

## Effects of *Phyllanthus niruri* on the severity of the common cold in children

Ari Dwi Ratna Kusumaningrum, Sumadiono, Yati Soenarto

### Abstract

**Background** Common cold is a self-limited disease, however it poses a significant burden on productivity and community health. Unfortunately, there has been no standard medication for childhood common cold, whereas some herbs with immunomodulating properties, such as *Phyllanthus niruri* extract (PNE), might be beneficial but has not been thoroughly studied.

**Objective** To evaluate the effect of PNE administration on the severity of common cold symptoms in children.

**Methods** We performed a randomized, double-blind, controlled trial in children aged 2-6 years who were diagnosed with a common cold at primary health care centers in Sewon and Jetis in Bantul, as well as in Gondomanan and Gedongtengen in Yogyakarta. Subjects were collected by consecutive sampling and parents were interviewed. We assessed illness severity by Hemila scoring for the common cold.

**Results** A total of 100 subjects were included with 50 subjects in each intervention group. After treatment, there was no significant difference in common cold severity between the PNE and the control groups for all symptom score components, including cough (0.87 vs 0.71,  $P=0.36$ ), nasal symptom (0.90 vs 1.10,  $P=0.54$ ), coryza (0.44 vs 1.10,  $P=0.54$ ), and systemic symptom (0.10 vs 0.10,  $P=0.94$ ).

**Conclusion** Administration of PNE for 6 days did not provide a significant benefit in reducing the severity of the common cold compared to placebo in children aged 2 – 6 years. [Paediatr Indones. 2012;52:346-51].

**Keywords:** common cold, children, *Phyllanthus niruri* extract, severity score

The common cold is an acute, respiratory tract infection, mainly caused by a rhinovirus. The common cold manifests as cough, coryza, sore throat, with or without systemic symptoms, and is usually self-limiting.<sup>1,2</sup> Symptoms reflect manifestations of the immune response against infection.<sup>3,4</sup> It has been estimated that children have colds 6–10 times per year.<sup>5</sup> Despite the self-limiting nature of colds, they have a significant effect on school attendance.<sup>6,7</sup> There is no standard medication for the common cold, and over-the-counter medications have not been proven to be effective in children.<sup>8,9,10</sup> Immunity will naturally eliminate the virus that causes the common cold.<sup>11,12</sup> Immunity may be improved by administration of immunomodulators.<sup>13,14</sup>

*Phyllanthus niruri* extract is herbal supplement with immunomodulatory activity.<sup>15,16</sup> An experimental study showed that PNE improved either non-specific or specific immune responses. PNE enhanced macrophage phagocytosis and chemotaxis, neutrophil chemotaxis, natural killer (NK) cell cytotoxicity, and complement hemolytic activity. It also improves

---

From the Department of Child Health, Gadjah Mada University Medical School, Yogyakarta, Indonesia.

**Reprint requests to:** Ari Dwi Ratna Kusumaningrum, Department of Child Health, Gadjah Mada University Medical School, Jalan Kesehatan No. 1 Sekip Yogyakarta 55284, Indonesia. Tel +62-274-561616, Fax +62-274-583745. E-mail: arri\_srg@yahoo.com

specific immune responses by inducing T-lymphocyte proliferation, increasing TNF- $\alpha$  and IL-4 secretion, and decreasing IL-2 and IL-10 secretion. In a clinical trial, PNE increased IFN- $\gamma$  and CD4 levels, and also increased CD4/CD8 ratios.<sup>17</sup> In addition, PNE was observed to enhance humoral immunity, especially in the production of immunoglobulin M (IgM) and immunoglobulin G (IgG).<sup>13</sup>

An unpublished study revealed a significant benefit of PNE administration on the severity of acute respiratory tract infection in children, but the sample size was too small.<sup>13</sup> Studies with a sufficient number of subjects are needed to further assess the effects of PNE on the common cold. The aim of this study was to determine the effect of PNE administration on the severity of common colds in children.

## Methods

We performed a double-blind, randomized, controlled trial from May to August 2011 in primary health care centers in Yogyakarta and Bantul. One hundred subjects were recruited by consecutive random sampling. Subjects were divided into two groups of 50 subjects each: a PNE group and a control group who received a placebo. The diagnostic criteria for common cold were cough and coryza, with clear or purulent mucous secretion of less than 10 days, with or without fever of  $<39^{\circ}\text{C}$ , good clinical condition and no abnormalities upon chest examination. Subjects were children living in Yogyakarta and Bantul, who visited primary health care centers. We included children aged 2-6 years with common colds of less than 2 day duration, who had good general appearance. Parents provided written informed consent. We excluded children with complicated

common colds, evidence of lower respiratory tract infection, or diarrhea. Nutritional status was assessed anthropometrically using weight-for-height based on the 2006 WHO growth standard.<sup>18</sup> Subjects were classified as overweight, well-nourished or undernourished. Weight was measured by a nurse using Camry® scales, with a precision of 0.1 kg. Height was measured using a height scale with a precision of 0.1 cm. Definitions of other variables are shown in **Table 1**.

The estimated required sample size was 100 (50 for each group), calculated by the unpaired hypothesis study formula, with  $\alpha=0.05$ ,  $\beta=0.2$  and an estimation of 32.5% difference between groups (minimum sample size was 38 per group). The treatment group received 5 mL of PNE syrup (Stimuno® DexaMedica with 25 mg PNE per 5 mL) three times a day for 6 days, while the placebo group received the same volume of placebo (glucose, water, and simple syrup). Children with fever were treated with paracetamol, as necessary. The research assistant labeled the drug by numbering A1-25, B1-25, C1-25, and D1-25. Randomization of the allocation was generated by computer. Labels were closed during the study and opened at the end of the study by researchers. The doctors at the primary health care centers performed physical examinations on the day of visit (day 0) and parents filled the symptoms form from the 1<sup>st</sup> to 6<sup>th</sup> day of treatment at home. Subjects were asked to return to the primary health care centers on the 6<sup>th</sup> day. We assessed the cold severity using the Hemila score for common colds.<sup>19</sup> The severity parameters were cough, nasal, throat and systemic symptoms, each receiving a score of 0 to 3. The side effects of therapy were recorded by parents. The outcome of the study was the severity of common cold. We calculated an

**Table 1.** Definitions of variables

Variables	Definitions
Good compliance	Subject consumed $>85\%$ of the prescribed supplements.
Smoking exposure	There was at least one smoker at home.
Schooling	Subject followed formal education in a school
Duration of illness on admission	Number of days between the onset of symptoms and admission to the hospital
Mother's education	Level of formal education, classified as elementary school, junior high school, senior high school, and graduate studies.
Positive contact history	Subject had been in contact with any person who had common cold
History of allergy	Subject was known to have a history of allergy

intra-class correlation coefficient test to measure data reliability.

This study was approved by the Ethics Committee for Medical Research and Health, Gadjah Mada University Medical School, Yogyakarta.

The severity of common cold was analyzed by the non-parametric test, Mann-Whitney U. We performed an intention-to-treat analysis for subjects who dropped out and were lost to follow up. We used the Statistical Package for the Social Sciences (SPSS) for Windows 15.0 version with a 95% confidence interval (CI).

## Results

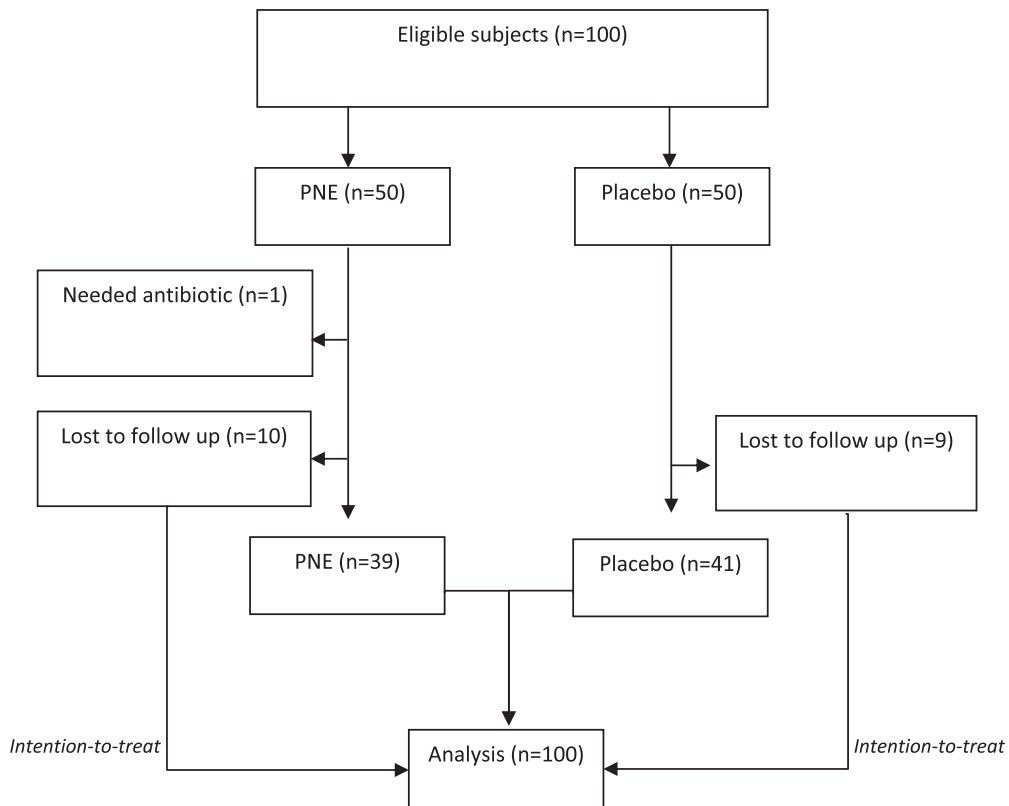
The study profile is shown in **Figure 1**. One subject in the PNE group dropped out because of antibiotic use. Ten subjects in the PNE group and 9 subjects in the placebo group were lost to follow up. However, we included all subjects who were initially randomized in this intention-to-treat analysis.

**Table 2** shows the basic characteristics of subjects. Secondary outcomes of side effects did not occur at all in either group.

We performed the Mann-Whitney U test with confidence interval of 95%. For each symptom, all P values from days 1-6 of treatment were  $> 0.05$ , indicated no significant differences between the PNE and control groups. Graphs of the mean common cold scores for days 1-6 of treatment of both groups are shown in **Figure 2**.

All subjects in both groups had similar initial scores for each symptom. For both groups, peak scores for cough and coryza were on the 2<sup>nd</sup> day, while peak scores for throat and systemic symptoms were on the 1<sup>st</sup> day of treatment.

Mean scores of both groups for cough, coryza, throat symptoms, and systemic symptoms were similar on days 1-6 of treatment. However, **Figure 2** shows that the coryza symptoms on the days 3-5, although not significant, were lower in the PNE group than in the placebo group (mean on day 1: 1.15 vs. 1.54,



**Figure 1.** Flow chart of the trial profile

**Table 2.** Baseline characteristics of subjects

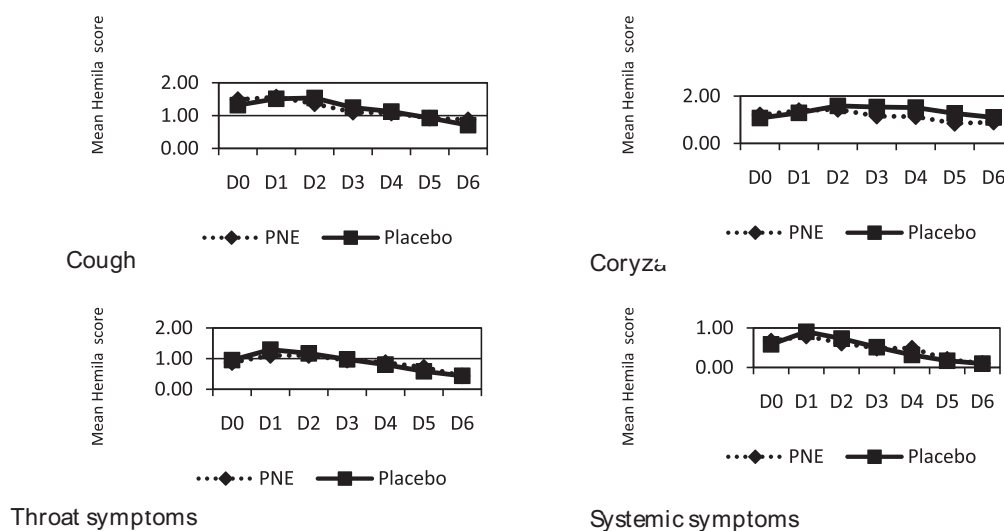
Characteristics	PNE n=50	Placebo n=50
Age, n (%)		
- 2 – 4 years	24(48)	25(50)
- 4 – 6 years	26(52)	25(50)
Gender, n (%)		
- Male	23(40)	32(58)
- Female	27(60)	18(42)
Smoke exposure, n (%)		
- Yes	28(56)	25(50)
- No	22(44)	25(50)
History of common cold contact, n (%)		
- Yes	35(70)	31(62)
- No	15(30)	19(38)
Duration of illness, n (%)		
- 1 day	14(28)	16(32)
- 2 days	36(72)	34(68)
Nutritional state (%)		
- Overweight	2(4)	4(8)
- Well-nourished	28(56)	32(64)
- Undernourished	20(40)	14(28)
History of allergies, n (%)		
- Yes	10(25)	9(18)
- No	40(75)	41(82)
Maternal educational level attained, n (%)		
- Elementary	6(12)	8(16)
- Junior high	14(28)	10(20)
- Senior high	26(52)	23(46)
- Post-high School	4(8)	9(18)
Attended school, n (%)		
- Yes	29(58)	26(52)
- No	21(42)	24(48)
Compliance, n (%)		
- Good	45(90)	38(76)
- Not good	5(10)	12(34)
Paracetamol treatment, n (%)		
- Yes	33(66)	27(54)
- No	17(34)	23(46)
Mean initial Hemila score		
- Cough	1.49	1.32
- Coryza	1.21	1.07
- Throat symptoms	0.87	0.95
- Systemic symptoms	0.67	0.59

respectively; day 2: 1.13 vs. 1.51, respectively; and day 3: 0.85 vs. 1.27, respectively). All scores had decreased by the 5<sup>th</sup> day of treatment.

## Discussion

We found no significant differences in common cold severity between the PNE and placebo groups. However, mean scores for coryza symptoms for days 3-5 of treatment were lower in the PNE group, although not statistically significant. Eccles found that the peak of common cold symptoms usually occurred on the 2<sup>nd</sup> – 3<sup>rd</sup> days of illness, with recovery in 7 – 10 days.<sup>20</sup> We found that on the 6<sup>th</sup> day of treatment, all subjects had their lowest scores, indicating clinical improvement.

Theoretically, the administration of PNE, due to its immune-modulator effects, might reduce the common cold symptoms and help the body to eliminate the virus.<sup>17</sup> However, our study showed that there was no significant difference in symptom scores between those who were treated with PNE and not. Firstly, it could probably caused by lack of PNE effect on common cold viruses. So far, there had been no direct evidence which showed that PNE could eliminate common cold viruses although it is biologically plausible considering its immune-modulator properties. Other reasons might relate to



**Figure 2.** Mean common cold scores of the PNE and placebo groups for days 1-6 of treatment.

the fact that the compliance of our subjects was not recorded in details and the common cold severity was assessed using parental questionnaire, which could raise subjectivity issues.

Another issue related to the insignificant treatment difference in our results was the sample size that might be too small to detect a small or moderate clinical difference. Another possible reason was that the distribution of subjects with allergic rhinitis was not evaluated and it could have affected the treatment outcome if the distribution was not comparable between the groups despite the randomization procedure.

Munasir found that PNE could normalize the fever faster compared to placebo, in upper respiratory tract infections in children.<sup>13</sup> However, the sample size of the study was small. Dirjomuljono et al. performed a study on the effects of combining *Nigela sativa* and *Phyllanthus niruri* (NSPN) for acute tonsilopharyngitis in adult patients. They found that NSPN administration helped significantly reduce the symptoms compared to placebo.<sup>21</sup> However, we cannot compare these results to our study, as we did not use *Nigela sativa*.

A limitation of our study was that we could not ensure parental objectivity, though, it could be minimized by proper randomization methods. In addition, the sample size was not large enough to detect small clinical differences. Also, we could not exclude allergic rhinitis with our diagnostic criteria. Administration of PNE for common cold needs further study with a larger sample size and daily evaluations by professionals to collect more objective data.

In conclusion, we found no significant differences in reduction of severity of common colds in children who received PNE 3 times a day for 6 days compared to those who received placebo.

The authors hereby declare that they had no conflict of interest.

### Acknowledgment

We would like to thank the Heads and staff of the Primary Health Care Centers of Sewon II Bantul, Jetis Bantul, as well as Gedongtengen and Gondomanan, Yogyakarta for their support and participation. Also, thanks to Dexa Medika for providing placebo supplements for this study.

### References

1. Virk A, Henry NK. Upper respiratory tract infections. In: Wilson W, Sande M, editors. Current diagnosis & treatment in infectious diseases. New York: McGraw-Hill; 2001. p. 98-117.
2. Yau FYS. Upper respiratory tract infection in children. [cited December 2011] Available from: [http://www.hksid.org/pdf/URTI\\_in\\_children.pdf](http://www.hksid.org/pdf/URTI_in_children.pdf)
3. Zhu Z, Tang WL, Gwaltney JM, Wu Y, Elias JA. Rhinovirus stimulation of interleukin-8 in vivo and in vitro: role of NF-kappa  $\beta$ . Am J Physiol. 1997;17:814-24.
4. McCoy L. Rhinovirus: an unstoppable cause of the common cold. The Science Creative Quarterly. 2004; [cited December 2011]. Available from: <http://www.scq.ubc.ca/rhinovirus-an-unstoppable-cause-of-the-common-cold>
5. Johnston S, Holgate S. Epidemiology of viral respiratory infection. In: Myint S, Taylor-Robinson D, editors. Viral and other infections of the human respiratory tract. London: Chapman & Hall; 1996. p. 1-38.
6. West JV. Acute upper airway infections. Br Med Bull. 2002;61:215-30.
7. Pappas DE, Hendley JO. Patient information: the common cold in children. Up to date. 2011; [cited January 2012]. Available from: <http://www.uptodate.com/contents/patient-information-the-common-cold-in-children>
8. Kelly, Leslee F. Pediatric cough and cold preparation. Pediatr Rev. 2004;25:115-23.
9. Madeline S, Blandino D. Treatment of the common cold. AAFP 2007. Available from: <http://www.aafp.org/afpsort>
10. Simasek M, Blandino DA. Treatment of the common cold. Am Fam Physician. 2007;75:515-20.
11. Hendrickson K. How the common cold affects the immune system. [cited December 2011]. Available from: <http://www.livestrong.com..>
12. Feldman S, Schwartz HI, Kalman DS, Mayers A, Kohrman HM, Clemens R, et al. Randomized phase II clinical trials of Wellmune WGP® for immune support during colds and flu season. J Appl Res. 2009;9:30-42.
13. Munasir Z. The role of phyllanthiherba in the treatment of upper respiratory tract infections in pediatric patients [unpublished work]. Jakarta: Clinical Research Division of DexaMedica Pharmaceutical; 2003.
14. Gwaltney JM, Hayden FG. Understanding colds. 2006. [cited 2010 October]. Available from: <http://www.commoncold.org/trtmnt.htm>
15. Williams JE. Review of antiviral and immunomodulating

- properties of plants of the Peruvian rain forest with a particular emphasis on una de gato and sangre de grado. *Altern Med Rev.* 2001;6:567-79.
16. Nworu CS, Akah PA, Okoye FB, Proksch P, Esimone CO. The effects of *Phyllanthus niruri* aqueous extract on the activation of murine lymphocytes and bone marrow-derived macrophages. *Immunol Invest.* 2010;39:245-67.
  17. Tjandrawinata RR, Ma'at S, Nofrianty D. Effects of standardized *Phyllanthus niruri* Linn., extract on changes in immunologic parameters: correlation between pre-clinical and clinical studies. *Dexa Medica J.* 2005;6:367-71.
  18. WHO. Child growth standarts. Weight for height. Available from: [http://www.who.int/childgrowth/standards/weight\\_for\\_height/en/index.html](http://www.who.int/childgrowth/standards/weight_for_height/en/index.html)
  20. Hemila H, Douglas RM. Vitamin C and acute respiratory infections. *Int J Tuberc Lung Dis.* 1999;3:756-61.
  21. Eccles R. Understanding the symptoms of the common cold and influenza. *Lancet Infect Dis.* 2005;5:718-25.
  22. Dirjomuljono M, Kristyono I, Tjandrawinata RR, Nofiarny D. Symptomatic treatment of acute tonsillo-pharyngitis patients with a combination of *Nigella sativa* and *Phyllanthus niruri* extract. *Int J Clin Phar Ther.* 2008;46:295-306.