computer-generated random number list ranging from APplus0.01 to APplus0.35. The unit secretary provided and delivered the numbers to the participants in opaque envelopes. The medical doctor and outcome assessors were blinded to the group assignments. The required sample size for this study was determined using G-Power software version 3.1.9.6 and based on a priori statistical power analysis. [29,30] The calculation was based on an expected difference in the means of IPSS scores between the two groups, as reported in previously published work [20], with an alpha level of 0.05 and a power of 0.80. This calculation resulted in an estimated sample size of 17.

Interventions

Double blinding was not implemented because this study was the first clinical examination to assess the effects of AP decoction as an adjunctive treatment for prediabetic individuals with LUTS in standard self-management interventions. Participants in both groups were educated and instructed in the self-management intervention program, which included guidance on diet, exercise, and lifestyle modifications following prescribed procedures. [31] As per the standard procedure outlined in Thai traditional medicine for decoction preparation and administration, which is prescribed in the treatment procedure for AP decoction, participants in the AP group also received AP decoction, 30 mL three times daily before meals, for 14 consecutive days. Patient compliance with the assigned treatments was monitored by reviewing a daily compliance chart and counting the empty AP bottles during each follow-up visit.

Outcome measurements

For 28 days, the participants underwent assessments at various time points, including screening (visit 0), 7 days (visit 1), 14 days (visit 2), 21 days (visit 3), and 28 days (visit 4). The primary outcomes were defined as changes in lower urinary tract symptoms, as indicated by the total IPSS score measured after overnight fasting at the screening visit and after the 4th week, and the IPSS score for nocturia (visit 7) recorded at baseline, the 1st, 2nd, 3rd, and 4th visits. Secondary outcomes included the measurement of clinical features of metabolic syndrome after overnight fasting at baseline and after four weeks. Safety assessments, including vital signs, adverse events, and levels of liver enzymes and renal function parameters, were conducted during the follow-up visits.

Statistical analysis

Statistical analysis involved presenting the data as mean ± SD, with all analyses performed using the Statistical Package for the Social Sciences software for Windows. The normal distribution of data was assessed using the Shapiro-Wilk test. Differences in the parameters

obtained before and after treatment were evaluated using paired t-tests or Wilcoxon signed-rank tests. Comparisons between the control and intervention groups were made using two-tailed independent samples t-tests and Mann-Whitney U tests. A P-value of 0.05 or below was considered statistically significant.

Results and Discussion

Numerous studies have reported an association between insulin resistance and hyperglycemia with the prevalence and incidence of LUTS, especially in older adults. [8-10,13,14] Despite the significant reduction in quality of life and interference with daily activities noted in men with mild-to-moderate symptoms [7], the primary treatment options have been limited to lifestyle advice, behavioral modifications, and watchful waiting. [32] In this context, using medicinal plants to improve LUTS, including symptoms such as nocturia, urge symptoms, and urinary flow weakening, or to enhance patients' quality of life (QoL) is of great interest. Our results, for the first time, highlight that the consumption of AP decoction (30 mL x TID AC) for two weeks as an add-on therapy for prediabetic patients with mild-to-moderate LUTS significantly improved the IPSS-QoL score and the mean number of nocturia episodes compared to the control group. These outcomes are consistent with other phytotherapies, such as pumpkin seed extract [21], Seoritae extract [19, 20], and Peponen capsule [33]. The reduction in nocturia, reported as a critical and bothersome irritative symptom, could account for a significant part of the improvement in the IPSS-QoL score.

As described in Table 1, Aphayathikun (AP), a traditional Thai polyherbal remedy specified in an ancient textbook named 'Manchu-Sara-Vichian,' consists of equal parts of *Terminalia chebula* (fruit), *Phyllanthus emblica* (fruit), *Vetiveria zizanioides* (root), and *Cyperus rotundus* (rhizome). Despite the traditional use of AP decoction for LUTS treatment, all medicinal components have been reported to possess biological activities that may be linked to LUTS treatment mechanisms (Table 1). Samples of AP were found to comply with the regulatory guidelines for traditional herbal decoction registration issued by the Thai Food and Drug Administration, particularly regarding safety limits for microbial contamination and heavy metal contents (Table 2). Furthermore, safety information and details about the LUTS-related biological activities, including free radical scavenging properties and anti-inflammatory activity of the AP decoction, are provided in Table 2.

Table 1: Herbal components of Aphayathikun and their reported biological activities

	Medicinal plants [References]			
	Cyperus rotundus Linn.	**Phyllanthus emblica Linn.**	**Terminalia chebula Retz.**	**Vetiveria zizanioides (L.) Nash**
Parts used	Rhizome	Fruit	Fruit	Root
Voucher specimen No.	MTM08-33	MTM08-72	MTM08-92	MTM20-01
Batch No.	10DEC17	20FEB18	12JAN17	08JUN18
Anti-inflammation activity	√[51]	√[52]	√[53]	√[50]
Antioxidant activity	√[40]	√[41]	√[42]	√[43]
5α-reductase inhibition	√[36]	ND	√[37]	ND
Hypoglycemic effects	√[28]	√[26]	√[25]	√[27]

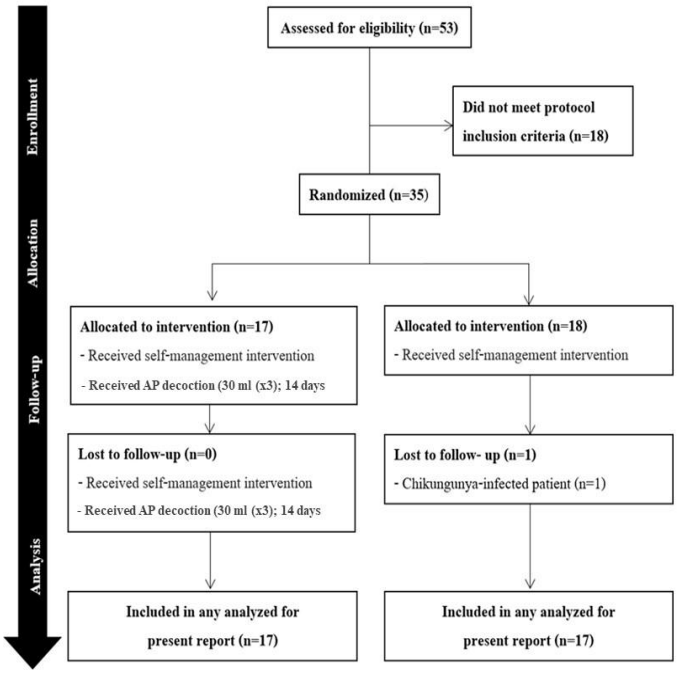

Figure 1: CONSORT diagram reflecting the flow of study participants through the study.

Table 2: General properties of Aphayathikun decoction

Parameters	**Observed values**
Total contents of;	
- Phenolics (mg Gallic acid/g extract)	8.39 ± 0.21
- Flavonoids (mg Catechin/g extract)	0.74 ± 0.06
Radical scavenging properties	
- ABTS (IC_{50}; mg/mL)	57.65 ± 0.22
- DPPH (IC_{50}; mg/mL)	173.67 ± 9.37
- Peroxyl radicals (µM Trolox/ µg extract)	48.93 ± 3.33
- Superoxide anion (IC_{50}; µg/mL)	84.56 ± 6.40
Anti-inflammatory activity (% Inhibition of NO)	16.69 ± 1.41
Microbial assessment (total count/mL of;)	
- *Escherichia coli*	Negative
- *Staphylococcus aureus*	Negative
- *Salmonella* spp.	Negative
- *Clostridium* spp.	Negative
Contents of in mg/kg of;	
- Arsenic	0.020
- Cadmium	0.000
- Lead	0.049
LD_{50} (mg/kg)	>2,000

Given the limited scientific evidence on traditional medicines and medicinal plants, the acceptance of phytotherapies has been quite limited. Traditionally, AP decoction has been employed for treating urinary and reproductive system problems, as described in an ancient national textbook, 'Manchu-Sara-Vichian.'[24] The formulation comprises *Cyperus rotundus* rhizomes, *Phyllanthus emblica* fruits, *Terminalia chebula* fruits, and *Vetiveria zizanioides* roots. However, the utilization of AP decoction has never been documented. Only a few studies on AP's components have indicated a promising effect on LUTS and the prostate by preventing testosterone-induced hyperplasia. Both *Cyperus rotundus* [36], and *Terminalia chebula* [37] have been reported to possess anti-androgenic properties, including acting as 5α-reductase inhibitors, which are the main mechanisms of standard treatment for men with BPH/LUTS, inhibiting the conversion of testosterone into dihydrotestosterone. *Terminalia chebula* has been clinically reported in Ayurvedic medicine for its anti-fertility effect and male contraceptive efficacy. [38]

Figure 1 depicts the CONSORT flow chart, illustrating the progression of participants through each stage of this randomized trial. Fifty-three prediabetic participants were considered for enrollment, with 18 patients not meeting the inclusion criteria, resulting in 35 eligible patients entering the randomization process. All participants received diabetes self-management advice, with AP decoction prescribed to the intervention group (AP group). Thirty-four participants completed the trial, with 17 subjects in each group. In contrast, only one participant in the self-management intervention group (SMI group) was excluded from the study due to a Chikungunya infection during the treatment period. The first participant was enrolled on November 5, 2018, and the final participant completed the trial on December 20, 2019. The baseline characteristics of the newly diagnosed prediabetic patients with mild to moderate LUTS, as presented in Table 3, showed no significant differences between the groups. The mean fasting blood glucose (FBG) levels in both the AP and SMI groups were 105.41 (14.06) and 104.35 (16.13) mg/dL, respectively (p=0.986). The mean IPSS total score at baseline was 6.47 (5.66) for the AP group and 6.41 (5.03) for the SMI group (p=0.518). The prostate-specific antigen (PSA) levels of the participants in both groups fell within the normal range. The frequencies of nocturia were 1.47 (0.62) and 1.76 (0.90) episodes per night for the AP and SMI groups, respectively (p=0.422).

At the follow-up visit after the 4th week of the interventions (Table 4), although a decrease in the total IPSS score and the IPSS voiding and storage subscores was observed, there were no statistically significant differences (p=0.413) in these scores between the AP and SMI groups. The mean (SD) IPSS total score of the AP group decreased from 6.47 (5.66) at the initial visit to 4.65 (3.27) at the end of the study, corresponding to a reduction of -1.82. However, this value did not differ significantly from the baseline (p=0.153). Notably, 10 out of 17 (58%) patients in the AP group showed improvement in the total IPSS score, while the score decreased in only 3 participants (17%) in the SMI group. The ratings for feelings of incomplete emptying and urgency of urination in the AP group participants significantly improved compared to the baseline.

Table 4: Effects of Aphayathikun in combination with self-management intervention on the International Prostate Symptom Score (IPSS) score at the 4th week

Parameters*	**Mean (SD); n=17**							
	Aphayathikun+self-management intervention			**self-management intervention**			**p-value**	
	Baseline (A)	**At 4th week (B)**	**p-value (A *vs.* B)**	**Baseline (C)**	**At 4th week (D)**	**p-value (C *vs.* D)**	**A *vs.* C**	**B *vs.* D**
Total score	6.47 (5.66)	4.65 (3.27)	0.153	6.41 (5.03)	6.12 (4.67)	0.726	0.518	0.413
Voiding score	3.24 (3.41)	2.41 (2.42)	0.375	2.76 (3.43)	2.76 (3.25)	0.565	0.812	0.973
Storage score	3.24 (2.65)	2.24 (1.30)	0.109	3.65 (2.29)	3.35 (2.23)	0.129	0.218	0.14
-Incomplete emptying	1.59 (1.54)	0.71 (0.77)	0.027	1.24 (1.43)	0.94 (1.29)	0.18	0.496	0.946
- Frequency	0.88(0.99)	0.88 (0.92)	1.000	1.29 (1.35)	1.12 (1.21)	0.257	0.413	0.78
- Intermittency	0.47 (0.87)	0.18 (0.39)	0.59	0.65 (1.16)	0.82 (1.18)	0.18	0.892	0.16
- Urgency	1.12 (1.49)	0.41 (0.50)	0.042	0.65 (0.93)	0.59 (0.87)	0.317	0.394	0.812
- Weak stream	0.82 (1.13)	1.12 (1.21)	0.399	0.35 (0.70)	0.53 (0.80)	0.257	0.231	0.15
- Straining	0.35 (0.78)	0.41 (0.79)	0.785	0.53 (0.87)	0.47 (0.80)	0.705	0.61	0.812
- Nocturia	1.24 (0.75)	0.94 (0.55)	0.132	1.71 (1.04)	1.65 (1.11)	0.564	0.274	0.067
IPSS-QoL	2.65 (1.49)	1.76 (1.09)	0.001	2.71 (0.84)	2.94 (1.14)	0.334	0.973	0.008

$p < 0.05$ was considered as statistically significant.
*Abbreviations: IPSS=International Prostate Symptom Score, IPSS-QoL=IPSS Quality of Life

Table 5: Changes in the total International Prostate Symptom Score (IPSS) score, IPSS Quality of Life (IPSS-QoL) score, voiding symptom subscore, and storage symptom subscore on the IPSS from the beginning of the study to 4 weeks in the self-management intervention (SMI) and Aphayathikun in combination with SMI groups

Parameters	**Mean change from baseline (SD); n=17**		
	Aphayathikun+SMI	**SMI**	**p-value**
Total score	-0.29 (1.64)	-1.82 (4.43)	0.223
Voiding score	0.00 (1.54)	-0.82 (2.89)	0.407
Storage score	-0.29 (0.77)	-1.00 (2.20)	0.556
IPSS-QoL	0.24 (0.90)	-0.88 (0.85)	0.001

$p < 0.05$ was considered as statistically significant

There were no significant changes in the albumin, total bilirubin, direct bilirubin, aspartate transaminase (AST), and alkaline phosphatase (ALP) levels. However, a notable improvement in alanine transaminase (ALT) levels in the AP group and a significant increase in creatinine levels in the SMI group were observed. At the end of this study, except for the creatinine level, all mentioned parameters were similar between the AP and SMI groups. The mean parameters of hepatic and renal functions were within normal limits; however, creatinine in the SMI group was significantly higher than in the AP group.

Interestingly, the administration of AP decoction for only two weeks improved total IPSS and voiding and storage scores from baseline to 4 weeks, although not statistically significant (p=0.375). Furthermore, IPSS sub-scale scores for urgency of urination and sensation of incomplete emptying were significantly reduced in the treatment group.

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Table 6: Effects of Aphayathikun (AP) in combination with self-management intervention (SMI) on nocturia episodes

Follow-up duration (weeks)	Mean (SD); n=17					Mean change from baseline (SD); n=17		
	AP+SMI (A)	p-value (*vs.* baseline)	SMI (B)	p-value (*vs.* baseline)	p-value (A *vs.* B)	AP+SMI	SIM	p-value
Baseline	1.47 (0.62)		1.76 (0.90)		0.422			
1st week	1.41 (0.61)	0.763	1.76 (1.09)	1.000	0.670	-0.06 (0.82)	0.00 (0.35)	0.505
2nd week	1.06 (0.82)	0.02	1.53 (0.94)	0.102	0.297	-0.41 (0.61)	-0.24 (0.56)	0.498
3rd week	0.88 (0.69)	0.013	1.71 (1.04)	0.564	0.095	-0.59 (0.79)	-0.06 (0.42)	0.021
4th week	0.88 (0.69)	0.013	1.59 (0.87)	0.18	0.039	-0.56 (0.79)	-0.18 (0.52)	0.089

$p < 0.05$ was considered as statistically significant.

Table 7: Effects of Aphayathikun in combination with self-management intervention (SMI) on metabolic syndrome-related parameters

Parameters*	Mean (SD); n=17							
	Aphayathikun+ self-management intervention			self-management intervention			p-value	
	Baseline (A)	At 4th week (B)	p-value (A vs. B)	Baseline (C)	At 4th week (D)	p-value (C vs. D)	A *vs.* C	B *vs.* D
FBG (mg/dL)	105.41 (14.10)	104.71 (18.94)	0.877	104.35 (16.1)	106.76 (24.08)	0.552	0.986	0.986
Insulin level (µU/mL)	21.90 (42.96)	10.31 (5.97)	0.758	13.71 (12.1)	10.59 (7.76)	0.980	0.850	0.823
BMI (kg/m^2)	25.91(3.97)	25.96 (0.80)	0.831	27.68 (4.48)	27.78 (4.57)	0.176	0.301	0.263
Waistline (cm)	88.41(5.42)	88.41 (5.42)	1.000	93.41(9.50)	93.53 (9.69)	0.317	0.118	0.118
Diabetes risk score	8.70 (1.92)	8.70 (1.92)	1.000	9.41 (2.06)	9.41 (2.06)	1.000	1.000	1.000
Blood pressure								
- Systolic (mmHg)	126.82 (18.06)	126.12 (15.99)	0.555	116.59 (13.39)	117.65 (13.14)	0.234	0.087	0.130
- Diastolic (mmHg)	84.12 (12.45)	82.65 (12.98)	0.085	78.29 (10.57)	78.18 (10.62)	0.808	0.202	0.467
Total cholesterol (mg/dL)	220.76 (37.14)	224.18 (37.00)	0.617	215.94 (54.82)	206.47 (58.69)	0.111	0.931	0.361
Triglycerides (mg/dL)	180.18 (94.8)	139.94 (99.56)	0.068	133.59 (54.2)	129.94 (90.66)	0.831	0.131	0.658
LDL (mg/dL)	135.76 (34.4)	144.06 (30.85)	0.248	144.29 (47.6)	136.41 (49.71)	0.020	0.610	0.454
HDL (mg/dL)	49.35(13.8)	52.47 (15.17)	0.392	43.35 (17.9)	43.65 (12.78)	0.443	0.241	0.030

$p < 0.05$ was considered as statistically significant

*Abbreviations: FBG= Fasting blood glucose, LDL=Low density lipoprotein, HDL=High density lipoprotein, BMI=Body mass index

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Table 8: Effects of Aphayathikun in combination with self-management intervention (SMI) on liver and kidney functions

Parameters	**Mean (SD); n=17**							
	Aphayathikun+ self-management intervention			**self-management intervention**			**p-value**	
	Baseline (A)	**At 4th week (B)**	**p-value (A vs. B)**	**Baseline (C)**	**At 4th week (D)**	**p-value (C vs. D)**	**A vs. C**	**B vs. D**
Albumin (gm/dL)	6.92 (9.55)	4.46 (0.15)	0.011	4.59 (0.15)	4.31 (0.30)	0.001	0.863	0.145
Total bilirubin (mg/dL)	0.72 (0.43)	0.70 (0.39)	0.690	1.42 (2.99)	0.81 (0.29)	0.421	0.418	0.233
Direct bilirubin (mg/dL)	0.18 (0.04)	0.23 (0.18)	0.062	1.23 (4.32)	0.24 (0.11)	0.112	0.284	0.152
AST (U/L)	29.47 (3.39)	30.00 (8.76)	0.975	30.71 (4.16)	25.29 (8.68)	0.011	0.349	0.112
ALT (U/L)	39.18 (13.12)	31.12 (13.24)	0.002	31.24 (11.25)	27.71 (9.41)	0.076	0.075	0.458
ALP (U/L)	80.18 (17.13)	75.53 (18.13)	0.078	78.41 (22.33)	67.35 (23.52)	0.021	0.667	0.163
Creatinine (mg/dL)	1.05 (0.21)	1.07 (0.34)	0.877	1.07 (0.21)	1.38 (0.20)	0.002	0.972	0.002

$p < 0.05$ was considered as statistically significant
*Abbreviations: AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, ALP=Alkaline phosphatase

Table 9: Behavioral scores and the World Health Organization Quality of life score of prediabetic patients with lower urinary tract symptoms

Parameters	**Mean (SD); n=17**							
	Aphayathikun+ self-management intervention			**self-management intervention**			**p-value**	
	Baseline (A)	**At 4th week (B)**	**p-value (A vs. B)**	**Baseline (C)**	**At 4th week (D)**	**p-value (C vs. D)**	**A vs. C**	**B vs. D**
Total score	100.82(11.92)	101.12(12.13)	0.663	95.00(11.04)	95.00(11.04)	1.000	0.6	0.302
- Physical health	27.18(3.94)	27.06(3.81)	0.651	25.06(2.77)	25.06(2.77)	1.000	0.149	0.854
- Psychological	25.12(3.40)	24.94(3.81)	0.414	21.47(3.10)	21.47(3.10)	1.000	0.079	0.090
- Social relationships	12.47(2.06)	12.47(2.40)	0.915	12.29(1.49)	12.29(1.49)	1.000	0.854	0.910
- Environment	25.12(3.40)	24.94(3.59)	0.414	29.47(4.37)	29.47(4.37)	1.000	0.002	0.006
Health behavior scores	68.65(14.16)	64.94(8.74)	0.100	70.47(12.24)	64.82(8.90)	0.330	0.370	0.150

This information aligns with previous studies suggesting that treating moderate LUTS patients (with a mean total IPSS of 14.8) by administering 500 mg of hydroethanolic pumpkin seed extract (equivalent to 10 g of pumpkin seeds) for 12 weeks can significantly impact their IPSS-QoL scores, as well as result in a highly significant reduction in nocturia. [38] Additionally, significant changes in total IPSS scores were observed during the first visit in the fourth week of this intervention. [21,38] The limitations of *in vivo* experiments on pumpkin seed extract suggest that its mechanism of action could be attributed to the inhibition of 5-α-reductase. [39]

The results obtained from this study align with the consumption of black soybean Seoritae, a well-established phytomedicine for LUTS and BPH/LUTS.[20] Several mechanisms, including antioxidant properties, have been proposed for Seoritae, which contains an abundance of isoflavones and anthocyanin. The beneficial effects of Seoritae extract have been reported in testosterone-induced BPH rat models, potentially preventing oxidative stress damage to prostate cells. [40] The AP decoction has demonstrated notable in vitro free radical scavenging properties and contains a significant amount of phenolics and flavonoids. In accordance with its herbal components, protective effects against oxidative stress-induced damage models have been documented for *Cyperus rotundus*,[41] *Phyllanthus emblica*,[42] *Terminalia chebula* [43], and *Vetiveria zizanioides*.[44] Although there is no available information on the activities of these medicinal plants on BPH models or their cytoprotective effects on prostate cells, ethyl gallate isolated from *Phyllanthus emblica* and a hydroalcoholic extract of *Cyperus rotundus* have demonstrated the ability to inhibit oxidative stress-mediated cell injuries in H2O2-treated PC12 and human neuroblastoma SH-SY5Y cells. [45,46] Additionally, the decoction obtained from *Terminalia chebula* has been shown to repress oxalate-induced cell injury in renal epithelial cells, [47] and the steam-distilled essential oil of *Vetiveria zizanioides* was found to reduce oxidative stress and lipid peroxidation in α-melanin-stimulating hormone-stimulated B16 murine melanoma cells. [48]

Previous studies support the role of inflammation in the progression of LUTS and the inhibitory effects of nonsteroidal anti-inflammatory drugs on the development or reduction of LUTS severity. [49,50] However, the AP decoction used in this study exhibited a relatively low *in vitro* anti-inflammatory effect on lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophage cells. In contrast, the essential oil of *Vetiveria zizanioides* was able to suppress inflammatory responses in LPS-induced inflammation in RAW 264.7 cells [51], while *Cyperus rotundus*,[52] *Phyllanthus emblica*,[53] and *Terminalia chebula*[54] demonstrated in vivo anti-inflammatory effects. It is worth noting that the ethanol extract of *Vetiveria zizanioides* root [27], the chloroform extract of *Terminalia chebula* fruits [25], quercetin isolated from *Phyllanthus emblica* methanol fruit extract [26], and the ethanol extract prepared from *Cyperus rotundus* rhizomes [28] have all shown anti-diabetic properties. However, consuming AP decoction for two weeks did not affect fasting blood glucose (FBG) and insulin levels.

In addition to some traditional Thai polyherbal formulations reported earlier [22,55,56], the standardized AP decoction used in this study was found to slow the progression of mild-to-moderate LUTS. However, some limitations of this study need to be addressed. An open-label design may introduce response bias, and the symptom severity measured using IPSS scales is susceptible to placebo effects. To gain further insights into the clinical efficacy of AP decoction, future studies should consider a longer duration of treatment, the inclusion of larger sample sizes encompassing moderate-to-severe LUTS, exploration of additional LUTS and BPH/LUTS-related parameters such as urinary flow rate and post-void residual volume, and investigation into the progression from prediabetes to diabetes.

Conclusion

This traditional polyherbal formulation, AP decoction, is effective and safe for managing mild-to-moderate LUTS in prediabetic patients with self-management interventions. It has been observed to improve the IPSS-QoL score and reduce the mean number of nocturia episodes. This effect may be attributed to AP decoction's high phenolic and flavonoid contents, which impart strong antioxidant properties. These antioxidants help protect against cellular damage induced by oxidative stress, particularly in hyperglycemic conditions. The standard extraction method for AP, as developed in this study based on traditional teachings, will be employed in future experiments to assess *in vitro* toxicity, sub-chronic toxicity, and further elucidate the *in vivo* protective mechanisms of this decoction under conditions of oxidative stress.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas 9th Edition. Diabetes Res Clin Pract. 2019; 157:107843.
2. Hostalek U. Global epidemiology of prediabetes - present and future perspectives. Clin Diabetes Endocrinol. 2019; 5:5.
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017; 128:40-50.
4. Priya G. Management of prediabetes. J Pak Med Assoc. 2018; 68(4):669-671.
5. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018; 14(2):88-98.
6. Tam CA, Helfand BT, Erickson BA. The relationship between diabetes, diabetes severity, diabetes biomarkers, and the presence of lower urinary tract symptoms: findings from the National Health and Nutrition Examination Survey. Urology. 2017; 105:141-148.
7. Park S, Ryu JM, Lee M. Quality of life in older adults with benign prostatic hyperplasia. Healthc. 2020; 8(2):158.
8. Kopp W. Diet-induced hyperinsulinemia as a key factor in the etiology of both benign prostatic hyperplasia and essential hypertension? Nutr Metab Insights. 2018; 11:1-11.
9. Calmasini FB, McCarthy CG, Wenceslau CF, Priviero FBM, Antunes E, Webb RC. Toll-like receptor 9 regulates metabolic profile and contributes to obesity-induced benign prostatic hyperplasia in mice. Pharmacol Rep. 2020; 72(1):179-187.
10. Ngai HY, Yuen KKS, Ng CM, Cheng CH, Chu SKP. Metabolic syndrome and benign prostatic hyperplasia: An update. Asian J. Urol. 2017; 4(3):164-173.
11. Lim KB. Epidemiology of clinical benign prostatic hyperplasia. Asian J. Urol. 2017; 4(3):148-151.
12. Sarkar PL, Lee W, Williams ED, Lubik AA, Stylianou N, Shokoohmand A, Lehman ML, Hollier BG, Gunter JH, Nelson CC. Insulin enhances migration and invasion in prostate cancer cells by up-regulation of FOXC2. Front. Endocrinol. 2019; 10:481-481.

13. Andersson KE. Oxidative stress and lower urinary tract symptoms: cause or consequence? BJU Int. 2019; 123(5):749-750.
14. Andersson KE. Oxidative stress and its possible relation to lower urinary tract functional pathology. BJU Int. 2018; 121(4):527-533.
15. Nomiya M, Andersson KE, Yamaguchi O. Chronic bladder ischemia and oxidative stress: new pharmacotherapeutic targets for lower urinary tract symptoms. Int J Urol. 2015; 22(1):40-46.
16. Dreikorn K. The role of phytotherapy in treating lower urinary tract symptoms and benign prostatic hyperplasia. World J Urol. 2002; 19(6):426-435.
17. Lowe FC, Fagelman E. Phytotherapy in the treatment of benign prostatic hyperplasia: an update. Urology. 1999; 53(4):671-678.
18. Fornara P, Madersbacher S, Vahlensieck W, Bracher F, Romics I, Kil P. Phytotherapy adds to the therapeutic armamentarium for the treatment of mild-to-moderate lower urinary tract symptoms in men. Urol. Int. 2020; 104(5-6):333-342.
19. Vela-Navarrete R, Alcaraz A, Rodríguez-Antolín A, Miñana López B, Fernández-Gómez JM, Angulo JC, Castro Díaz D, Romero-Otero J, Brenes FJ, Carballido J, Molero García JM, Fernández-Pro Ledesma A, Cózar Olmos JM, Manasanch Dalmau J, Subirana Cachinero I, Herdman M, Ficarra V. Efficacy and safety of a hexanic extract of Serenoa repens (Permixon(®)) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies. BJU Int. 2018; 122(6):1049-1065.
20. Bae WJ, Park HJ, Koo HC, Kim DR, Ha US, Kim KS, Kim SJ, Cho HJ, Hong SH, Lee JY, Hwang SY, Kim SW. The effect of Seoritae extract in men with mild to moderate lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Evid. Based Complementary Altern. Med. 2016; 2016:1-7.
21. Vahlensieck W, Theurer C, Pfitzer E, Patz B, Banik N, Engelmann U. Effects of pumpkin seed in men with lower urinary tract symptoms due to benign prostatic hyperplasia in the one-year, randomized, placebo-controlled GRANU Study. Urol. Int. 2015; 94(3):286-295.
22. Wetchakul P, Goon JA, Adekoya AE, Olatunji OJ, Ruangchuay S, Jaisamut P, Issuriya A, Kunworarath N, Limsuwan S, Chusri S. Traditional tonifying polyherbal infusion, Jatu-Phala-Tiga, exerts antioxidant activities and extends lifespan of *Caenorhabditis elegans*. BMC Complement Altern Med. 2019; 19(1):209.
23. Limsuwan S, Jarukitsakul S, Issuriya A, Chusri S, Joycharat N, Jaisamut P, Saising J, Jetwanna KW, Voravuthikunchai SP. Thai herbal formulation 'Ya-Pit-Samut-Noi': Its antibacterial activities, effects on bacterial virulence factors and *in vivo* acute toxicity. J Ethnopharmacol. 2020; 259:1-13.
24. Thunthivehthchakul V. Manchusaravichian. In: *Tumra Paetsart Sonkhrau Chabub Luang.* (3rd ed.). Bangkok: The WatPho Thai Traditional Medical School; 1957. p 62-69.
25. Nalamolu KR, Nammi S. Antidiabetic and renoprotective effects of the chloroform extract of *Terminalia chebula* Retz. seeds in streptozotocin-induced diabetic rats. BMC Complement Altern Med. 2006; 6:17.
26. Srinivasan P, Vijayakumar S, Kothandaraman S, Palani M. Anti-diabetic activity of quercetin extracted from *Phyllanthus emblica* L. fruit: In silico and *in vivo* approaches. J. Pharm. Anal. 2018; 8(2):109-118.
27. Karan SK, Pal D, Mishra SK. Anti-hyperglycaemic effect of *Vetiveria zizanioides* (L.) nash root extract in alloxan induced diabetic rats. Asian J Chem. 2013; 25(3):1555-1557.
28. Singh P, Khosa RL, Mishra G, Jha KK. Antidiabetic activity of ethanolic extract of *Cyperus rotundus* rhizomes in streptozotocin-induced diabetic mice. J. Pharm. Bioallied Sci. 2015; 7(4):289-292.
29. OECD. Test No. 425: Acute Oral Toxicity: Up-and-Down Procedure, OECD Guidelines for the Testing of Chemicals, Section 4, OECD
30. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007; 39(2):175-191.
31. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009; 41(4):1149-1160.
32. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001; 344(18):1343-1350.
33. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019; 202(3):558-563.
34. Hamvas A, Corradi G, Hegedüs M, Frang D. Experience with the Peponen capsule in the management of benign prostatic hyperplasia. Int Urol Nephrol. 1991; 23(1):51-55.
35. Murata K, Noguchi K, Kondo M, Onishi M, Watanabe N, Okamura K, Matsuda H. Inhibitory activities of Puerariae Flos against testosterone 5α-reductase and its hair growth promotion activities. J. Nat. Med. 2012; 66(1):158-165.
36. Kumar T, Chaiyasut C, Rungseevijitprapa W, Suttajit M. Screening of steroid 5α-reductase inhibitory activity and total phenolic content of Thai plants. J. Med. Plant Res. 2011; 5(7):1265-1271.
37. Ghosh A, Pakhira BP, Tripathy A, Ghosh D. Male contraceptive efficacy of poly herbal formulation, contracept-TM, composed of aqueous extracts of *Terminalia chebula* fruit and *Musa balbisiana* seed in rat. Pharm. Biol. 2017; 55(1):2035-2042.
38. Leibbrand M, Siefer S, Schön C, Perrinjaquet-Moccetti T, Kompek A, Csernich A, Bucar F, Kreuter MH. Effects of an oil-free hydroethanolic pumpkin seed extract on symptom frequency and severity in men with benign prostatic hyperplasia: A pilot study in humans. J. Med. Food. 2019; 22(6):551-559.
39. Fruhwirth GO, Hermetter A. Seeds and oil of the Styrian oil pumpkin: components and biological activities. Eur. J. Lipid Sci. Technol. 2007; 109:1128-1140.
40. Jang H, Bae W-J, Yuk S-M, Han D-S, Ha US, Hwang S-Y, Yoon S-H, Kim S-W, Han C-H. Seoritae extract reduces prostate weight and suppresses prostate cell proliferation in a rat model of benign prostate hyperplasia. Evid Based Complement Alternat Med. 2014; 2014:1-8.
41. Ardestani A, Yazdanparast R. *Cyperus rotundus* suppresses AGE formation and protein oxidation in a model of fructose-mediated protein glycoxidation. Int. J. Biol. Macromol. 2007; 41(5):572-578.
42. Rao TP, Sakaguchi N, Juneja LR, Wada E, Yokozawa T. Amla (*Emblica officinalis* Gaertn.) extracts reduce oxidative

stress in streptozotocin-induced diabetic rats. J. Med. Food. 2005; 8(3):362-368.
43. Suchalatha S, Srinivasulu C, Devi S. Antioxidant activity of ethanolic extract of *Terminalia chebula* fruit against isoproterenol-induced oxidative stress in rats. Indian J Biochem Biophys. 2005; 42(4):246-249.
44. Hewawasam RP, Jayatilaka KAPW, Mudduwa LKB, Pathirana C. Ameliorative effects of *Asparagus falcatus* L. and *Vetiveria zizanioides* (L.) Nash on carbon tetrachloride induced oxidative stress in mice. Indian J. Tradit. Know. 2017; 16(3): 417-424.
45. Zhang Y, Zhao L, Guo X, Li C, Li H, Lou H, Ren D. Chemical constituents from *Phyllanthus emblica* and the cytoprotective effects on H_2O_2-induced PC12 cell injuries. Arch Pharm Res. 2016; 39(9):1202-1211.
46. Kumar KH, Khanum F. Hydroalcoholic extract of *Cyperus rotundus* ameliorates H_2O_2-induced human neuronal cell damage via its anti-oxidative and anti-apoptotic machinery. Cell Mol Neurobiol. 2013; 33(1):5-17.
47. Tayal S, Duggal S, Bandyopadhyay P, Aggarwal A, Tandon S, Tandon C. Cytoprotective role of the aqueous extract of *Terminalia chebula* on renal epithelial cells. Int Braz J Urol. 2012; 38(2):204-214.
48. Peng H-Y, Lai C-C, Lin C-C, Chou S-T. Effect of *Vetiveria zizanioides* essential oil on melanogenesis in melanoma cells: downregulation of tyrosinase expression and suppression of oxidative stress. Sci. World J. 2014; 2014:1-10.
49. Gates MA, Hall SA, Chiu GR, Kupelian V, Fitzgerald MP, Link CL, McKinlay JB. Nonsteroidal antiinflammatory drug use and lower urinary tract symptoms: results from the Boston area community health survey. Am. J. Epidemiol. 2011; 173(9):1022-1031.
50. Samarinas M, Gacci M, de la Taille A, Gravas S. Prostatic inflammation: a potential treatment target for male LUTS due to benign prostatic obstruction. Prostate Cancer Prostatic Dis. 2018; 21(2):161-167.
51. Chou S-T, Lai C-P, Lin C-C, Shih Y. Study of the chemical composition, antioxidant activity and anti-inflammatory activity of essential oil from *Vetiveria zizanioides*. Food Chem. 2012; 134(1):262-268.
52. Soumaya K-J, Dhekra M, Fadwa C, Zied G, Ilef L, Kamel G, Leila C-G. Pharmacological, antioxidant, genotoxic studies and modulation of rat splenocyte functions by *Cyperus rotundus* extracts. BMC Complement Altern Med. 2013; 13:28.
53. Dang GK, Parekar RR, Kamat SK, Scindia AM, Rege NN. Antiinflammatory activity of *Phyllanthus emblica*, *Plumbago zeylanica* and *Cyperus rotundus* in acute models of inflammation. Phytother Res. 2011; 25(6):904-908.
54. Shaikh RU, Pund MM, Gacche RN. Evaluation of anti-inflammatory activity of selected medicinal plants used in Indian traditional medication system *in vitro* as well as *in vivo*. J. Tradit. Complement. Med. 2016; 6(4):355-361.
55. Chanthasri W, Jo Aan G, Singkonpong N, Sudkhaw T, Maneenoon K, Limsuwan S, Sanpinit S, Wetchakul P, Chusri, S. Antioxidant and lifespan-extending effects of a rejuvenating Thai traditional polyherbal remedy (Phy-Blica-O) in *Caenorhabditis elegans*. Trop J. Pharm Res. 2021; 5: 1554–1568.
56. Tuekaew J, Siriwatanametanon N, Wongkrajang Y, Temsiririrkkul R, Jantan I. Evaluation of the antioxidant activities of Ya-hom Intajak, a Thai herbal formulation, and its component plants. Trop J. Pharm Res. 2014; 13: 1477-1485.