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Symptomatic treatment of acute tonsillopharyngitis patients with a combination of *Nigella sativa* and *Phyllanthus niruri* extract

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Key words
Nigella sativa –
Phyllanthus niruri –
acute tonsillopharyngitis

Abstract. Acute tonsillopharyngitis is characterized by tonsil or pharyngeal inflammation and mostly is a virus in origin; thus, treatment that covers both the inflammation and inadequate immune response against the pathogenic organism is needed. NSPN extract containing *Nigella sativa* and *Phyllanthus niruri* extracts has both antiinflammatory and immunomodulatory effects. A comparative, parallel, randomized, double-blind, placebo-controlled study with a treatment period of 7 days was conducted to examine clinical effectiveness of *Nigella sativa* and *Phyllanthus niruri* extract (NSPN extract). Of 200 enrolled patients, 186 patients completed the study, 12 patients withdrew and 2 patients were principally screened failure but inadvertently included. NSPN capsules, each containing 360 mg *Nigella sativa* and 50 mg *Phyllanthus niruri* extracts, were orally administered 3 times 1 capsule daily for 7 days. At Hour 5 or 6 of the first dosing of study medication, the sore throat assessed as swallowing pain and difficulty, was markedly alleviated in the NSPN group. In line with the significant alleviation of pain, from Days 0 to 2 of treatment, subjects in the NSPN group also needed significantly less escape "analgesic" therapy (paracetamol tablets) than those in the placebo group. At the end of treatment (Day 7), a significantly greater proportion of patients in the NSPN group than in the placebo group had their sore throat completely relieved. NSPN extract was also found to be safe and well tolerated in acute tonsillopharyngitis patients. This study proved significant benefits of NSPN extract in the treatment of acute tonsillopharyngitis as compared to placebo.

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Introduction

Tonsillopharyngitis is a respiratory tract infection causing inflammation to the pharynx. The predominant symptom is a sore throat. The infection, with subsequent inflammation, may be localized to the pharynx alone or it may include several other locations as well. The most common etiological agents are different viruses and Group A-β-hemolytic Streptococcus (GABHS) [Gunarson et al. 2001].

The most common cause of tonsillopharyngitis is viral in origin, hence, no antibiotic is usually needed but for treating tonsillopharyngitis due to bacteria. Antibiotics and immune system act synergistically to eradicate bacteria such as Streptococcus pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae and Mycoplasma pneumoniae. If left untreated or inadequately treated, streptococcal pharyngitis (STP) may lead to rheumatic fever or glomerulonephritis [Erlichman et al. 2000]. Treatment failure or recurrent infection is a common problem in acute tonsillopharyngitis [Gunarson et al. 2001].

Current treatment for tonsillopharyngitis is both symptomatic and causative, i.e. antibiotic treatment [Galioto et al. 1995]. Symptomatic treatment alone was usually needed for viral tonsillopharyngitis as for nonbacterial tonsillopharyngitis, antibiotics definitely do not play a role. Whereas regarding antivirals, there are 4 available antivirals to date, but their use is limited only to influenza A and B infections.

As previously described, acute tonsillopharyngitis is characterized by tonsil or pharyngeal inflammation and mostly is a virus in origin, thus, treatment that covers both inflammation and inadequate immune response against pathogenic organism is needed in acute tonsillopharyngitis. NSPN extract con-

taining *Nigella sativa* and *Phyllanthus niruri* extracts has both antiinflammatory and immunomodulatory effects. The antiinflammatory effect has preclinically and empirically been proven attributable to *Nigella sativa* extract [Abdel Fattah et al. 2000, Al Ghamdi 2001, El Dakhakny et al. 2002, Houghton et al. 1995, Randhawa and Al Ghamdi 2002], whereas the immunomodulatory effect has widely been known from preclinical and clinical data as a predominant activity of *Phyllanthus niruri* extract [Tjandrawinata et al. 2005]. A combination of both extracts is logically assumed to have an additive or synergistic effect and will be beneficial in inflammation-infection treatment.

Methodology

Study population

Adult male or female patients with clinically diagnosed acute tonsillopharyngitis (i.e. the presence of erythematous and/or exudative tonsils with any one of the following symptoms: sore throat, dysphagia, odynophagia, fever and accompanying tender, enlarged cervical lymph nodes) were eligible for the recruitment if they had at least moderately severe throat pain. Patients were required to be 18 – 60 years old with sore throat pain intensity scale/STPIS (moderately severe sore throat) score greater than 50 mm on a 100 mm VAS in which the end-points were no pain (0 mm) and very intense pain (100 mm), and with a score of 4 or more on the 10-point tonsillopharyngitis scale/TPS (obvious diagnosis of tonsillopharyngitis). These symptoms also had to be evident within ≤ 48 hours at screening.

Exclusion criteria included use of immunosuppressant within 2 weeks previous to the study, local treatment such as anesthetic spray within 2 hours and/or antiinflammatory treatment within 3 days prior to the study, under medication or other disease condition such as diabetes, severe hypertension that could interfere with the study, known or suspected hypersensitivity to the drugs, had mouth breathing as a result of severe nasal congestion (nasal congestion assessment/NCA).

Women of child bearing potential were withdrawn from the study if they were pregnant, nursing, or planning a pregnancy during the study. Other withdrawal criteria included the use of systemic treatment with any other antiinflammatory or immunomodulation substance, any severe adverse event, and participation in any other clinical trial during the course of the study.

The present study was approved by the appropriate institutional review boards, and all clinical investigations were conducted in accordance with the Declaration of Helsinki Principles and Good Clinical Practice. Written informed consent was obtained from all patients.

Randomization and blinding procedures

Enrolled patients were assigned to receive study treatment based on random numbers provided by the sponsor. In this double-blind and placebo-controlled study, blinding code was prepared based on randomization using block randomization methods prepared by the sponsor.

Study medication

Patients were randomized in a 1 : 1 ratio to receive NSPN extract capsule (PT. Dexa Medica, Palembang, Indonesia), or placebo capsule. Both the investigational drugs and placebos in this study were similar in appearance, smell and taste and, thus, disabling deblinding by smell or taste.

Extract characterization

Description: black to brown thick liquid, slightly aromatic odor, bitter.

Microbial limit test:

- total microbial counts ≤ 10,000 cfu/g
- molds count ≤ 10,000 cfu/g
- Pseudomonas aeruginosa negative
- E. coli negative
- Staphylococcus aureus negative
- Salmonella negative

Chemical test

Preservatives:

- a. Nipagin < 0.1%
- b. Nipasol < 0.1%

– c. Sodium benzoate	< 0.1%
– d. Sorbic acid	< 0.1%
Chemical substance	
– a. Antalgin	negative
– b. Dexamethasone	negative
– c. Paracetamol	negative
Phytochemical test:	
– Quercetin identification	positive
– Thymoquinone identification	positive

Treatment regimen

Either NSPN or placebo capsules were orally administered at the same dosage, i.e. 3 times 1 capsule daily for a 7-day treatment period.

Efficacy measures

Clinical evaluations were made at baseline (Day 0), Day 2 and Day 7. Primary efficacy assessment was mean or median time to resolution of sore throat. Mean or median time to resolution of sore throat was assessed as the lengths of time from the start of treatment until the first time the sore throat condition resolved simultaneously and remained so for 1 day. Secondary efficacy assessments were pain intensity on swallowing, difficulty in swallowing, global pain relief according to visual analogue scales and categorical term; time to overall alleviation of illness or other symptoms; number and frequency of escape treatment needed, and frequency (percentages) of patients who have taken antibiotics.

A sore throat pain intensity scale (STPIS) and tonsillopharyngitis score (TPS) were used to assess the severity of sore throat. STPIS was assessed by measuring the pain intensity on 100 mm visual analogue scales (VAS). TPS is an index that takes account as a sum of the intensity ratings (on a 0- to 2-point scale) of each five clinical features of tonsillopharyngitis (oral temperature, oropharyngeal coloration, oropharyngeal erythema, cervical adenopathy and cervical adenitis) [Bijur et al. 2001, Boureau et al. 1999, Schachtel et al. 1984a,b, 1988].

A continuous 100 mm VAS with end-points of no pain to very intense pain (change in pain scale/CPS) was used to evaluate the pain intensity on swallowing and a continuous 100 mm VAS with end-points of no difficulty to very great difficulty (change in difficulty in swallowing scale/CDSS) was used to evaluate the difficulty in swallowing. These resolutions of sore throat self-evaluations by patients were done at hourly intervals for 6 hours after the first dose of the treatment.

Relief of sore throat pain using a numeric scale (end-points 0% relief to 100% relief, in blocks of 10%, measured as maximum reduction in pain scale/MRPS) and of difficulty in swallowing using a numeric scale (end-points 0% relief to 100% relief, in blocks of 10%, measured as maximum reduction in difficulty in swallowing scale/MRDS) were evaluated by the patients at Day 2. A sore throat relief rating/STRR as a 5-point grading of relief (no relief, some relief, moderate relief, considerable relief, complete relief) was also self-evaluated by patients at Days 2 and 7 to describe the relief of sore throat compared to the condition before taking medication.

Global evaluation of treatment was assessed using a 4-point scale (none, moderate, good, excellent) at Days 2 and 7 by investigators (iGETE) and patients (pGETE). Outcome measurements used in this study are ones frequently used by investigators of the study on daily clinical practice. Moreover, these are validated measurements for sore throat pain evaluation which has been proven by several clinical studies [Bijur et al. 2001, Boureau et al. 1999, Schachtel et al. 1984, 1988].

Antibiotic administration was withheld up to Day 2, and patient's condition was re-examined and judged clinically by investigators at Day 2 whether antibiotic prescription was needed. The number of escape therapy taken by the patient was counted.

Safety measures

Patients were monitored for signs and symptoms of adverse events at every post-baseline study visit.

Statistical analysis

The hypothesis of interest in this study was whether the mean time of sore throat resolution by NSPN extract is shorter than that of

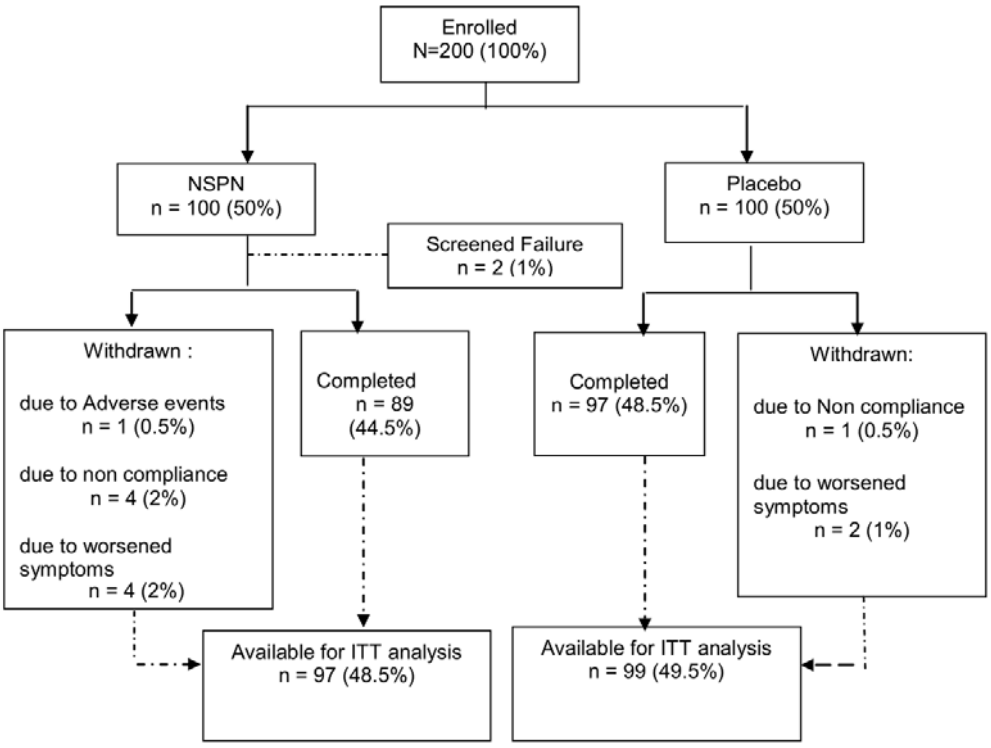

Figure 1. Flowchart showing progression of patients throughout the trial.

placebo. From a previous study [Leelarasamee et al. 2000], the standard deviation (SD) of the sore throat resolution was 2 days. A difference of 1 day between groups was judged clinically significant. Using an α-significance of 0.05 and 90% power to detect the difference, a total of 200 patients were needed to be enrolled to yield 170 patients completing the study, assuming a 15% withdrawal rate. All analyses in this study were done for the ITT (intention-to-treat) population and all statistical analyses were at 5% significance level (2-tailed).

Results

Patients

A total of 200 patients were enrolled from 9 study sites in Surabaya, Indonesia. The sites included both hospital and primary healthcare practice. The study started on August 15, 2006, and completed on December 14, 2006. Of the 200 patients enrolled, 2 patients were screened failure, 98 patients were treated with NSPN extracts, and 100 patients were treated with placebos. Of the 198 patients, 186 (93%) completed the trial (Figure 1), 12 (6%) were withdrawn from the study, 6 (3%) due to worsened symptoms, 1 (0,5%) due to adverse event, and the other 5 (2,5%) due to noncompliance with the protocol.

Enrolled subjects were at least middle-aged, with comparable demographic characteristics between groups, the NSPS and placebo groups. There was a higher proportion of females in both the NSPN and placebo group (69.1 and 70.7%, respectively). All patients had their acute tonsillopharyngitis moderate-to-severe with sore throat intensity of about 70 mm on a 100 mm VAS. Of them, patients whose tonsillopharyngitis severity was clinically classified as moderate by the investigator scored themselves between 50 – 85 mm on STPIS, whereas those classified as severe, 65 – 100 mm. Demographic and baseline characteristics for the patients of this study are summarized in Table 1. A strong positive correlation between TPS and STPIS was also found at the baseline of the study as shown in Table 2.

Efficacy evaluation

Time to sore throat resolution of every individual patient could not be accurately measured as there were only 4 patients (3 of the

Table 1. Demographic and baseline characteristics of the patients.

Characteristic	(n = 196)		
	NSPN (n = 97)	Placebo (n = 99)	p
Age (y)			
Mean (SD)	34.86 (11.81)	36.01 (12.05)	N/A
Median	35	35	
Range	18 – 60	18 – 59	
Gender			
Male, n (%)	30 (30.9)	29 (29.3)	N/A
Female, n (%)	67 (69.1)	70 (70.7)	
BMI (kg/m^2)			
Mean (SD)	22.43 (4.03)	23.04 (4.10)	N/A
Median	21.63	22.35	
Range	16.02 – 36.98	15.01 – 42.24	
Interval between 1st symptoms & 1st dose (hour)			
Mean (SD)	29.34 (12.39)	27.68 (13.57)	0.373
Median	28.0	26.0	
Range	0.50 – 53.0	1.3 – 67.0	
Total TPS score			
Mean (SD)	5.8 (1.48)	5.7 (1.25)	0.765
Median	6	6	
Range	4 – 10	4 – 10	
Other pharyngitis score			
Mean (SD)	3.5 (1.71)	3.6 (1.55)	0.547
Median	3	4	
Range	0 – 8	0 – 7	
Total NCA score			
Mean (SD)	0.45 (1.07)	0.35 (0.90)	0.528
Median	0	0	
Range	0 – 5	0 – 4	
STPIS (VAS – mm)			
Mean (SD)	70.73 (11.21)	71.84 (10.91)	0.385
Median	70	70	
Range	50 – 100	50 – 100	
Pain rating			
Mild, n (%)	0	0	N/A
Moderate, n (%)	60 (61.9)	64 (64.6)	
Severe, n (%)	37 (38.1)	35 (35.4)	

TPS = tonsillopharyngitis score, NCA = nasal congestion assessment, STPIS = sore throat pain intensity scale, VAS = visual analogue scale.

NSPN group and 1 of the placebo group) who had their sore throat fully resolved within the first 6 hours of treatment. Whereas at the next observation, i.e. Visit 2 (2 days of treatment), there were only 11 patients (6 of the NSPN group and 5 of the placebo group) who had their sore throat fully resolved. And at the last visit, almost all patients in both groups had their disease fully resolved. Therefore, prior to the release of database, the study group

Table 2. Correlation between TPS and STPIS at baseline.

	STPIS at baseline	
Total score TPS at baseline	Pearson Correlation	0.356[b]
	p	0.000
	N	196

[b]Correlation is significant at the level of < 0.01. TPS = tonsillopharyngitis score, STPIS = sore throat pain intensity scale.

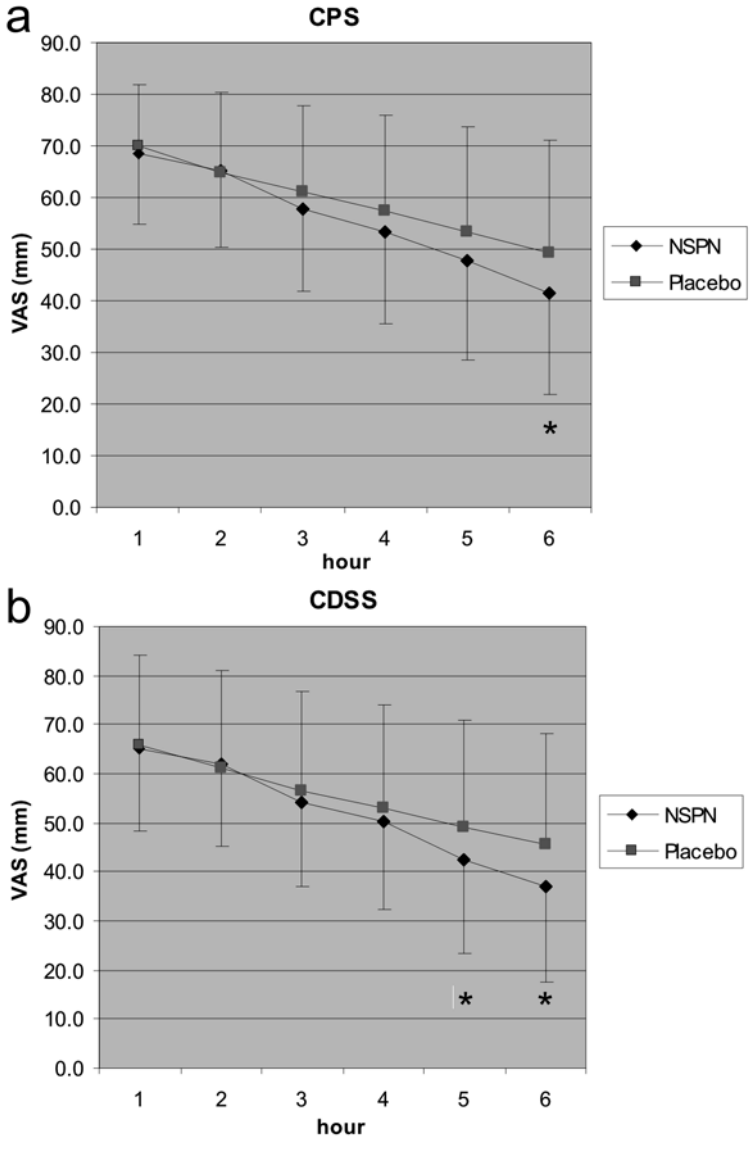

Figure 2. a) CPS values in the first 6 hours, B) CDSS values at the first 6 hours. CPS: change in pain scale. CDSS: change in difficulty in swallowing scale.

agreed that primary efficacy endpoint was not statistically analyzed.

Compared with placebo, NSPN extract treatment resulted in a significant greater reduction in both the pain intensity (CPS) and the swallowing difficulty (CDSS) (Figure 2). Figure 2 shows a significant difference between groups and was achieved as early as 6 hours after the first dose for change in pain score (CPS) and first 5 hours for change in difficulty of swallowing (CDSS). NSPN extract treatment also resulted in significantly greater relief of sore throat pain and on difficulty of swallowing which was assessed on Day 2 as maximum reduction in pain scale (MRPS) and maximum reduction in difficulty of swallowing scale (MRDS), respectively (Figure 3). A significant difference by lower score in severity of sore throat (TPS) assessed on Day 2 was also found in the NSPN group as compared to placebo (Figure 4).

The patients' self-assessment showed that 60% of the patients in the NSPN group had a complete relief from the symptom, compared to only 38,4% of patients in the placebo group. Global evaluation performed by both investigators (iGETE) and the patients (pGETE) showed that NSPN provided better efficacy than placebo, though statistically they were not significantly different. At the end of treatment (Day 7), a significantly greater proportion (60.0%) of patients in the NSPN group compared to only 38.4% of patients' in the placebo group had their sore throat completely relieved ($p = 0.022$) as shown by STRR (Table 3). The distribution of scores for the patients' overall self-assessment of sore throat relief in the NSPN group showed significantly greater relief from baseline to Day 7 compared with the placebo group ($p \leq 0.05$ compared to placebo) as tabulated in Table 3. This study also indicated that NSPN extract treatment resulted in significantly less patients who needed escape therapy throughout the study (with a significantly less amount of escape therapy needed) (Table 4).

Safety evaluation

All patients who had taken at least 1 dose of the study medication were included in the safety evaluation. One patient in the placebo

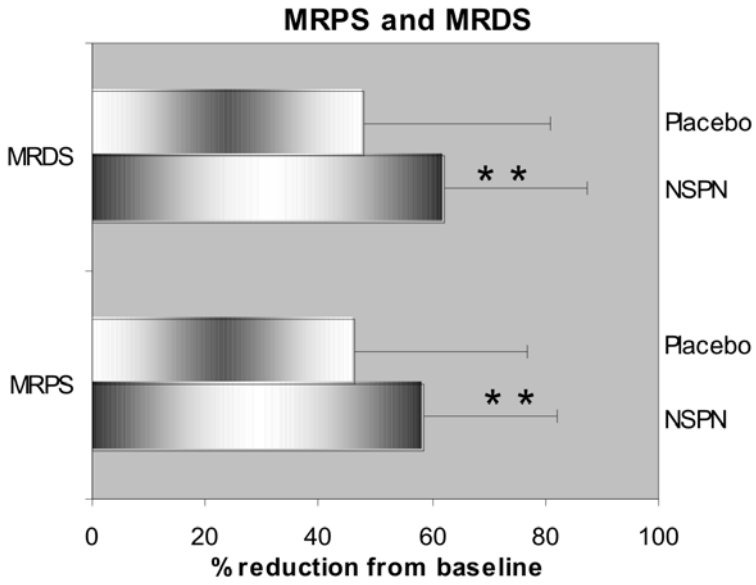

Figure 3. MRPS and MRDS at Day 2. MRPS, maximum reduction in pain scale, MRDS, maximum reduction in difficulty in swallowing scale, **p < 0.01.

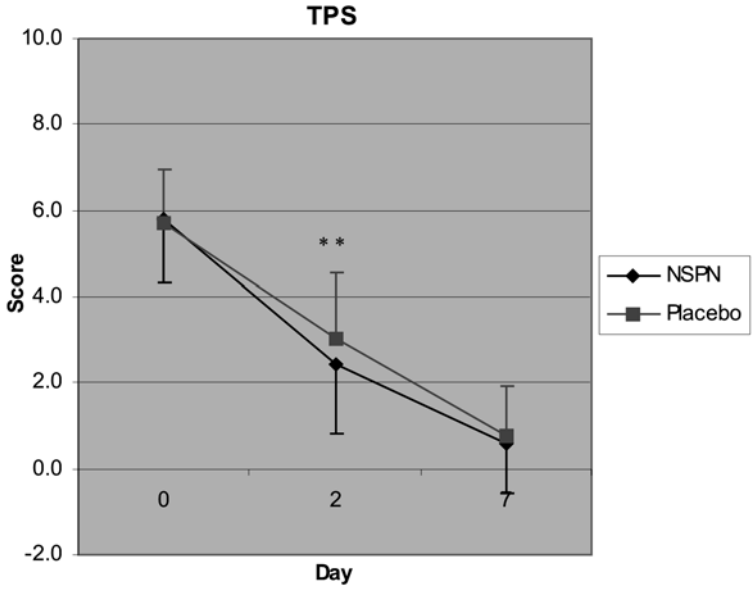

Figure 4. TPS values at baseline and posttreatment visits. TPS, tonsillopharyngitis score, **p < 0.01.

group could not be analyzed as the patient had never appeared at any follow-up visit and was eventually lost to follow-up. There were 18 preferred terms of adverse events (Table 6) with a total frequency of 85 reported by 29 patients (29.0%) in the NSPN group and 22 patients (22.2%) in the placebo group. None of them fulfilled the criteria of serious adverse events. The majority (80.23%) of adverse events were mild in severity, 16.28% were moderate and only the remaining 3.49% were severe.

Discussion and conclusions

Discussion

Acute tonsillopharyngitis with sore throat as its main symptom is common for most people and well-suited as a model for the evaluation of an agent which has antiinflammatory activity, such as NSPN extract. Whereas immunomodulatory activity of the extract is beneficial particularly because most acute tonsillopharyngitis cases are usually of viral origin, which require an adequate immune system for complete recovery. All enrolled patients in this study were those with moderate-to-severe sore throat and most of them without nasal congestion (Table 1).

The results of the present study showed that, compared with placebo, NSPN extract can result in significantly complete relief to acute tonsillopharyngitis symptoms. Two sensory qualities of throat pain were used in this study, i.e. swollen throat and difficulty in swallowing. These parameters were easily self-identified by the patients. The degree of pain at baseline, measured on the visual analogue STPIS conformed to the categories of pain intensity, obtained by conventional descriptive pain ratings (DPR) and was consistent with the TPS (Table 2), which provided an objective measurement of the physical findings and a method for relating severity with the initial pain state.

Reduction of sore throat pain and difficulty of swallowing were seen to be greater in the NSPN extract group at Hour 6 after baseline. As measured by VAS, the absolute difference in pain intensity reduction was gradually greater between groups every next single hour. NSPN extract provided reduction in pain intensity (CPS) by 29.3 mm at Hour 6, which was about 7 mm (28.9%) better than that of placebo. The reduction in pain intensity was accompanied by the alleviation of swallowing difficulty (CDSS), which also showed significantly favorable results toward NSPN extract at Hours 5 and 6. It can be seen that as early as 5 – 6 hours after the first dose, NSPN extract has readily exerted its efficacy in relieving the main symptoms of tonsillo-

Table 3. Treatment efficacy.

Variables	NSPN (n = 97) n (%)	Placebo (n = 99) n (%)	p
iGETE at Day 2, n (%)			
None	3 (3.2)	14 (14.1)	0.584
Poor	20 (21.1)	21 (21.2)	
Good	66 (69.5)	59 (59.6)	
Excellent	6 (6.3)	5 (5.1)	
pGETE at Day 2, n (%)			
None	2 (2.1)	18 (18.2)	0.101
Poor	13 (13.7)	15 (15.2)	
Good	68 (71.6)	51 (51.5)	
Excellent	12 (12.6)	15 (15.2)	
STRR at Day 2, n (%)			
None	3 (3.2)	14 (14.1)	0.088
Some relief	13 (13.7)	19 (19.2)	
Moderate relief	37 (38.9)	40 (40.4)	
Considerable relief	33 (34.7)	17 (17.2)	
Complete relief	9 (9.5)	9 (9.1)	
iGETE at Day 7, n (%)			
None	1 (1.1)	7 (7.1)	0.423
Poor	11 (11.6)	18 (18.2)	
Good	62 (65.3)	56 (56.6)	
Excellent	21 (22.1)	18 (18.2)	
pGETE at Day 7, n (%)			
None	3 (3.2)	13 (13.1)	0.414
Poor	7 (7.4)	10 (10.1)	
Good	55 (57.9)	48 (48.5)	
Excellent	30 (31.6)	28 (28.3)	
STRR at Day 7, n (%)			
None	0 (0)	3 (3.0)	0.022[a]
Some relief	9 (9.5)	15 (15.2)	
Moderate relief	16 (16.8)	24 (24.2)	
Considerable relief	13 (13.7)	19 (19.2)	
Complete relief	57 (60.0)	38 (38.4)	

[a]significant with $p < 0.05$. iGETE = investigator's global evaluation of treatment efficacy; pGETE = patient's global evaluation of treatment efficacy; STRR = sore throat relief rating.

pharyngitis, i.e. sore throat. Such efficacy was likely to be attributed to the *Nigella sativa* which imparts antiinflammatory and analgesic properties to the NSPN extract. One of the active substances of *Nigella sativa* which has much been proven both in vitro and preclinically to exert antiinflammatory and analgesic as well as antinociceptive effects, was thymoquinone [Abdel Fattah et al. 2000, Al Ghamdi 2001, Randhawa and Al Gamdhi 2002].

Up to Day 2, patients in the NSPN group experienced significantly greater reduction in pain intensity and swallowing difficulty than those in the placebo group. It is shown by MRPS and MRDS value that was assessed at the 2nd day of the treatment. The 100 mm visual analogue MRPS and MRDS indicated a

Table 4. Requirements of escape therapies and antibiotics.

Variables	NSPN (n = 97) n (%)	Placebo (n = 99) n (%)	p
Requirement for escape therapy, n (%)	61 (62.9)	74 (74.7)	0.050[a]
Number of escape therapy needed			
Up to Day 2 – mean (SD)	3.1 (2.06)	3.9 (2.26)	0.032[a]
Up to Day 7 – mean (SD)	6.0 (4.82)	6.8 (4.47)	0.118
Requirement of antibiotics[c], n (%)	3 (3.1)	2 (2.0)	0.634

[a]significant with $p < 0.05$, [c]antibiotic administration was withheld up to Day 2, and patient's condition was re-examined and judged clinically by investigators at Day 2 whether antibiotic prescription was needed (i.e. when patient's condition was getting worse versus baseline).

Table 5. Number of subjects exposed to adverse events.

Adverse events (AE)	Total (n = 199)	Group	
		NSPN (n = 100)	Placebo (n = 99)
Number of subjects exposed to AE – n (%)	51 (25.6)	29 (29.0)	22 (22.2)
Number of adverse events – n (%)	86 (100.0)	46 (52.9)	40 (46.5)
Serious adverse events (SAE)	0	0	0
Other adverse events	86 (100.0)	46 (53.5)	40 (46.5)

more precise estimation of percent reduction in pain and swallowing difficulty than obtainable from a categorical or ordinal scale. In this current study both subjective parameters (as self-assessed by the patients) demonstrated results consistent with the TPS and the other score of pharyngitis symptoms, which provided more objective assessment on treatment efficacy. The TPS and its reduction (improvement) at Day 2 were also significantly better in the NSPN group than those in the placebo group. Even though the other score of pharyngitis symptoms was not significantly different, there was still a favorable result toward the NSPN. At the end of treatment (Day 7), the differences between groups in the TPS as well as the other pharyngitis symptom score were both diminished since most patients in both groups recovered from the acute tonsillopharyngitis.

The greater reductions of pain intensity, swallowing difficulty and other clinical symptoms of tonsillopharyngitis (as measured by the TPS and the other pharyngitis symptom score) in the NSPN group were undoubtedly describing the efficacy of NSPN extract. Such efficacy was also well-confirmed by the analysis of requirement for escape therapy (paracetamol) in both groups. In this study, we found that significantly less patients in the NSPN group required escape therapy than in the placebo group. The patients did not take escape therapy for the first 6 hours as recorded in their individual diaries. The numbers of paracetamol tablets needed within the first 2 days of treatment were also significantly lower in the NSPN group, although the total numbers were not different at the end of treatment. These results mean that within the first 2 days, patients in the NSPN group had their sore throat alleviated greater than those in the placebo group; thus, only less numbers of patients in the NSPN group needed escape therapy and even with less numbers of such therapy as well.

In this current study, the effectiveness of NSPN extract in the treatment of acute tonsillopharyngitis was not influenced by baseline severity of the symptoms, indicating that the extract can be used for a wide range of tonsillopharyngitis severity, especially those with moderate-to-severe ones. Furthermore, as treatment effectiveness was also assessed by the patients using both the VAS and sub-

Table 6. Adverse events by system organ class and preferred term.

Description of AE	Frequency of events (AE) and no. of subjects exposed (n)	
	NSPN (97)	Placebo (99)
	AE	AE
Special sense, other disorders		
Taste perversion	1	–
Central and peripheral nervous disorders		
Dizziness	4	1
Gastrointestinal system disorders		
Anorexia – Appetite loss	3	9
Nausea	3	4
Vomiting	1	1
Diarrhea – Stool loose	1	1
Flatulence – Bloating	2	–
Dyspepsia – Stomach upset	–	1
Abdominal pain – Epigastric pain not food-related	1	–
Constipation	2	–
Respiratory system disorders		
Rhinitis	2	–
Heart rate & rhythm disorders		
Palpitation	–	2
Psychiatric disorders		
Nervousness	–	1
Somnolence – Drowsiness	6	6
Body as a whole – general disorders		
Fatigue	6	8
Urinary system disorders		
Polyuria – Urine volume increased	14	5
Skin and appendage disorders		
Pruritus – Itching	–	1

jective rating scales (pGETE and STRR), the study demonstrated that patients expectations for complete relief of their illness were greatly fulfilled by the NSPN extract.

Antibiotic therapy was allowed to be prescribed at Day 2 only when patients' tonsillopharyngitis state got worse as judged clinically by the investigator. In this case, the patients might have likely been inflicted with bacterial rather than viral tonsillopharyngitis. There was no difference between groups in requirement for antibiotic therapy. Of a total of 196 evaluable patients' data, only 3 (3.1%) patients in the NSPN group and 2 (2.0%) patients in the placebo group required antibiotics. This indicated that only 2 – 3% of the tonsillopharyngitis cases in this study were caused or complicated by bacterial infections. Most of the cases might be caused by other pathogens, such as viruses or other undetermined etiology. Nevertheless, it is not impossible to say that the percentage of bacterial-infected cases in this study might be higher than just 2 – 3%. Some of the other possible bacterial acute tonsillopharyngitis cases might not need antibiotics, as NSPN extract itself has been proven to have such an antibacterial activity as shown by an in vitro study of the same extract [Sunardi and Tjandrawinata 2006]. In the study, NSPN extract was proven to be active against Gram (+) and (–) bacteria, including Streptococcus pneumoniae, one of the most common pathogenic bacteria in tonsillopharyingitis cases. The antibacterial activities of the NSPN extract which contains both *Nigella sativa* and *Phyllanthus niruri* were even much higher than those demonstrated by either individual herbal extract [Hanafi and Hatem 1991, Sunardi and Tjandrawinata 2006], suggesting that a combination of both herbal extracts provides a synergistic effect in delivering the antibacterial activities of NSPN [Sunardi and Tjandrawinata 2006].

NSPN extract was well tolerated and safe for acute tonsillopharyngitis patients, with an incidence of adverse events similar to that for placebo (Table 5). Tolerability was assessed based on patient diaries collected and direct interview with each patient performed every post-treatment visit. The most common adverse events were polyuria, fatigue, somnolence, and loss of appetite (Table 6). Of these, only polyuria was probably related to NSPN treatment. Polyuria might result from the increased water intake by the subjects as this had been advised by the investigators to help them restore their health condition from tonsillopharyngitis. However, such adverse effect was more likely to be attributed to the *Phyllanthus niruri* extract, one of the components in NSPN. The herb has been reported to have such an effect [Unander et al. 1995]. However, in several previous and current studies, we have not found any clinically significant consequences of polyuria due to *Phyllanthus niruri* extract, such as hypo-

tension or dehydration. Nevertheless, caution has to be taken, especially when the NSPN extract is used by hypotensive or dehydrated patients. Only one (1%) patient in the NSPN group was withdrawn due to adverse events (polyuria). There was no discontinuation of treatment due to adverse events in all remaining patients. We assumed that full range safety measures were not necessary for this study because it lasted for a short period of time, each patient received study medication for no longer than 7 days. Furthermore, this trial studied on acute tonsillopharyngitis symptoms only. However, a preclinical study on acute toxicity of the extract had been carried out earlier. Results from this preclinical study showed that the extract was safe with LD_{50} > 15 ml/kg body weight.

Conclusion

NSPN extract at a dose of 3 times 1 capsule daily demonstrated its benefits over the placebo in reducing sore throat, the predominant symptom in acute tonsillopharyngitis. NSPN extract was also found to be safe and well tolerated in acute tonsillopharyngitis patients. In brief, this study demonstrated significant benefits of NSPN extract in the treatment of acute tonsillopharyngitis as compared to placebo.

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Abbreviations

CDSS: Change in difficulty in swallowing scale, **CPS:** Change in pain scale, **DPR:** Descriptive pain ratings, **GABHS:** Group A-β-hemolytic Streptococcus, **iGETE:** Investigators' global evaluation of treatment, **ITT:** Intention-to-treat, **MRDS:** Maximum reduction in difficulty in swallowing scale, **MRPS:** Maximum reduction in pain scale, **NCA:** Nasal congestion assessment, **NSPN:** *Nigella sativa* and *Phyllanthus niruri*, **pGETE:** Patient's global evaluation of treatment, **SD:** Standard deviation, **STP:** Streptococcal pharyngitis, **STPIS:** Sore throat pain intensity scale, **STRR:** Sore throat relief rating, **TPS:** Tonsillopharyngitis scale, **VAS:** Visual analogue scales.

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