http://dx.doi.org/10.30651/jqm.v6i1.9711

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Research Article

The effect of ginger (*Zingiber officinale*) extract on the neutrophil level and CAT (COPD Assessment Test) scores in workers with COPD due to dust exposure

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ARTICLE INFO

Submitted : 30th August 2022
Accepted : 22nd December 2021
Published : 25th January 2022

Keywords:

COPD, CAT score, neutrophil, ginger

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that does not fully return to normal and is associated with the increased inflammatory response in the airways due to exposure to noxious particles or gases. Workers are susceptible to exposure to steam, dust, gases, and fumes in the work environment. Administration of antioxidants can be beneficial in COPD patients by reducing oxidative stress to reduce the inflammatory response. Ginger contains various active ingredients that act as antioxidants. The research design is a quasi-experimental study with a pre-test and post-test approach. The research subjects were 30 subjects workers diagnosed with COPD. Subjects were divided into two groups: the control group was given standard therapy, the treatment group was given standard therapy and ginger extract. The treatment was given for one month, then the neutrophil and the COPD Assessment Test (CAT) scores were checked. The data were analyzed with an unpaired difference test. The treatment group (-5.67 +2.32) experienced more CAT decline than the control group (-0.73 +1.28) and showed a significant difference; this was evidenced in the unpaired difference test on the post-pre difference value (p = <0.001). The treatment group (-4.93 +4.43) experienced more neutrophil decline than the control group (0.27 +1.10) and showed a significant difference; this was evidenced in the unpaired difference test on the post-pre difference value (p = < 0.001). Administration of ginger extract can reduce neutrophil levels and CAT scores in COPD workers due to dust exposure.

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INTRODUCTION

A number of respiratory illnesses in workers have been linked to exposure to inhaled dust. Occupations with exposure to high amounts of dust such as wood mills, cigarettes, and rice mills are associated with an increased prevalence of respiratory symptoms such as shortness of breath, coughing, irritation of the eyes and nose, and the risk of developing chronic obstructive pulmonary disease (COPD) (Asri et al., 2020; Löfstedt et al., 2017). This progressive disease is characterized by airflow limitation that does not fully return to normal and is associated with increased inflammatory response in the airways caused by exposure to harmful gases or particles. A study conducted in Spain found that COPD prevalence was 9% in men aged over 40 years and 20% of those over 65 years (Aisanov et al., 2019). Overall, 10-15% of COPD sufferers are associated with occupational exposure (Fishwick et al., 2015). The incidence of COPD is relatively high among workers due to exposure to steam, dust, gas, and smoke in the work environment. This makes COPD one of the most challenging diseases in the future (Molen et al., 2018; Perhimpunan Dokter Paru Indonesia, 2016).

Establishing a COPD diagnosis should be considered in patients with symptoms of chronic cough, shortness of breath, and sputum production with a history of exposure to motor vehicle fumes, cigarette smoke, household smoke, burning smoke, and chemical fumes or dust in the workplace. In COPD, the abnormal inflammatory response that occurs in COPD involves neutrophils along with other inflammatory cells, including macrophages and CD81 T lymphocytes, which play a role in producing structural changes in the airways (Stockley, 1999).

The COPD Assessment Test (CAT) score is a method in the form of a validated, easy-to-implement questionnaire consisting of eight statement items to find out about health status in COPD (Report, 2009; Stockley, 1999). The CAT score also serves as a component for clinical assessment, helping to monitor the effects of COPD such as rehabilitation programs or improvement of exacerbations so that the therapy given can be optimal (Feliz-Rodriguez et al., 2013; Roca et al., 2013).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed international standard treatment guidelines for stable and exacerbating COPD patients. These guidelines have been through extensive clinical trials and evidence. Giving standard therapy did not stop the progression of the disease. Therefore, the provision of additional therapy is needed to further slow down, stop, or replace the damage that has occurred. The basis for giving this additional therapy still refers to the pathogenesis of COPD in the form of oxidative stress, inflammation, protease-antiprotease imbalance, and apoptosis (Global Initiative for Chronic Obstructive Lung Disease, 2014; Roca et al., 2013).

Administration of antioxidants can be beneficial in COPD patients by reducing oxidative stress so that it can reduce the inflammatory response. Ginger is a herbal medicine that has a high antioxidant effect. Ginger extract is obtained easily, and the price is relatively low because there are many ginger extract products on the market. Ginger contains many components of active ingredients, such as phenolics and terpenes. Ginger acts as an antioxidant by inhibiting the production of reactive species antigens and lipid peroxidase (Hansel & Barnes, 2009; Mao et al., 2019).

The purpose of this study was to analyze the effect of giving ginger extract on respondents suffering from COPD due to dust through the assessment of neutrophils in the blood and CAT

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scores. The results of this study are expected to be helpful in the field of occupational health. Regular administration of ginger is thought to prevent and reduce the severity of COPD due to dust exposure.

METHODS

This was a quasi-experimental study, with pre-test and post-test control groups design and using consecutive sampling. The study was conducted at the Muhammadiyah Hospital in Central Java, sampling from June – August 2021.

The subjects are workers with COPD due to dust exposure who are routinely controlled at the Pulmonary Polyclinic at the Muhammadiyah Hospital in Central Java. The inclusion criteria were patients in stable condition, aged more than 40 years, having a work history of more than 15 years, not an active smoker, and willing to participate in the study. The exclusion criteria were patients with chronic renal failure, patients with diarrhea, patients who received other herbs during the study, and the discontinuous criteria were patients who withdrew from the study and patients who experienced severe side effects during treatment.

The sample size was determined based on unpaired numerical analysis, with a total sample size of 30 people. This study used a sample size of 30 subjects consisting of 15 subjects in the treatment group and 15 subjects in the control group.

The treatment group received standard COPD therapy plus ginger extract, while the control group received standard COPD therapy. Treatment using ginger extract capsules from Borobudur herbal products, and this research has received ethical approval with the issuance of ethical clearance no: 067/EC/FK/2021 issued by the Health Research Ethics Committee, Faculty of Medicine, Muhammadiyah University, Semarang.

Data analysis was performed using SPSS 21. Comparison between the independent and dependent variables using a different test. The difference test is the result of a test to see the difference between two samples. Measurement of neutrophil samples using an automatic hematology analyzer with whole blood sampling and measurement of CAT score using a standardized CAT questionnaire. This study uses paired samples with paired t-test. CAT score difference before and after administration of ginger extract in COPD patients who received ginger extract compared to the control group will be analyzed using an unpaired t-test. The effect of giving ginger extract on CAT score between pre and post-treatment was analyzed using a different test technique pre-post treatment (paired t-test).

RESULTS

Characteristics of Research Subjects

The study results obtained the characteristics of the research subjects in the form of age, gender, occupation, length of work, and education. The statistical test used for categorical data is the chi-square test / Fisher exact test, while the statistical test for numerical data is the Mann-Whitney test. Normality test was done by Shapiro Wilk test. The significance value used in this study is = 5%. The results are as seen in Table 1.

Table 1 shows that the results of the statistical test of patient characteristics in the treatment group and control group with a p-value >0.05 (there is no significant difference) are age ($p = 0.383$), occupation ($p = 0.761$), length of work ($p=0.080$), and education ($p=0.519$). In comparison, the gender is $p = 0.0003$ ($p <0.05$), which means there is a significant difference between patients in the treatment and control groups.

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Table 1. Characteristics of Research Subjects

No	Characteristics	Group		Total	p-value
		Treatment	Control		
1	Age (years)	64.00 +12.58	60.27 +10.37	62.13 +11.48	0.383
2	Gender				0.003*
	Male	13 (86.7%)	5 (33.3%)	18 (60.0%)	
	Female	2 (13.3%)	10 (66.7%)	12 (40.0%)	
3	Work				0.761
	Construction Laborers	4 (26.7%)	2 (13.3%)	6 (20.0%)	
	Ricemill worker	4 (26.7%)	6 (40.0%)	10 (33.3%)	
	Stone craftsman	1 (6.7%)	3 (20.0%)	4 (13.3%)	
	DL sweeper	1 (6.7%)	1 (6.7%)	2 (6.7%)	
	Bricklayer	2 (13.3%)	1 (6.7%)	3 (10.0%)	
	Carpenter	3 (20.0%)	2 (13.3%)	5 (16.7%)	
	Length of work	33.87 +9.41	27.67 +6.78	30.77 +8.65	0.080
4	Education				0.519
	Elementary school	8 (53.3%)	5 (33.3%)	13 (43.3%)	
	Junior high school	6 (40.0%)	8 (53.3%)	14 (46.7%)	
	Senior High School	1 (6.7%)	2 (13.3%)	3 (10.0%)	

Information: *[a]Numerical data is normally distributed, independent test t test;*
[b]Nominal categorical data; frequency (%), chi square test/fisher exact test;
[c] Numerical data is not normally distributed or ordinal categorical data, Mann Whitney test;
**significant at =5%*

Table 2. CAT Score Difference Between Control Group and Treatment Group (*Zingiber officinale*)

No	Group	CAT			
		Pre	Post	p	Post – Pre
1	Treatment	30.67 +2.16	25.00 +2.14	<0.001[c]	-5.67 +2.32
2	Control	30.40 +1.30	29.67 +1.11	0.046[d]	-0.73 +1.28
	p	0.305[a]	<0.001[a]		<0.001[b]

Note: *Observation results are described with a mean ± SD,*
a*: unpaired group difference test did not pass the normality requirement (Mann Whitney);*
b: *unpaired group difference test passed the normality requirement (independent t-test););*
c*: test for different groups in pairs passed the normality requirement (pair t-test);*
d*: The paired difference test did not pass the normality requirement (Wilcoxon rank test).*
Changes are declared significant if the test results in p < 0.05.

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Different Test of CAT Pre, Post, and Post-Pre Differences Control Group and Treatment Group (*Zingiber officinale*)

Based on the Shapiro Wilk test, the distribution of data from CAT observations in the unpaired group difference test did not pass the normality requirement; the different test with Mann-Whitney was pre-test and post-test data. In contrast, the data that met the assumption of normality used the independent t-test test, namely the post-pre difference data. The paired difference test of the treatment group passed the normality requirement, the difference test was carried out with the paired t-test, while the control group did not pass the normality requirement. The different test was carried out with the Wilcoxon rank test. The results are shown in Table 2.

Based on Table 2 the treatment and control groups experienced a statistically significant change in the decrease in CAT. The subjects of the *Zingiber officinale* supplementary treatment group experienced a more significant reduction in CAT than the control group and showed statistically significant differences. Thus, the *Zingiber officinale* group was more effective in reducing CAT compared to the control group.

Pre, Post, and Post-Pre Neutrophil Difference Test for Control Group and Treatment Group (*Zingiber officinale*)

Based on the Shapiro Wilk test, the distribution of data from observations of neutrophils in the unpaired group difference test passed the normality requirements, the different test with independent t-test, namely pre-test and post-test data. Meanwhile, data that did not meet the assumption of normality using the Mann Whitney test, namely the post-test difference data. The paired difference test of the treatment and control groups passed the normality requirement. The difference test was carried out with the paired t-test as seen on Table 3.

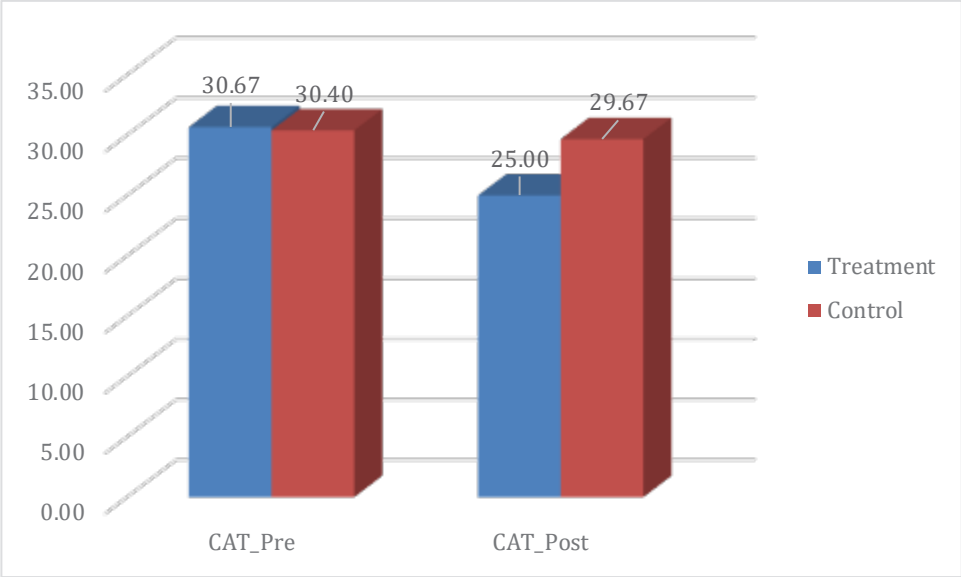

Figure 1. Comparison of CAT Score Results between treatment (*Zingiber officinale*) and control group

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Table 3. Neutrophil Difference Test Between Control and Treatment Group (*Zingiber officinale*)

NO	Group	Neutrophil			
		Pre	Post	p	Post – Pre
1	Treatment	60.80 +6.78	55.87 +6.85	0.001	-4.93 +4.43
2	Control	60.20 +4.28	60.47 +4.41	0.364	0.27 +1.10
	P	0.774[a]	0.037		<0.001[b]

Information: *The results of observations are described with a mean ± SD,*
a: *unpaired group difference test passed the normality requirement (Independent t-test);*
b: *unpaired group difference test did not pass the normality requirement (Mann Whitney);*
c: *test for different groups in pairs passed the normality requirement (pair t-test).*
Changes are declared significant if the test results in p < 0.05, neutrophil in cells/µL

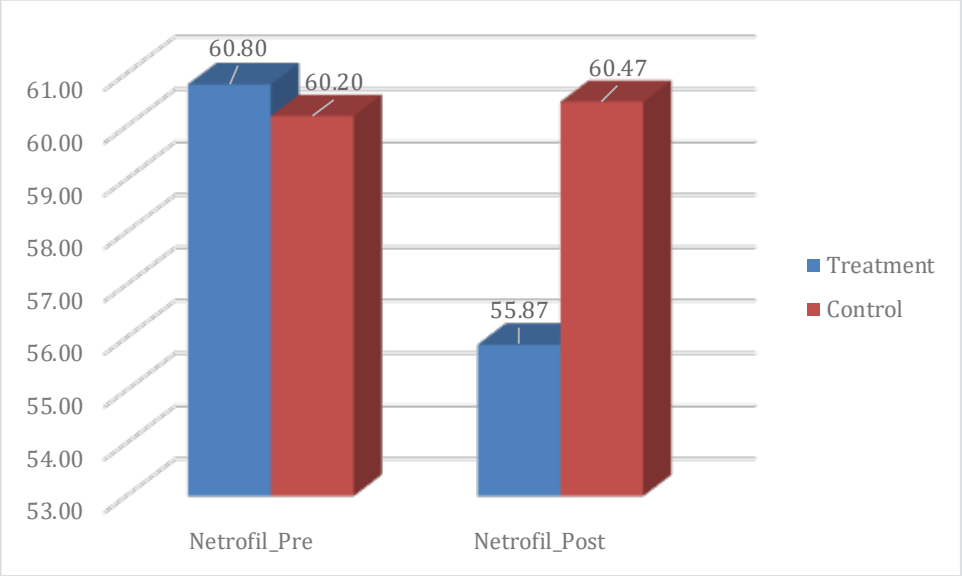

Figure 2. Comparison of Neutrophil Examination Results between treatment groups (*Zingiber officinale*) and control (cells/µL)

Based on the results of Table 3, the treatment group experienced a statistically significant change in neutrophil decline. In contrast, the control group did not experience a significant change in neutrophils. Subject which receive additional *Zingiber officinale* treatment, experienced more neutrophil reduction than the treatment group and showed a statistically significant difference. Thus, the *Zingiber officinale* group was more effective in reducing neutrophil levels than the control group.

DISCUSSION

Lung disease due to oxidative stress occurs due to molecular changes in the complex interactions of multiple genes and oxidants. These changes are due to oxidants' direct or indirect action on target cells. The direct action of oxidants is in the form of peroxidation of cell membrane lipids, proteins, and deoxyribonucleic acid (DNA). The indirect action of oxidants is through protease activation, antiprotease inactivation, transcription of proinflammatory mediators,

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and apoptosis (Barnes PJ, Drazen JM, Rennard S, 2529; Löfstedt et al., 2017; Mao et al., 2019).

Administration of antioxidants can be beneficial in COPD patients by reducing oxidative stress so that it can reduce the inflammatory response. Ginger is a herbal medicine that has a high antioxidant effect. Ginger contains many components of active ingredients, such as phenolics and terpenes. Ginger acts as an antioxidant by inhibiting the production of reactive species antigens and lipid peroxidase (Fishwick et al., 2015; Perhimpunan Dokter Paru Indonesia, 2016).

The COPD Assessment Test (CAT) is a method in the form of a validated, easy-to-apply questionnaire consisting of eight statement items to find out about health status in COPD (Global Initiative for Chronic Obstructive Lung Disease, 2014; Molen et al., 2018). The CAT score can be used for all patients diagnosed with COPD unstable and exacerbating COPD at all degrees of severity (Report, 2009; Stockley, 1999). The results showed that subjects given additional treatment with Zingiber officinale (-5.67 +2.32) experienced more CAT reduction than the control group (-0.73 +1.28) and showed statistically significant differences evidenced in the unpaired difference test. on the value of the post-pre difference (p = <0.001). Thus, the *Zingiber officinale* group was more effective in reducing CAT score compared to the control group.

The active components in ginger induce bronchodilation by modulating intracellular calcium Ca21 in airway smooth muscle. Ginger induce relaxation of human airways rapidly and significantly. The four active components were then tested to relax airway smooth muscle in the guinea pig and human tracheas: [6] -gingerol, [8] -gingerol, and [6] -shogaol induced rapid relaxation of airway smooth muscle (100–300 mM), whereas [10]-gingerol failed to induce relaxation. In human airway smooth muscle cells, exposure to [6]-gingerol, [8]-gingerol, and [6]-shogaol, but not [10]-gingerol (100 mM), blunted the subsequent Ca21 response to bradykinin (10 mM). Another study conducted on rats treated with nebulized [8]-gingerol (100 mM), 15 minutes before the administration of methacholine, significantly reduced airway resistance. These new data suggest that ginger and its isolated active components, [6]-gingerol, [8]-gingerol, and [6]-shogaol, relax airway smooth muscle, and [8]-gingerol attenuates airway hyperresponsiveness, breath, in part by altering Ca21 regulation. This purified active component can provide an alternative to single therapy or combined with primary therapies, including ß2-agonists, in airway disease (Feliz-Rodriguez et al., 2013; Hansel & Barnes, 2009; Perhimpunan Dokter Paru Indonesia, 2016; Roca et al., 2013). Based on the description above, it is known that the active substance in ginger can reduce the production of oxidative stress, suppress the formation of lipid peroxidase and nitric oxide. Inhibition of oxidative stress formation will inhibit the decrease in elastin degradation, thereby inhibiting airway damage. Airflow obstruction in COPD can be identified through the COPD CAT scoring examination. Thus the hypothesis which states that "*There is an effect of giving ginger extract on the CAT score of workers with COPD due to dust exposure*" is proven.

Neutrophils are one of the phagocyte systems in the human body that have the largest component. The role of neutrophils is crucial in terms of the body's defense from foreign dangers ranging from acute to chronic processes. COPD attacks the airways and has such systemic manifestations as elevated C-reactive protein. Activation of peripheral blood neutrophils by cytokines has been shown to occur. This activation is thought to be related to disease severity. Systemic neutrophils in COPD patients enhance extracellular

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chemotaxis and proteolysis (Shetkar & Pyati, 2018).

This study shows that the subjects given additional treatment with *Zingiber officinale* (-4.93 +4.43) experienced more neutrophil reduction compared to the control group (0.27 +1.10) and showed statistically significant differences. This is evidenced in the no different test paired on the post-pre difference value (p= <0.001). Thus, the *Zingiber officinale* group was more effective in reducing neutrophil levels than the control group.

The anti-inflammatory effect of ginger may be related to inhibiting the biosynthesis of prostaglandins and leukotrienes. Several other studies have shown that gingerols actively inhibit arachidonate 5-lipoxygenase, a leukotriene biosynthetic enzyme. The compound [8]-gingerol in ginger has been shown to inhibit the expression of cyclooxygenase-2 (COX-2), which is induced during inflammation to increase the formation of prostaglandins. Some of the anti-inflammatory effects of ginger appear to be related to decreased IκBα degradation and impaired translocation of nuclear factor-κB (NF-κB) p65. The main scientific evidence indicates that ginger and its various components have anti-inflammatory effects both in vitro and ex vivo. However, data supporting ginger as an effective anti-inflammatory agent in humans in vivo is incomplete (Barbu et al., 2011; Cho et al., 2015; Desai et al., 2012; Global Initiative for Chronic Obstructive Lung Disease, 2014; Koh et al., 2009; Mao et al., 2019; Oemiati, 2013; Perhimpunan Dokter Paru Indonesia, 2016). Thus, giving ginger as an antioxidant can be beneficial in COPD patients by reducing oxidative stress so that it can reduce the inflammatory response, which has an impact on decreasing neutrophils.

The limitations of this study are the lack of samples that are treated, and there are still other confounding factors that cause COPD. It is hoped for further research so that the subject is more comprehensive and these confounding factors can be controlled.

CONCLUSION

There is an effect of giving ginger extract on reducing neutrophil levels and CAT scores in COPD workers due to dust exposure. Therefore, the supplementation in the form of ginger can be recommended so that the quality of life of these workers will improve.

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