Original Article

The Efficacy and Safety of *Andrographis paniculata* Extract for the Treatment of Acute Nonspecific Upper Respiratory Tract Infections: A Randomized Double Blind Placebo Controlled Trial

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Background: The efficacy and safety of *Andrographis paniculata* (Burn.f.) Wall. ex Nees in the treatment of acute nonspecific upper respiratory tract infection (NS-URI) are still less clear due to the diversity of herbal preparations, dosages, and few large clinical trials. The authors aimed to investigate the therapeutic efficacy and safety of the crude extract from *A. paniculata* in acute NS-URI.

Materials and Methods: Patients aged 18 to 60 years old from government hospitals, with acute NS-URI were enrolled between January 2018 and August 2019. Drug allocation was randomized in block of six. The crude extract of *A. paniculata* was packed in capsules containing 20 mg of andrographolide and given thrice daily for four days. The placebo capsules were physically identical. Ten tablets of paracetamol were also given as symptom-rescue drug. They were followed at days 4 to 7, and 14 to 30.

Results: Eight hundred sixty-two patients were enrolled between January 2018 and August 2019. Thirty-three patients withdrew from the study, therefore, 829 patients remained in the final analysis. Four hundred nineteen cases (50.5%) received the crude extract, and 410 cases (49.5%) received the placebo. The demographic data, clinical manifestation, and laboratory findings at the enrollment were similar in both groups. At the first follow-up, the rates of severity of each and combined symptoms decreased similarly, and almost all patients felt much better or recovered on day 7. Paracetamol was used by 205 (48.9%) and 185 (45.1%) patients in the experimental and control groups, respectively, and about three tablets taken in each group. Patient satisfaction rates were also similar in both groups. Adverse effects were mild and self-limited in 18 (4.3%) and 9 (2.2%) patients in the experimental and control groups, respectively.

Conclusion: The therapeutic efficacy of the crude extract or active ingredient from *A. paniculata* for acute NS-URI was not confirmed. Both groups showed similarly mild and few adverse drug reactions.

Trial registration: The present study protocol was registered at the Thai Clinical Trials Registry (TCTR 20170329002; date: March 26, 2017).

Keywords: *Andrographis paniculata*; Andrographolide; Acute nonspecific upper respiratory tract infections; Common cold; Pharyngitis; URI

Received 24 March 2021 | Revised 30 April 2021 | Accepted 11 May 2021

J Med Assoc Thai 2021;104(7):1204-13

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How to cite this article:

Leelarasamee A, Suankratay C, Hunnangkul S, Udompunturak S, Krittayaphong R, Poonsrisawat J, et al. The Efficacy and Safety of *Andrographis paniculata* Extract for the Treatment of Acute Nonspecific Upper Respiratory Tract Infections: A Randomized Double Blind Placebo Controlled Trial. J Med Assoc Thai 2021;104:1204-13.

doi.org/10.35755/jmedassocthai.2021.07.13037

Andrographis paniculata, (Burn.f.) Wall. ex Nees is one of the most commonly prescribed medicinal plants as traditional herbal medicine in Thailand and other Asian countries[1-4]. It has been claimed useful for the treatment or prevention of various diseases such as inhibition of replication of the HIV virus, prevention of common cold, and used as antimalarial, antidiarrheal, antibacterial, even suppression of various cancer cells through its anti-inflammatory properties of the andrographolide, which is the major labdane diterpenoid extracted from the herb[5-10]. The attempt to detect the antibacterial action of the herb among the bacterial pathogens of respiratory tract

infection had failed in one in vitro and in vivo study[11].

Up to now, the number of large clinical trials to show the therapeutic efficacy and safety of *A. paniculata* with known dosage of andrographolide for upper respiratory tract infection has been scarce though numerous case series and textbook of herbal medicine have claimed its usefulness in this regard[3,12]. It has been known that the compositions of active phytochemicals widely differ in terms of the part used, geography, season, and time of harvesting. Hence, the known dosage of the compositions especially the andrographolide in clinical uses are crucial for therapeutic and safety comparisons among the studies[13]. The authors were able to find 3 large clinical trials related to the treatment of upper and lower respiratory tract infections (RTIs) using this herbal medicine, all of which showed effectiveness in reducing symptoms of upper RTIs due to indirect antiviral properties of andrographolide in variety of viral infections[1,14-16]. However, a recent systematic review and meta-analysis including 33 randomized controlled trials (RCTs), with 7,175 patients with upper RTIs, revealed that the methodological quality of the trials was overall poor and *A. paniculata* used in the studies were commercial products, but seldom reported manufacturing or quality control details[12].

In Thailand, the efficacy and safety of *A. paniculata* (Burn.f.) Wall. ex Nees in the treatment of acute nonspecific upper respiratory tract infections (NS-URI) face similar dilemma. Hence, the authors aimed to verify the efficacy and safety of this herb grown locally in Thailand and with known amount of andrographolide in the compound using a well-designed, placebo-controlled trial. If the crude extract with known amount of andrographolide proved efficacious, it will be promoted as a first-line treatment for acute NS-URI among Thai population, and hopefully will reduce the use of antibiotic-based regimen for simple pharyngitis and common cold.

Materials and Methods

Study design

The authors conducted a multicenter, randomized, double blind placebo controlled trial to assess the efficacy and safety of a 4-day course of thrice daily dose of the herbal compound containing 60 mg of andrographolide to treat acute NS-URI in adult Thai patients.

The crude extract of *A. paniculata* were obtained by freeze-drying of solvent extract of the aerial stem and leaves, then grinding into powder and packed in capsules according to good manufacturing practice guidelines. The capsules were irradiated with gamma ray before use. The quality of the finished product and content of andrographolide per capsule were assured by the analyses of Thai Herbal Products Co. Ltd., and Faculty of Pharmacy, Mahidol University, Thailand (Analysis no. T 6002 Q 02, T 6003 Q 03, and report no. RH60 066 by MUPY-CAPQ). In brief, the mean weight of andrographolide in the compound was found to be 20.42 mg per capsule. Microbial cultures of the powder were negative for all bacteria, candida, and molds. Disintegration times of the capsule samples in the water were found to be 5.2 to 6.5 minutes from a normal range within 30 minutes. Arsenic and Cadmium concentrations were found to be at 0.01 ppm or less, and undetectable for lead. The qualities of placebo capsules were physically similar. Furthermore, they were also evaluated through similar quality assurance methods and found to be similar except no andrographolide was detected. The authors used the herbal compound containing known amount of the andrographolide with the aim to assess the "entourage effect" of the herb if they could enhance or synergize the healing effect when the full spectrum of the compounds that naturally occur in the *A. paniculata*, are consumed together. The known amount of andrographolide in the compound would serve as a "core ingredient" to compare the efficacy and safety of this herb in any future clinical study.

Inclusion and exclusion criteria

The inclusion criteria were adults aged 18 to 60 years old that attended the OPD clinics of government hospitals within 72 hours after the onset of URI symptoms, and were diagnosed as acute NS-URI, which had one or more symptoms such as fever, sore throat, nasal congestion, or dry infrequent cough, and had modified Centor score of 2 or less. The patients agreed to take the assigned medication and return for the first follow-up at days 4 to 7. They were able to receive a phone call for interview about the illness and symptoms in the second follow-up at days 14 to 30 and signed the informed consents. The patients were excluded if bacterial infection of the upper respiratory tract was clinically suspected, having high fever with a body temperature over 38.6°C, or with chills, positive rapid test for influenza viruses, warning symptoms of upper airway obstruction or pneumonia, antibiotics or other herbs intake within 48 hours, a history of allergy to *A. paniculata* or its extract and paracetamol, alcohol addiction or daily drink of alcohol or wine more than 40 grams, have a history of drug abuse or drug addicts in the past

year, pregnancy or breastfeeding, on chemotherapy, or recent organ transplantation.

When the eligibility criteria were met, the patients were physically examined by doctors and had their blood tests before they were assigned to either experimental (AP) group or control group by a predetermined group assignments using the block randomization method. A block size of six (A, B, C, D, E, and F) was used and the numbers were generated by the randomization online software. Blocks were then randomly chosen to determine the patients' assignment into the groups. Both groups received 12 capsules of study drug or placebo as treatment for four days. The sealed placebo capsule looked physically identical. Both groups received 10 tablets of paracetamol (500 mg per tablet) and were advised to use it only to relieve the remaining symptoms if they felt needed. They were informed to record the number of paracetamol taken for this purpose.

Patients also received self-assessment forms to assess subjectively the symptoms severity daily from day 1 to day 4 of enrolment using visual analog scale (VAS). Scores were recorded by making a handwritten mark on a score that represented a continuum among "0=no symptom" and "10=most severe symptom".

Follow-up period

At the second visit on days 4 to 7, which was the first follow-up, a second blood chemistry analysis was performed. Research assistants interviewed the patients about the results of treatment, adverse effect, and their satisfaction on the assigned medication. They were informed of the second follow-up by telephone call or home visit to interview the adverse reactions they may experience after day 7. The trial was stopped in August 2019 when the number of the enrolled participants reached the pre-specified target.

Statistical analysis

Descriptive statistics was used for statistical analysis. Demographic data, laboratory results, VAS score, adverse events were presented as number of case (n) and percent (%), mean and standard deviation (SD) or median and interquartile range (IQR). Clinical and safety outcomes between the two groups were compared using chi-square statistic and Mann-Whitney U test were used to compare the number of paracetamol tablets used in each group. The PASW Statistics software, version 18.0 (SPSS Inc., Chicago, IL, USA) was used throughout the statistical analyses. Comparison of seven symptoms, which included fever, sore throat, rhinorrhea, nasal congestion, cough severity, cough frequency, and headache, and combined symptom severity using VAS scores assessed by the patients on each day were analyzed using two-way repeated measures ANOVA.

Sample size was calculated using nQuery software 6.0 (Statistical Solutions, Ireland). The authors based sample size calculations on the effect size by using the difference of the VAS of combined symptoms severity (rhinorrhea, nasal mucosal edema, injected pharynx, injected tonsil, hoarseness of voice) from day 4 and day 1 between the two groups. The effect size was estimated to be 0.20, type I error of 0.05, and power of 0.8. The sample size was determined to be 394 patients per group. Assuming a dropout rate of 10% and adjustment for interim analysis, the sample size yielded 510 patients per group.

The analysis was initially masked (hence Drug A and B groups), and type of treatment was made unknown to participants, care providers, investigators, and outcomes assessors. The principal investigator (Leelarasamee A) asked the statisticians to combine the data from the six groups into Drug group A (A, C, and F labels) and Drug group B (B, D, and E labels) and the statistician analyzed and presented the data of both groups. All had to agree on the result of the analysis before Leelarasamee A revealed that the Drug group B was the AP group (experimental group) received the thrice daily dose of 60 mg of andrographolide for four days.

The trial received permission from the Ministry of Public Health IRB (no. 03-2560) on June 2, 2017 and was registered at the Thai Clinical Trials Registry (TCTR) as TCTR 20170329002.

Data of all cases in the analyses are available on request.

Results

Between January 2018 and August 2019, 874 cases were assessed for eligibility and 12 cases did not meet the inclusion criteria, then 862 cases were randomized into AP group (n=434 cases) and control group (n=428 cases). Fifteen and eighteen cases were excluded or lost follow-up in the AP and control groups, respectively. Among these, one case in the AP group developed frequent, dry cough (bronchitis), two cases in each group developed skin rash, and the rest were unable to contact. Hence, 419 and 410 cases were left in the AP and control groups, respectively, for final analyses (Figure 1).

The numbers of participants enrolled in each hospital are shown in Table 1. Those who developed

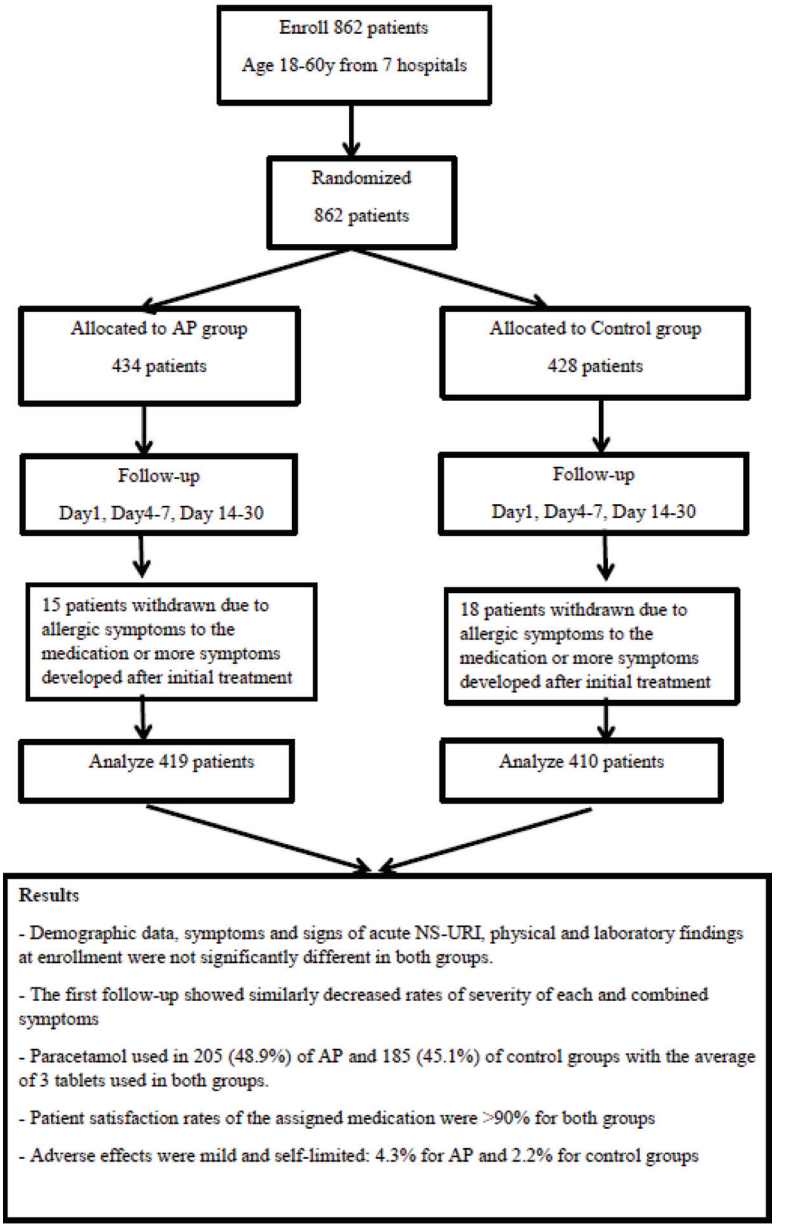

Figure 1. Flow diagram of the RCT study process.

mild adverse events and continued through the study period were found in 18 and 10 cases in the AP and control groups, respectively. The demographic characteristics, symptoms, and signs of acute NS-URI, physical, and laboratory findings of the trial participants at baseline of both groups were similar as shown in Table 2. The diagnoses were reached as common cold in 236 (56.3%) versus 238 (58%) cases, acute nasopharyngitis in 139 (33.2) versus 125 (30.5) cases, and acute rhinitis in 44 (10.5%) versus 47 (11.5%). Overall, the characteristics, clinical, and laboratory findings, diagnoses were well balanced between the two groups. Comparison of symptoms severity as subjectively recorded by the patients in Table 3 showed initial higher scores for each symptom and gradually decreased each day until all the scores were less than 2 or 1 on day 4. The combined symptoms severity scores decreased similarly in both groups and were not statistically different (p=0.883). Most patients felt much better or recovered on day 7. All relevant symptoms and signs interviewed and examined by nurses and physicians at day 1 and days

Table 1. Number of cases by enrollment, follow-up and occurrence of adverse drug events in each hospital between January 2018 and August 2019

Government hospital[1]	Enrollment (n)	Case withdrawal (n)	Complete follow-up (n)	Adverse drug events (n)
SPL	242	15	227	20
SPR	227	8	219	5
PNK	200	7	193	2
SCP	86	0	86	1
PPK	72	3	69	0
STN	20	0	20	0
CLB	15	0	15	0
Total	862	33	829	28

SPL=Somdetphraphutthalertla Hospital; SPR=Sawan Pracharak Hospital; PNK=Pranangklao Hospital; SPS=Sawangdandin Crown Prince Hospital; PPK=Prapokklao Hospital; STN=Surat Thani Hospital; CLP=Chulabhorn Hospital; (n)=number of cases

[1] Acronyms of each government hospital participated in the trial

Table 2. Demographic characteristics, clinical findings, and laboratory data of the two groups at day 1 (total n=829)

Demographic data	AP group[1] (n=419); mean±SD	Control group (n=410); mean±SD
Age (years)	38.9±11.3	38.3±11.4
Height (cm)	160.8±8.1	160.4±7.6
Weight (kg)	64.6±14.4	62.2±13.0
Systolic BP (mmHg)	122.9±15.9	121.9±15.4
Diastolic BP (mmHg)	76.3±11.3	75.4±10.9
Pulse rate (beats per minute)	85.9±13.7	85.2±13.6
Respiratory rate (breath per minute)	18.3±2.0	18.4±1.9
Temperature (°C)	36.8±0.5	36.8±1.0
Female; n (%)	315 (75.2)	315 (76.8)
Concurrent diseases; n (%)	97 (23.2)	94 (22.9)
Hypertension	44 (10.5)	28 (6.8)
Diabetes mellitus	18 (4.3)	11 (2.7)
Cancer	5 (1.2)	1 (0.2)
Others	60 (38.0)	73 (43.5)
History of concurrent drug use; n (%)	81 (19.3)	76 (18.5)
History of drug allergy; n (%)	25 (6.0)	27 (6.6)
Symptoms[2]; n (%)		
Fever or chill	81 (19.3)	84 (20.5)
Sore throat	365 (87.1)	359 (87.6)
Cough	347 (82.8)	347 (84.6)
Rhinorrhea	284 (67.8)	296 (72.2)
Nasal congestion	250 (59.7)	279 (68.2)
Sneezing	230 (54.9)	224 (54.6)
Hoarseness of voice	135 (32.2)	129 (31.5)

Demographic data	AP group[1] (n=419); mean±SD	Control group (n=410); mean±SD
Signs[2]; n (%)		
Rhinorrhea	257 (61.3)	274 (66.8)
Injected pharynx	244 (58.2)	252 (61.5)
Nasal mucosal edema	196 (46.8)	220 (53.7)
Injected tonsil	61 (14.3)	68 (16.6)
Hoarseness of voice	52 (12.4)	50 (12.2)
Laboratory parameters; n (%)		
Hematocrit		
• Normal range	418 (99.8)	410 (100)
WBC (over 2 x UNL)	0 (0)	0 (0)
% Lymphocyte (within normal range)	415 (99.0)	405 (98.8)
Platelets count (lower than 2 x LNL)	1 (0.2)	1 (0.2)
AST		
• Normal	414 (98.8)	405 (98.8)
• Over 2 x UNL	5 (1.2)	5 (1.2)
ALT		
• Normal	408 (97.4)	405 (98.8)
• Over 2 x UNL	11 (2.6)	5 (1.2)
BUN over 2 x UNL	0 (0.0)	2 (0.5)
Creatinine over 2 x UNL	2 (0.5)	3 (0.7)

BP=blood pressure; WBC=white blood cell; UNL=upper normal limit values; LNL=lower normal limit values; AST=aspartate aminotransferase; ALT=alanine aminotransferase; BUN=blood urea nitrogen; SD=standard deviation

[1] AP group represented the patients who took 20.4 mg of andrographolide per capsule three times a day for 4 days

[2] Symptoms interviewed by nurse, signs examined by doctor, VAS of symptom severity scoring was evaluated by the patients

Table 3. Comparison of symptom severity evaluated on each day by the patients using VAS

Symptoms to be given VAS score	AP group[1] (n=419)				Control group (n=410)			
	VAS score; mean±SD				VAS score; mean±SD			
	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
Fever	2.2±2.3	1.7±2.1	1.1±1.7	0.7±1.4	2.2±2.4	1.7±2.1	1.0±1.6	0.6±1.3
Sore throat	3.8±2.4	2.8±2.2	2.0±2.0	1.4±1.8	3.8±2.5	2.8±2.2	1.9±2.0	1.3±1.8
Cough severity	3.5±2.4	2.9±2.3	2.2±2.2	1.7±1.9	3.4±2.5	2.7±2.3	2.1±2.2	1.6±2.1
Rhinorrhea	3.0±2.6	2.5±2.4	1.9±2.2	1.5±2.1	3.2±2.8	2.6±2.5	1.8±2.1	1.4±1.9
Nasal congestion	2.9±2.6	2.4±2.3	1.8±2.0	1.3±1.9	3.2±2.6	2.4±2.2	1.8±2.0	1.3±1.8
Cough frequency	3.0±2.2	2.6±2.2	2.1±2.1	1.5±1.9	3.1±2.4	2.5±2.2	2.1±2.2	1.5±2.0
Headache	2.7±2.5	2.0±2.1	1.5±2.0	0.9±1.8	2.9±2.5	2.2±2.3	1.3±1.8	0.8±1.4
Combined symptoms severity[2]	4.2±2.1	3.3±2.1	2.5±2.1	1.8±1.9	4.4±2.1	3.3±2.2	2.4±2.0	1.7±1.9

VAS=visual analog scale; SD=standard deviation

VAS scores ranged from 0 to 10; 0=no symptom; 10=most severe

[1] AP group represented the patients who took 20.42 mg of andrographolide per capsule three times a day for 4 days

[2] p-value (between AP and control groups) was 0.883 by the two-way repeated measures ANOVA

Table 4. Symptoms and signs presented on day 1 and disappeared on day 4 to 7 by interview and physical exam in each group

	AP group (n=419); n (%)	Control group (n=410); n (%)	p-value
Interviewed by nurse assistants			
Fever on day 1	84 (20.0)	81 (19.3)	0.084
• Disappeared on day 4 to 7	75 (89.3)	78 (96.3)	
Sore throat on day 1	359 (85.7)	365 (87.1)	0.479
• Disappeared on day 4 to 7	231 (64.3)	244 (66.8)	
Cough on day 1	347 (82.8)	347 (82.8)	0.543
• Disappeared on day 4 to 7	157 (45.2)	165 (47.5)	
Running nose on day 1	296 (70.6)	284 (67.8)	0.181
• Disappeared on day 4 to 7	161 (54.4)	170 (59.9)	
Nasal congestion on day 1	279 (66.6)	250 (59.7)	0.269
• Disappeared on day 4 to 7	187 (67.0)	156 (62.4)	
Sneezing on day 1	224 (53.5)	230 (54.9)	0.450
• Disappeared on day 4 to 7	164 (73.2)	161 (70.0)	
Hoarseness of voice on day 1	129 (30.8)	135 (32.2)	0.766
• Disappeared on day 4 to 7	76 (58.9)	82 (60.7)	
Physical exam by doctors			
Nasal discharge on day 1	274 (65.4)	257 (61.3)	0.064
• Disappeared on day 4 to 7	171(62.4)	180 (70.0)	
Pharyngitis on day 1	252 (60.1)	244 (58.2)	0.547
• Disappeared on day 4 to 7	181 (71.8)	181 (74.2)	
Erythema of nasal mucosa on day 1	220 (52.5)	196 (46.8)	0.001
• Disappeared on day 4 to 7	135 (61.4)	166 (84.7)	
Injected tonsil on day 1	68 (16.2)	61 (14.6)	0.192
• Disappeared on day 4 to 7	62 (91.2)	51 (83.6)	
Hoarseness of voice on day 1	50 (11.9)	52 (12.4)	0.413
• Disappeared on day 4 to 7	40 (80.0)	38 (73.1)	

AP group were the patients who took the crude extract of andrographolide

Table 5. Patients' satisfaction and reuse of the assigned medication for the acute NS-URI in each group surveyed at day 7

	AP group; n (%)	Control group; n (%)	p-value
Satisfaction scale			
Very satisfied	53 (12.8)	56 (13.9)	0.178
More than satisfied	206 (49.8)	208 (51.6)	
Satisfied	129 (31.2)	115 (28.5)	
Partly satisfied	11 (2.7)	18 (4.5)	
Not at all satisfied	15 (3.6)	6 (1.5)	
Total[1]	414 (100)	403 (100)	
Patients' answers to take the assigned medication for the next episode of URI			
No	34 (8.2)	30 (7.4)	0.895
Yes	265 (64.0)	263 (65.3)	
No response[2]	115 (27.8)	110 (27.3)	
Total[1]	414 (100)	403 (100)	

URI=upper respiratory tract infection

[1] Only patients who were willing to provide the answers

[2] The patients did not give the answer

4 to 7 were also not statistically different. Table 4 also reveals the similar recovery rates from each symptom and sign assessed on day 1 and day 4 to 7 by research nurses and physicians. The numbers of patients taking paracetamol tablet were 205(48.9%) and 185 (45.1%) and the median (IQR) of numbers of the tablet taken during the study period were each 3 (3, 6) in the AP and control groups respectively without statistical difference. Table 5 shows patient satisfaction rates with the assigned medicine, which were also not clinically or statistically different. Only

15 (3.6%) and 6 (1.5%) cases were not satisfied with the assigned medicine in both groups and the 265 (64%) and 263 (65.3%) patients from both groups would re-take the assigned medicine if they felt sick with the same illness. Finally, the adverse effects were reported similarly as mild and self-limited in 18 (4.3%) and 9 (2.2%) cases in the AP and control groups, respectively.

Discussion

The superior efficacy of crude extract of *A. paniculata*, equivalent to 60 mg of andrographolide per day, for 4-day treatment of acute NS-URI over the placebo was not demonstrated in the present study. In fact, there were various symptoms and signs of acute NS-URI to be assessed for efficacy, but they all showed no difference between the groups. The resolution of fever, sore throat, cough, running nose, nasal congestion, sneezing, and hoarseness of voice on day 1 and day 4 interviewed by nurses were not statistically different. The examination of nasal discharge, pharyngitis, erythema of nasal mucosa, injected tonsil, and hoarseness of voice examined on day 1 and day 4 by physicians were also not statistically different. The non-superiority of *A. paniculata* for the treatment of acute NS-URI was also substantiated by the VAS, which was used to assess daily the symptoms and signs severities before and after treatment by the patients. The result of VAS also showed no statistical difference between the two arms during the 4-day treatment. In addition, the numbers of patients who took paracetamol, numbers of paracetamol taken, and patients' satisfaction all of them were also similar in both groups. The adverse effects between the two arms were also not significantly different.

The present study results were different from the previous randomized double-blind placebo-controlled studies. A study by Saxena et al demonstrated the effectiveness of an extract of *A. paniculata* (KalmCold™) in reducing symptoms of NS-URI[17]. The difference was probably due to different treatment dosage, duration, and nature of the herb or disease spectrum in the enrolled patients, or chance and bias in the design of the comparator study and the negative effect in this study true effect. The extract of *A. paniculata* developed by different companies may give different active ingredients, purity, excipients, and results in different efficacy. Different ethnicity, such as Thai and India in the present study, and Saxena's studies may account for the different response. However, the previous studies and meta-analyses showed the conflicting results either with the presence or absence of the efficacy of crude extract of *A. paniculata* on NS-URI. The severity of patients in the present study may be too mild to demonstrate the different efficacy since only 20 percent had fever with a mean temperature of only 36.8°C. The authors chose acute NS-URI because it is mostly caused by viruses requiring no antibiotic treatment and occurs first before becoming the lower respiratory tract infection. The authors plan to perform the study that includes patients with more severe acute NS-URI as well as lower respiratory tract symptoms. In addition, the specific etiologic virus of acute NS-URI will be determined since different virus will probably be differently responsive to *A. paniculata*. The time-kill kinetic study of viral clearance in oropharynx should be studied as well. Due to high quality control of the finish product of andrographolide capsule in each lot, the variation in amount of active ingredient could not be accounted for the failure to demonstrate efficacy in the present study. Since the herbal medicine is quite safe, it is possible to increase the dosage to 100 or 120 mg per day. The treatment with other forms of *A. paniculata* extract such as chewing formulation will be studied as well, since there should be increased contact time of the herb with the virus residing in the oropharynx, exerting the entourage effect and instant antimicrobial activity in the infected oral and pharynx.

There are some limitations in the present study due to enrolled less severely ill acute NS-URI patients, and pediatric patients were excluded, hence, resulting in limited generalizability and applying only in mild cases. The return rate of symptom diaries for assessment of VAS was 95%, higher than those reported from the previous studies, which had 75% to 80% rates[1,15-17]. The present study might be underpowered to determine a modest effect on the primary outcome, if the difference of effect size from both groups is less than 0.2 by the difference of mean VAS of combined symptom score from baseline day 1 and days 4 to 7 between the experimental and control arms. A larger study may have identified the statistically significant difference between the two arms but may have no clinical significance. Lastly, the pharmacokinetic and pharmacodynamic studies were not evaluated in the studied patients, hence, the authors cannot exclude the low therapeutic serum levels of the andrographolide after oral intake. The present study result may support a recent review suggesting that further modification of the chemical structure and optimization of delivery system are needed to enhance the pharmacological activity and

increase the therapeutic index of andrographolide and its derivatives in various clinical settings[18].

The present study has many strengths. To the authors' knowledge, this is the first and largest study that is a multicenter randomized double blind placebo controlled study in Thailand. All patients were Thai and attended the primary care setting in various parts of Thailand. The adherence with medication was 96.2% with 829 of 862 patients, and the primary outcome was obtained from 829 patients, which was very high. The patients' baseline characteristics allocated to both groups were well balanced. The herb was planted, prepared for clinical use, and packed into the capsules in Thailand and the dosage of andrographolide in each capsule was made known. Unfortunately, it may be a first local clinical trial with large enrollment that cannot confirm the substantial benefits of the crude extract or active ingredient of *A. paniculata* intake for any therapeutic efficacy in acute NS-URI. The investigators did not observe any increase adverse reaction either.

Conclusion

The investigators were unable to demonstrate the therapeutic efficacy of *A. paniculata* (Burn.f.) Wall. ex Nees in the treatment of acute NS-URI over the placebo effect. The adverse drug reactions were almost similar in both groups. Further study to show the effectiveness or efficacy of *A. paniculata* (Burn.f.) Wall. ex Nees in the treatment of acute NS-URI may not be worthwhile unless the study design is modified to compare the speedy recovery of each symptom of acute NS-URI or the daily eradication rates of the respiratory viruses and may need to standardize the dosing regimen.

Acknowledgements

The authors highly appreciated the collaboration and contribution from the following physicians, nurse, pharmacist and research assistants at the Ministry of Public Health and many hospitals as follow: Marut Jirasetsiri MD, Pramote Stienrut MD, Anchalee Chutaputti PharmD, PhD, Duangkaew Panyaphu BSc, MPharm, PhD, Monthaka Teerachaisakul PharmD, PhD, Nitapha Inchai MS (Pharmaceutical Sciences), Pratchayanan Poonniam BTM, Thai Traditional Medicine Research Institute, Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, Thailand; Renugar Panichjaroennam RN, Aujchara Jitsuk BATM (Applied Thai Traditional Medicine), Kewalee Silapacharanan BATM (Applied Thai Traditional Medicine), Sawan Pracharak Hospital, Thailand; Suwit Mahaviriyo BSc (Pharmacy), Ratchanee Longsaward APN, Somdetphraphutthalertla Hospital, Thailand; Teeranuch Chala-em RN, Wadsana Udomsriyothin RN, Sunantha Lohpongpaibul BSc (Pharmacy), Pranangklao Hospital, Thailand; Rossamalin Intayuang MSc (Pharm Clinical Pharmacy), Nattida Takong RN, Cert. Critical Care Nursing, Sawang Daen Din Crown Prince Hospital, Thailand; Wasana Sookpaisal MNS (Nursing Administration), Sirimon Boonkoy BSc (Oriental Medicine), Phitchapha Homa MSc (Oriental Medicine), Prapokklao Hospital, Thailand; Taweegrit Siripongboonsitti MD, Dip. Thai Board Intern Med, Kriangkrai Tawinprai MD, Dip. Thai Board Intern Med, Chulabhorn Hospital, Thailand; Chawanee Chayakul MD, Dip. Thai Board Intern Med, Nattha Maunsuta MA, Suratthani Hospital, Thailand; Jirapa Panthusait MD, Dip. Thai Board Fam Med, Supaksorn Keawking BSc (Oriental Medicine), Sudatip Charatpinit RN, Udon Thani Hospital, Thailand.

In addition, the investigators are grateful to Miss Wannaporn Loysawadi, Mr. Thatchai Petdeekai, the Royal College of Physicians of Thailand for data management, communication among researchers, and secretarial services and the officers of the Medical Association of Thailand for the secretarial services.

Ethics approval and consent to participate

The present study protocol was approved by the Institutional Review Board (IRB) of the Ministry of Public Health, Thailand (document reference no. 03-2560) on June 2, 2017. The Thai names of the Ethics committee in the meeting that approved the study were attached. The English names of the Ethics committee were separately attached and the recognition of the Ethics committee by the SIDCER was also attached.

Availability of data and materials

The data in the analyses were attached in an Excel file.

Authors' contributions

Leelarasamee A Conceptualization, Methodology, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition. Suankratay C Conceptualization, Methodology, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing,

Supervision, Project administration. Hunnangkul S Conceptualization, Methodology, Software, Validation, Formal analysis, Data Curation, Writing - Review & Editing, Supervision, Project administration. Udompunturak S Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing, Supervision. Krittayaphong R Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision. Poonsrisawat J Conceptualization, Methodology, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Project administration, Funding acquisition. Wongsakorn N Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Local Project administration. Ittipanitphong C Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Local Project administration. Sirimai S Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Local Project administration. Prakairoongthong P Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Local Project administration. Rattanamaneekorn S Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Local Project administration. Chaicharoenpong K Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Local Project administration. All authors have approved the final version of the present study article submitted for the publication.

Funding disclosure

The present study was funded by the Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, Nonthaburi, Thailand, and the Medical Association of Thailand.

However, the study was performed without any involvement from the department or any member of the department committee member, Ministry of Public Health or from the Medical Association of Thailand. The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be constructed as potential conflict of interest. The authors also wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Conflicts of interest

The authors declare that they have no conflict of interests

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