Sys Rev Pharm 2021;12(1): 686-691
A multifaceted review journal in the field of pharmacy

The Effect of Ginsenoside 4% on Inflammation, Bacteremia and Clinical Improvement in Community Acquired Pneumonia Patients

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is the most common cause of morbidity and mortality, despite all advanced diagnostic tools and management. Ginseng (Panax ginseng) is one of the herbs commonly used in Asia. Ginsenoside is a biologically active saponin compound found in Panax ginseng and plays a role as an immunomodulator, antibacterial, and anti-inflammation. Neutrophil lymphocyte ratio (NLR) can be used as a bacteremia predictor. Procalcitonin (PCT) level can help to monitor antimicrobial therapy response.
Objective: This study aimed to analyze the effect of ginseng extract on procalcitonin level, NLR, and the length of clinical improvement in patients with CAP
Methods: Of 32 hospitalized CAP patients with a pretest-posttest quasi-experimental study was conducted in Dr. Moewardi Hospital, Surakarta, Indonesia from April to June 2020. Sampling was done by the consecutive sampling technique with ginseng extract with a dose of 2 x 100 mg as the variable. The dependent variables were PCT level, NLR, and the length of clinical improvement.
Results: Procalcitonin level and NLR decreased significantly in the treatment group getting p values of <0.001, while in the control group, the p values were 0.14 and 0.27, respectively. There was a significant difference in the length of clinical improvement between control (7.06±0.93) and treatment (5.69±0.95) groups (p = 0.001).
Conclusion: Administering ginseng extract as an adjunct therapy for inpatients with CAP can lower procalcitonin level and NLR and accelerate clinical improvement.

Keywords: CAP, clinical improvement, ginseng extract, NLR, procalcitonin

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INTRODUCTION

Pneumonia is defined as acute inflammation in lung parenchyma caused by microorganisms such as bacteria, viruses, fungi, and parasites. Community-acquired pneumonia (CAP) results in high morbidity, mortality, and cost around the globe. The Global Burden of Disease Study reported that lower respiratory tract infection was the second most cause of death in 2013. It is estimated that the incidence of pneumonia is around 1.5 - 14 cases in 1,000 individuals annually. Its mortality rate reaches 41.7 per 100,000 people. Costly treatment for pneumonia patients can be reduced by several approaches, including appropriate and adequate antibiotics, shortening the length of stay (LOS), and introducing vaccines.[1,2.]

A prospective study by Widmer *et al*. in Switzerland in 2008 conducted on 875 pneumonia patients found that factors influencing Los were a clinical condition of the patient, the need for homecare, comorbidity, multilobar lung disorder, the complication of the disease, and the severity of pneumonia marked by high procalcitonin (PCT) level, C-reactive protein (CRP), patient's risk class based on Pneumonia Severity Index (PASI), and the patient's need of intensive care unit. [3,4]

Biomarker examination can help clinicians in determining a diagnosis, therapy, and prognosis of patients with pneumonia. Procalcitonin in circulation can increase thousand-fold over its average level in various severe systemic inflammatory conditions, particularly those induced by a bacterial infection. Procalcitonin during inflammation is produced through direct induction by lipopolysaccharide (LPS) or toxic metabolite from microbe and indirect induction of various inflammatory cytokines, namely interleukins (IL) -1ß, IL-6, tumor necrosis factor (TNF) -α, and other inflammatory mediators. [5,6] Neutrophil lymphocyte ratios (NLR) are a value derived from simple laboratory examination, and it is used to find out and evaluate the presence of systemic inflammation. [7-9]

Choosing empirical antibiotic plays an essential role in controlling the disease. However, irrational use, high incidence of antibiotic resistance, and microorganism mutation result in minimum microorganism elimination. Using an herb remedy has been increasing, and it has been considered as an adjunct therapy for infectious disease. Herb remedy is widely available in markets, inexpensive, and safe as it owns minimal side effects. Plants interact with various microorganisms and produce tiny microbial compounds (< 500 DA), limiting harmful pathogenic microorganisms. A combination of natural products with an antibiotic may give a synergic effect on antibiotic and minimize toxicity.[11-12.]

Ginseng is one of the herbal plants widely studied by Asians for over 5,000 years, but it has not been accepted yet in western countries. Panax ginseng is one of the widely known oriental herbal medicines which is commonly used by people. Ginseng ranks in the top 4 most commonly consumed food supplements.[13,14.]

In this study, the researchers wanted to explore ginseng's role, which was initially a food supplement, then developed into anti-microbe and anti-inflammation. This

study was conducted to investigate the effect of ginseng administration as an anti-inflammatory on pneumonia assessed by the decreases of procalcitonin level and NLR and acceleration of clinical improvement in CAP patients.

MATERIALS AND METHODS

This pretest-posttest quasi-experimental clinical study was performed in patients with community-acquired pneumonia (CAP) who were hospitalized in the Dr Moewardi hospital, Surakarta, Indonesia, between April and June 2020. The subject selection used a consecutive sampling technique. The sample size was 16 samples for each control and treatment group. Patients with CAP requiring hospitalization inward, aged over 18 years old, willing to join in the study, having a pneumonia severity index (PSI) or PORT score of 51 - 130 were included in this study. We excluded patients with nosocomial pneumonia, comorbidity, or immunocompromised conditions such as HIV and chronic kidney failure, pregnancy, and cardiac patients undergoing warfarin therapy. The discontinue criteria were death during follow up, withdrawal from the study, severe adverse events from the ginseng extract during the study period, and loss to follow up.

All subjects who met the inclusion criteria were informed about the goal of this study and signed informed consent. We used an incidental sampling technique for determining patients receiving ginseng extract. These subjects received empirical as well as definitive antibiotics based on the culture finding and standard symptomatic drugs. Subjects in the treatment group got additional therapy of ginseng extract with a dose of 2 x 100mg per day during the hospitalization. Procalcitonin level and NLR were examined on days 0 and 3. We assessed the length of clinical improvement based on stable clinical criteria comprising stable vital signs in 24 hours such as the axillary temperature of < 37.8^{0}C, respiratory rate of ≤ 24 bpm, heart rate of ≤ 100 bpm, systolic blood pressure of ≥ 90mmHg, and oxygen saturation of ≥ 90% or PaO_2 pressure of ≥ 60mmHg when breathing in room air, ability to maintain oral intake, and normal mental status.

This research was ethically reviewed and approved by the Dr. Moewardi hospital Committee for Research on Human Subjects (Medical) with number 638/III/HREC/2020. All data were analyzed with SPSS 21 for Windows. We used a paired t-test for normal distribution data, and if the data were not distributed normally, we applied the Wilcoxon test. The p-value of ≤ 0.05 was considered statistically significant.[15]

RESULTS

We obtained 32 inward patients who were eligible to follow this study. However, 3 patients dropped out of the study because two patients were lost to follow up, and one patient experienced heart palpitation after consuming ginseng extract. The remaining 32 samples were assigned to control and treatment groups. The study subjects' baseline characteristics were sex, age, body mass index (BMI), job, smoking history, hospitalization history, and comorbid disease. We assessed the homogeneity of these variables to fulfill the requirement for clinical study procedure eligibility. The categorical variables were sex, job, smoking history, hospitalization history, and comorbid disease, and the numerical variables include age and BMI. All subject characteristic data of both groups were homogenous (p>0.05) (Table 1)

Table 1. The baseline characteristics of the study subjects

Variable	Group		p
	Control (n=16)	Treatment (n=16)	
Sex			1.00
Male	11 (68.8%)	11 (68.8%)	
Female	5 (31.3%)	5 (31.3%)	
Age	58.06±8.28	60.38±10.26	0.488
BMI	18.74±2.53	19.81±2.78	0.266
Occupation			0.932
Laborer	1 (6.3%)	2 (12.5%)	
Housewife	2 (12.5%)	2 (12.5%)	
Farmer	6 (37.5%)	4 (25.0%)	
Civil servant	3 (18.8%)	3 (18.8%)	
Enterpreneur	4 (25.0%)	5 (31.3%)	
Smoking			0.734
Yes	11 (68.7%)	9 (56.2%)	
No	5 (31.3%)	7 (43.8%)	
Hospitalization			0.264
Yes	4 (25.0%)	7 (43.8%)	
No	12 (75.0%)	9 (56.2%)	
Comorbid			0.103
Lung cancer	5 (31.3%)	2 (12.5%)	
IPF	0 (0.0%)	1(6.25%)	
Pneumothorax	2 (12.5%)	0 (0.0%)	
COPD	2 (12.5%)	8 (50.0%)	
Stroke	2 (12.5%)	0 (0.0%)	
Tuberculosis	4 (25.0%)	2 (12.5%)	
Thymoma	1 (6.25%)	3 (18.75%)	

Note: Age and BMI were analyzed with a T-test. Gender, occupation, smoking status, hospitalization history, and comorbidities were analyzed using the Chi-square / Fisher exact test.

The effect of ginseng extract administration on procalcitonin level

The early PCT level's mean in the control group was 1.44±0.51. Then on day 3, it became 1.13±0.43 showing a significant decrease by 0.31±0.14 (p=<0.001). Meanwhile, in the treatment group, the early PCT level's mean was 1.56±0.57. On the third day, it decreased significantly to 0.81± 0.47. This demonstrated a decreased mean value up

to 0.75±0.21 (p=<0.001). There was a statistically significant difference regarding the decrease of PCT level on day three between both groups, in which the PCT level in the treatment group was lower than that of the control group (p≤0.001). (Table 2)

Table 2. The comparison of the mean value of PCT level between control and treatment groups

Group	Day 0	Day 3	p	Δ day 3 - 0
Control	1.44±0.51	1.13±0.43	<0.001[c]	-0.31±0.14
Treatment	1.56±0.57	0.81±0.47	<0.001[c]	-0.75±0.21
p value	0.526[a]	0.014[b]		< 0.001[b]

Note: The results are described in mean±SD; a: Independent t-test; b: Mann Whitney test; c : Wilcoxon test; p-value of < 0.05 = statistically significant

The effect of administering ginseng extract on serum NLR level.

The mean serum NLR level of the control group on day 0 was 7.08±0.85, and on day three, it declined to 5.67±0.83. There was a significant decrease by 1.41±0.37 from day 0 to day 3 (p<0.001). Meanwhile, in the treatment group, the mean levels of serum NLR on days 0 and 3 were 7.15±0.80 and 5.11±0.51, respectively. Thus, there was a significant decrease by 2.04±0.51 (p<0.001). The comparison test obtained that the mean level of NLR in the treatment group was significantly lower than that of the control group (p<0.001). (Table 3)

Table 3. The comparison test on serum NLR level between control and treatment groups

	NLR (%)			
Group	Day 0	Day 3	p	Δ
Control	7.08±0.85	5.67±0.83	<0.001[c]	-1.41±0.37
Treatment	7.15±0.80	5.11±0.51	<0.001[c]	-2.04±0.51
p value	0.817[a]	0.027[a]		<0.001[b]

Note: The results are described in mean±SD; a: Independent t test; b: Mann Whitney test; c: Paired t test: p value of <0.05 = statistically significant.

The effect of ginseng extract on the length of clinical improvement

The mean length of clinical improvement in the control group was 7.06±0.93 days, while in the treatment group, it was 5.69±0.95 days. There was a significant difference between the control and treatment groups (p=0.001). (Table 4)

Table 4. The comparison test on the length of clinical improvement between control and treatment groups

	Group		
Variable	Control (n=16)	Treatment (n=16)	p
Length of clinical improvement (day)	7.06±0.93	5.69±0.95	0.001

Note:The results are described in mean±SD, the comparison test used the Mann Whitney test and the p-value of <0.05 was statistically significant.

DISCUSSION

Community-acquired pneumonia is one of the most common acute infections requiring hospitalization, and it also has high morbidity and mortality rates worldwide. A definite diagnosis of pneumonia can be confirmed by taking anamnesis, physical examination, and other supportive examinations such as chest X-ray, blood, and culture tests. Biomarker examination, like procalcitonin, can help in determining the pneumonia severity. Procalcitonin examination can guide the decision for either requiring outpatient treatment or hospitalization. Moreover, it helps in giving antibiotic therapy. Procalcitonin concentration of >0.25µg/L is indicative for antibiotic administration. Neutrophil Lymphocyte Ratio (NLR) level is easily obtained by using a simple laboratory examination, which can be used to recognize and evaluate the presence of systemic inflammation. Antibiotic treatment is not always effective in sterilizing the whole respiratory system so that additional medicine is needed. Therefore, herbal medicine has been greatly developed, especially in patients with recurrent infection and comorbidity. [6-9,16]

A modern study has reported that ginseng radix contains an important biological effect for modulating the functions of the central nervous, cardiovascular, endocrine, and immune systems, improving metabolism, and erection dysfunction. It also has anti-cancer and antioxidant

properties. Another study suggested that ginseng radix plays a role in infection or antimicrobial disease.[17,18.]

Ginseng is an herbal plant mainly containing ginsenoside. Ginsenoside has an anti-inflammatory effect by inhibiting the interaction of LPS with TLR4 in macrophages, the production of TNF-α due to LPS stimulation, the activation of NF-$_K$B signal, and the production of IL-8. Ginsenoside can also suppress TLR2 expression resulting in the inhibition of IL-2 and IFN-γ.[18-20.]

The effects of ginseng use on procalcitonin.

Procalcitonin is a pro-peptide precursor of calcitonin. Procalcitonin is regulated as a response to the microbial toxin and specific bacterial pro-inflammatory mediators, IL-1ß, IL-6, and TNF-α. Procalcitonin level will decline along with the decrease of pro-inflammatory mediators during recovery. The physiologically normal level of PCT in serum is below 0.1 ng/ml, and this can increase up to a hundred folds in systemic bacterial infection.[5,22.]

In the present study, the decrease of PCT level on day 3 in the subjects receiving additional ginseng extract therapy was significantly greater than in the control group. Administering antibiotics can reduce pro-inflammatory cytokine release so that the PCT level in the blood decreases as well. Giving standard therapy added with ginseng extract could lower PCT levels significantly. This is due to the synergy effect between antibiotic and ginseng extract. Thus, it accelerates the decrease of serum PCT level. Ginseng extract administration can inhibit NF-$_K$B activity resulting in the inhibition of pro-inflammatory cytokine release. Panax ginseng can enhance phagocyte activity of macrophage and NK cells.[18,23.]

Our finding is in line with that of Ahn *et al* study reporting that administering ginseng extract to subjects with Staphylococcus aureus reduced the bacterial colony formation in the blood, lymph, and kidneys significantly, which might correlate with bactericidal macrophage. Pretreatment using Ginsana could lower IL-ß, IL-6, IL-12. IL-18, TNF-α, and IFN-γ levels. A study by Choi *et al* study in 2012 revealed that the KRG water extract with MIC_{50} mg/ml activated antibacterial on Listeria monocytogenes by inducing cell morphological damage and the loss of bacterial cell wall integrity. Yuan *et al* study conducted in rats induced lipopolysaccharide (LPS) in 2014 showed that administering ginsenoside Rb1 to those study animals improved the lung injury marked by decreased neutrophil infiltration as well as bleeding, inhibited the activation NF-$_K$ß leading to the decreases of TNF-α, MCP-1, and IL-8.[24-27.]

The effect of ginseng extract on serum NLR

Epithelial cell damage results in the augmentations of inflammatory cytokine, chemokine, and various growth factors, Growth factor, induces the formation and differentiation of polymorphonuclear (PMN), and increases neutrophil count. The interaction of specific microbial adhesin with cellular receptors causes the activation of the NF-$_K$ß transcription factor, producing various pro-inflammatory cytokines or chemokines (IL-1ß, IL-6, IL-8, IL-17, IL-18, and TNF-α). Pro-inflammatory cytokines will activate vascular endothelium producing chemoattractant, which enables transendothelial migration from neutrophil and reactant in the acute phase. Dendritic cell response can recognize microbe from the activation of major histocompatibility complex (MHC) and complement factor. Major histocompatibility complex which reacts with $CD4^+$ will activate early apoptosis in lymphocyte binding to the pathogen. This early apoptosis is for limiting inflammatory response and the spread of infection, which mainly occurs in severe infection.[7-9.]

In our study, the subjects in the control group receiving antibiotics only experienced a decrease in serum NLR. Antibiotic can lessen cytokine release so that it reduces neutrophil migration into the infection site, inhibits the synthesis of pro-inflammatory cytokines and chemokines, and facilitates the release of anti-inflammatory cytokines. Another antibiotic mechanism in reducing neutrophil count is decreasing granulopoiesis and inducing antibodies against hapten formation in the neutrophil. Our subjects in the treatment group who received both antibiotic and ginseng extract had much lower serum NLR than those in the control group. This shows the synergic effect of both of them. Bactericidal action of ginsenoside is by disrupting the bacterial cell potential membrane integrity, inhibiting DNA mutagenesis, anti-quorum sensing, as well as anti-adhesive activity, and modulating immune system.[2,28-30.]

A similar finding was obtained by Song *et al* in 2008 in Denmark, reporting that there was an improvement of microscopic lung disorder (p=0.0003) and decrease of PMN percentage of bronchial washing (p=0.0006) in rats infected with *P.aeruginosa* receiving intramuscular ginseng extract of 2mg/kg BW for two weeks, Nguyen *et al* in 2015 performed a study in Korea revealed that rats infected *S.pneumoniae* receiving ginseng extract with the dose of 100mg/kg BW for 15 days experienced decreases of TNF-α, IL-1ß, TLR-4, and neutrophil infiltration after 48 hours of infection.[31,32]

The effect of ginseng extract on clinical improvement

We observed that subjects receiving both antibiotic and ginseng extract had faster clinical improvement than those in the control group who only got antibiotics. This can be due to adding ginseng extract to standard therapy, modulating the immune system, inhibiting NF-$_K$ß activity, and reducing pro-inflammatory cytokine production. This decreased systemic inflammatory reaction will diminish symptoms and accelerate clinical improvement.

Scaglione *et al*. reported a similar finding conducted to 75 chronic bronchitis patients undergoing either standard antibiotic therapy or standard therapy added with ginseng extract (G155®) 100 mg twice a day. The result showed that bacterial elimination and clinical improvement were significantly better in those receiving this combined therapy, with an average improvement time of 5.9 days as compared to 6.7 days in a standard therapy group. The patient is considered cured and discharged when the infection symptoms like fever, cough, dyspnea, and wheezing diminish or even disappear. The vital signs are within normal limits, and the patient has good oral intake.[10,17.]

This present study is limited by the small sample size and few inflammatory mediators. Thus, further study using more samples and inflammatory mediators affecting pneumonia is needed to understand more about the role of ginseng extract as an adjunct therapy to treat pneumonia, especially anti-inflammation and antimicrobial. Further investigation of ginseng metabolites is needed as oral ginseng bioavailability is low due to low absorption rates of ginseng saponins compound. Ginseng nanoparticle may play a better role to improve bioavailability and increase ginseng's therapeutic effects outcome. During the pandemics of COVID-19 anti-inflammation finding is a promise to investigate more in the patient with pneumonia COVID-19.

CONCLUSION

Administering ginseng extract in patients with community-acquired pneumonia receiving standard therapy can significantly lower procalcitonin level and serum NLR. In addition to those benefits, ginseng extract can accelerate clinical improvement significantly.

ACKNOWLEDGEMENT

The author appreciates to all the participants, who gave willingness to participate and all supports to this study.

AUTHORS' CONTRIBUTIONS

Yusup Subagio Sutanto, Reviono Reviono and Jatu Aphridasari designed the study, making of protocol and managed the work done. Anita Ramlie performed the study and data analysis. Anita Ramlie prepared management patients, sample and laboratory test. Hendra Kurniawan prepared the formulation and completed the manuscript writing.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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