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# *THE EFFECTS OF PINUS MASSONIANA (PINE POLLEN) AS ADJUVANT THERAPY ON LEUCOCYTES, T LYMPHOCYTES, C-REACTIVE PROTEIN, AND D-DIMERS IN HOSPITALIZED COVID-19 PATIENTS*

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## *ABSTRACT*

***Introduction:*** *SARS-CoV-2 infection has caused the Corona Virus Disease-19 (COVID-19) pandemic until present day. Pine pollen has been known and used as a medicine and has benefits for immunity.* ***Aim:*** *To determine the effects of Pinus massoniana (pine pollen) as an adjuvant on leukocytes count, T lymphocytes (CD4, CD8) count, plasma C-reactive protein level, plasma D-dimer level in hospitalized COVID-19 patients with moderate-severe clinical manifestation.* ***Materials and Method:*** *We used a double blind pretest-posttest control group design, with 2 groups, namely control (placebo) and treatment. The subjects were selected by simple random sampling, male and female patients aged 20-60 years. Peripheral blood samples were taken before and after treatment. Patients were given pine pollen or placebo 3 x 4 capsules (3 g / day) for 7 days. Data were analyzed by SPSS 23.0 t-test with significant value of $p < 0.05$.* ***Results:*** *The patients of treatment group were 16 people (13 male, 3 female), average age 46,25 years and control 13 people (10 male, 3 female), average age 47,92 years. The leukocytes count increased not significantly in the treatment group (p=0.499; 8.03%) while control increased significantly (p=0.027; 36.42%). The leukocytes count of control was 4,5 times greater than treatment group. The CD4 count increased significantly in the treatment group (p=0.004; 73.44%) and control (p=0.048; 28.97%), and the it was 2,5 times greater than control. The CD8 count increased significantly in the treatment group (p=0.005; 72.90%) and control (p=0.033; 34.66%), and it was 2,1 times greater than control. CRP levels were significantly reduced in the treatment*

*group (p=0.001; 71.61%) and control (p=0.001; 78.13%). D-dimer levels decreased significantly in the treatment group (p=0.048), while the control increased but not significantly (p=0.200). The D-dimer level in the treatment group decreased by 37.93%, while the control increased by 43.70%.* ***Conclusion:*** *Further research is still needed to explore the effect of pine pollen on cellular immunity which in this case is T lymphocytes, especially CD4 and CD8, and hemostasis (coagulation) especially D-dimer. Pine pollen is beneficial for immune modulation in COVID-19 patients.*

***Keywords:*** *COVID-19, pine pollen, leukocytes, T lymphocytes, C-reactive protein, D-dimer.*

**ABSTRAK**

**Pendahuluan:** Infeksi SARS-CoV-2 menimbulkan pandemi *Corona Virus Disease-19* (COVID-19) hingga saat ini. Serbuk bunga pinus (*pine pollen*) adalah herbal yang telah digunakan sebagai pengobatan dan bermanfaat untuk imunitas. **Tujuan:** Untuk mengetahui efek serbuk *Pinus massoniana* (pine pollen) sebagai adjuvan terhadap jumlah leukosit, jumlah limfosit T (CD4, CD8), kadar *C-reactive protein* plasma, kadar D-dimer plasma pada pasien COVID-19 rawat inap bermanifestasi klinis sedang-berat. **Material dan Metode:** Kami menggunakan *double blind pretest-posttest control group design,* dengan 2 kelompok yaitu kontrol (plasebo) dan perlakuan. Para subyek dipilih secara *simple random sampling*, pasien laki-laki dan perempuan berusia 20-60 tahun. Sampling darah tepi diambil sebelum dan sesudah perlakuan. Pemberian pine pollen 3 x 4 kapsul (3 g / hari) selama 7 hari. Data dianalisis dengan uji t SPSS 23.0 nilai signifikan $p < 0,05$. **Hasil:** Pasien kelompok perlakuan adalah 16 orang (13 laki-laki, 3 perempuan), rata-rata berusia 46,25 tahun, dan kontrol 13 orang (10 laki-laki, 3 perempuan), rata-rata berusia 47,92 tahun. Jumlah leukosit meningkat tidak bermakna pada kelompok perlakuan (p=0,499; 8,03%) sedangkan kontrol meningkat bermakna (p=0,027; 36,42%). Peningkatan jumlah leukosit kontrol 4,5 kali daripada perlakuan. Jumlah CD4 meningkat bermakna pada kelompok perlakuan (p=0,004; 73,44%) dan kontrol (p=0,048; 28,97%), dan peningkatan CD4 2,5 kali daripada kontrol. Jumlah CD8 meningkat bermakna pada kelompok perlakuan (p=0,005; 72,90%) dan kontrol (p=0,033; 34,66%), dan peningkatan CD8 2,1 kali daripada

kontrol. Kadar CRP berkurang bermakna pada kelompok perlakuan (p=0,001; 71,61%) dan kontrol (p=0,001; 78,13%). Kadar D-dimer berkurang (37,93%) secara bermakna pada kelompok perlakuan (p=0,048), sedangkan pada kontrol meningkat (43,70%) namun tidak bermakna (p=0,200). **Kesimpulan:** Penelitian lebih lanjut masih dibutuhkan untuk eksplorasi efek pine pollen terhadap imunitas seluler yang dalam hal ini yaitu limfosit T, khususnya CD4 dan CD8, dan hemostasis (koagulasi) khususnya D-dimer. Pine pollen bermanfaat untuk modulasi imunitas pada pasien COVID-19.

**Kata kunci:** *COVID-19, pine pollen, leukosit, limfosit T, C-reactive protein, D-dimer.*

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## INTRODUCTION

SARS-CoV-2 infection has caused the Corona Virus Disease-19 (COVID-19) pandemic since December 2019. Indonesia is one of the countries with the highest incidence in Southeast Asia. (1)

This virus originated in bats and was transmitted to humans via an unknown intermediate animal in Wuhan, Hubei province, China in December 2019. The incubation period for this disease ranges from 2 to 14 days. The disease is mild in most people; in some people (usually the elderly and people with comorbidities), it can develop into pneumonia, Acute Respiratory Distress Syndrome (ARDS), and Multiple Organ Dysfunction (MOD). (2)

Fever, dry cough, shortness of breath, myalgia, fatigue, a tendency to leukopenia, and progressive pneumonia on radiological findings, which may be the cause of ARDS, based on clinical and laboratory findings similar to those seen in COVID-19, SARS-CoV, and MERS-CoV. This may suggest that the pathogenesis may also be similar. (3)

SARS-CoV-2 is spread mainly through direct contact with saliva droplets or fluids that come out of the respiratory tract of an infected person when they cough or sneeze.(4) After binding to the cell surface of the angiotensin converting enzyme-2 (ACE-2) receptor by the spike glycoprotein, the virus enters the cell cytoplasm, where it releases its RNA genome and replicates, resulting in the formation of new viral particles. Then, the cell is destroyed and the virus spreads to other cells.

Apart from the majority of patients with mild COVID-19, patients with the severe type can rapidly progress to ARDS, MOF, and even death (5). Therefore, exploring potential risk factors for the severity of COVID-19 is critical to delay or halt disease progression. Previous studies have revealed that patients with advanced age and underlying disease are more likely to have more severe disease (5), and aberrant immune-inflammatory responses and cytokine storms may play an important role in disease progression. (6)

The results of the analysis of laboratory tests in cases of COVID-19 showed that the number of leukocytes (white blood cells) increased, especially neutrophils but reduced lymphocytes. An increase in leukocytes, an increase in neutrophils, and a decrease in lymphocytes was positively correlated with the severity of the clinical condition and mortality. The number of monocytes, basophils, eosinophils was reduced but there was no correlation with the severity of the clinical condition. The decrease in lymphocytes is thought to be the result of functional fatigue of cellular immunity, especially cytotoxic T cells (7).

*C-reactive protein* (CRP) is used as a marker of inflammation. CRP is used as a prognostic factor for cardiovascular disease. Elevated CRP has a positive correlation with the risk of cardiovascular disease, as well as with the severity of acute pancreatitis. CRP stimulates pro-apoptotic cytokines and pro-inflammatory mediators, namely TNF-α, IL-1β, and reactive oxygen species. CRP increases p53 gene expression, that triggers cell death (8). A study by Wang, 2020, on COVID-19 cases showed that CRP levels were significantly positively correlated with the severity of the disease and the size

of the lung lesions. CRP levels in patients with mild symptoms, 1.52 ± 1.56 mg/L, moderate symptoms 16.76 ± 18.58 mg/L, severe symptoms 54.15 ± 1.06 mg/L, and critical 105.00 ± 12.73 mg/L. The more severe the condition of the COVID-19 patient, the higher the CRP level (9). The study by Sharifpour et. al., 2020, also showed that CRP levels were positively correlated with the clinical condition of the severity of COVID-19 patients. The median CRP level of patients admitted to the intensive care unit (169 mg/L (IQR=111-234 mg/L)) was higher than that of patients admitted to a regular inpatient setting (130 mg/L (IQR=82-191 mg/L)). Median CRP levels of patients who died (206 mg/L (IQR=157-288 mg/L)) were higher than those of patients who survived (114 mg/L (IQR=72-160 mg/L)). CRP levels increased linearly during hospitalization, and reached a peak on day 5 of treatment. CRP levels can be used as a prognostic marker for the clinical condition of COVID-19 patients. (10)

D-dimer is elevated in COVID-19 patients. D-dimer is a prognostic factor in the clinical outcome of COVID-19 patients. D-dimer levels were higher in severe than mild clinical conditions, in ARDS conditions than in non-ARDS, in patients who died than those who survived (11). D-dimer and prothrombin time were higher in COVID-19 patients in intensive care than in non-intensive care. D-dimer levels > 1 g/ml at hospital admission were positively correlated with mortality. The explanation for the increase in D-dimer is that viral infection in the pulmonary vascular endothelium via the ACE-2 receptor causes endothelial apoptosis. The coagulation process is triggered by endothelial apoptosis. Increased blood clots due to hypercoagulation cause hyperfibrinolysis resulting in increased fibrin degradation products and D-dimer (12).

Pine pollen has been known and used as a medicine since the Tang dynasty in China. Pine pollen is used to treat urinary disorders, blood circulation, heart and stomach ailments, restore stamina (13).

Pine pollen contains amino acids, vitamins (A, B, D, E), minerals (Ca, P, Fe, Mg, Zn, Na, K), phytosterols (brassinosteroids), flavonoids, methylsulfonylmethane

(MSM). Phytosterols or phytosteroids are steroid hormones found in plants. Phytosterols can be found in onions, garlic, celery, broccoli, cucumber, pepper, potatoes, carrots, soybeans, tomatoes, ginger, cabbage and pine. Brassinosteroids are polyhydroxy steroid hormones that were originally found in the pollen of Brassica napus. The highest levels of brassinosteroids are in seeds and pollen. Brassinosteroids bind to steroid receptors in the cytoplasm (animal cells) thereby triggering gene expression and protein synthesis. Brassinosteroids enhance immunity against viruses by inhibiting viral activity. Brassinosteroids are able to inhibit several viruses such as poliovirus type 1 (RNA virus), Indiana strain vesicular stomatitis virus (RNA virus), Herpes simplex virus-1 (DNA virus), Measles virus (RNA virus). Brassinosteroids inhibit viral RNA multiplication. Brassinosteroids have anti-inflammatory effects, namely reducing levels of IL-6, IFN-α, IL-10, malondialdehyde, CRP, leukotrienes (14).

Research on treatment regimens to treat inflammation (cytokine storm) in COVID-19 is urgently needed. Patients can be prevented from falling into a severe condition if the inflammatory process can be controlled so that it does not cause organ damage. This study is useful to provide information about adjuvant therapy regimens for the treatment of COVID-19. The speed of healing of COVID-19 patients can reduce COVID-19 complications and reduce the duration of hospital stay. Pine pollen is expected to be used to increase cellular immunity in cases of COVID-19.

## MATERIALS AND METHOD

The study obtained ethical approval from Health Research Ethics Committee, Faculty of Medicine, Widya Mandala Catholic University Surabaya and permission from the hospital. The study used a double-blind pretest-posttest control group design. The study used 2 groups, namely control (received placebo) and treatment (received pine pollen), with a total of 18 patients per group (based on Federer formula).

Patients in Gotong Royong Hospital, Surabaya, were selected by simple random sampling and had to meet the inclusion and exclusion criteria. Peripheral blood samples

were taken on day 0 (before treatment) and day 8 (after treatment). Blood samples were tested in Laboratory of Gotong Royong Hospital, Surabaya, and Prodia Laboratory (private and independent laboratory).

The inclusion criteria were aged 20-60 years, male and female, moderate-severe clinical manifestation, diagnosed COVID-19 within 7 days, hospitalized and given COVID-19 protocol therapy. The exclusion criteria were hospitalized in intensive care unit, pregnancy, post partum, lactation, dysphagia, digestive disorders (vomit, diarrhea, malabsorption), bacterial or fungal infection, chronic liver disease or liver failure, history of liver transplantation, aplastic anemia, HIV/AIDS, immunocompromised caused by diseases or drugs or radiotherapy, malignancy.

The treatment was given orally in the form of capsules of size 0 containing 250 mg of pine pollen, with the rule of taking 3 x 4 capsules per day, 8 hour intervals, for 7 days. The pine pollen was purchased in the form of powder from Xi'an Pincredit Bio-tech Co., Ltd., China. We used placebo Avicel PH 102 (microcrystalline cellulose) for control group with same rule of taking. Microcrystalline cellulose is oral tablet filler which is inert and safe.

The data were performed as mean ± SD and analyzed by descriptive statistics, normality test, homogeneity test, t test, which were processed with the SPSS 23.0 program with a significant value of $p < 0.05$. Monitoring of the subject's condition was carried out up to 14 days after the treatment ended.

## RESULT

The number of patients in the control group was 18 people, with 5 patients dropping out (2 patients died, 3 patients lost to follow-up), so that 13 patients participated in the study. The number of patients in the treatment group was 22 people, with 6 patients dropping out (3 patients died, 3 patients lost to follow-up), so that 16 patients participated in the study. Based on gender, the treatment group consisted of 13 male patients and 3 female patients, the control group consisted of 10 male patients and 3 female patients. The mean age of patients in the control group was 47.92 years (30-59 years), while the treatment group was 46.25 years (21-

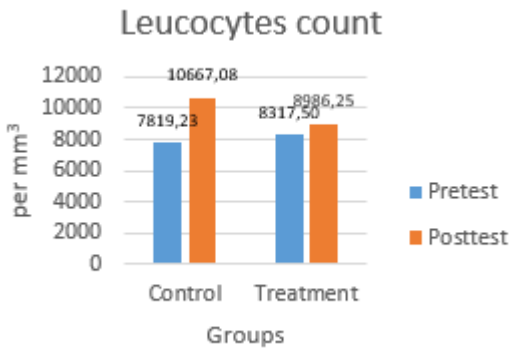
59 years). After the research treatment for 14 days there were no reports of complaints or symptoms due to treatment.

COVID-19 patients who were research subjects had comorbid diseases, namely hypertension, diabetes mellitus, coronary heart disease, chronic kidney failure, chronic hepatitis. The average length of hospitalization was 9 days. Symptoms and signs experienced by patients are cough, runny nose, shortness of breath, nausea, vomiting, weakness, fever, painful swallowing, diarrhea, decreased appetite, anosmia (loss of smell), headache, decreased oxygen saturation, pneumonia, coagulopathy (coagulation disorders), hypokalemia, hyponatremia.

The drugs that the patients received were remdesivir, favipiravir, levofloxacin, dexamethasone, pantoprazole, ondansetron, paracetamol, N-acetylcysteine, fondaparinux, IL-6 receptor antagonist, ranitidine, insulin, multivitamin, vitamin C, vitamin D, convalescent plasma transfusion, alprazolam, codeine.

**Total Leucocytes**

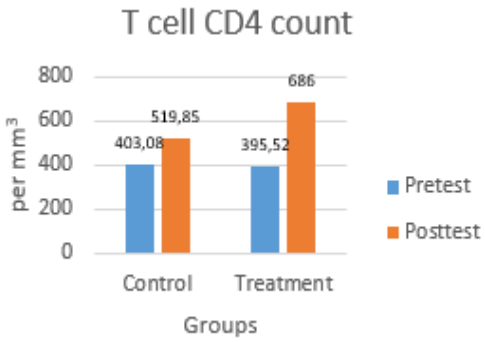
The leucocytes count of control group were 7,819.23 ± 2,974.49 / $mm^3$ (pretest) and 10,667.08 ± 3,954.19 / $mm^3$ (posttest). The leucocytes count of treatment group were 8,318.13 ± 4,057.04 / $mm^3$ (pretest) and 8,986.25 ± 3,102.44 / $mm^3$ (posttest). The number of leukocytes increased in the posttest in both group. The increase was significant in the control group (p=0.027), while in the treatment group it was not significant (p=0.499). The increase in the control group was 36.42%, while the increase in the treatment group was 8.03%. The increase in the number of leukocytes was not significantly different between the control and treatment (p=0.340).



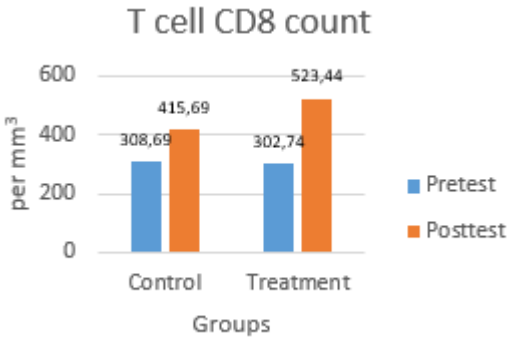

**Lymphocytes**

The CD4 T lymphocytes count of control group were 403.08 ± 230.63 / $mm^3$ (pretest) and 519.85 ± 242.90 / $mm^3$ (posttest). The CD4 T lymphocytes count of treatment group were 395.52 ± 244.21 / $mm^3$ (pretest) and 686.00 ± 239.74 / $mm^3$ (posttest).

The number of CD4 T lymphocytes increased in the posttest in both group. The increase was significant in the control group (p=0.048) and in the treatment group was significant (p=0.004). The increase in the control group was 28.97%, while in the treatment group it was 73.44%. The increase in CD4 cells was not significantly different between the treatment and control groups (p=0.346).

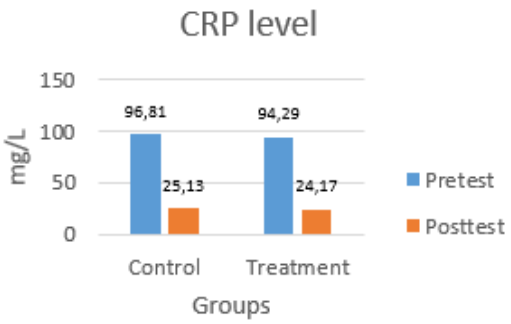



The CD8 T lymphocytes count of control group were 308.69 ± 166.91 / $mm^3$ (pretest) and 415.69 ± 205.15 / $mm^3$ (posttest). The CD8 T lymphocytes count of treatment group were 302.74 ± 236.91 / $mm^3$ (pretest) and 523.44 ± 190.33 / $mm^3$ (posttest). The number of CD8 T lymphocytes increased in the posttest examination in both group. The increase in the control group (p=0.033) and in the treatment group was significant (p=0.005). The increase in the control group was 34.66%, while in the treatment group it was 72.90%. The increase in the number of CD8 T cells was not significantly different between the control and treatment groups (p=0,232).



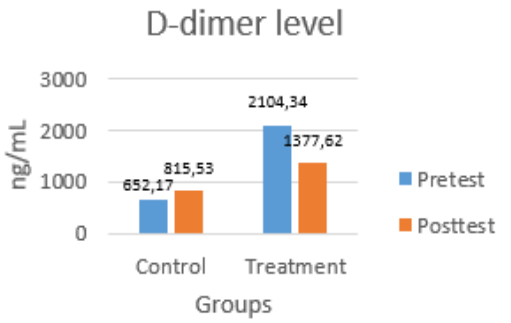

**CRP Levels**

CRP levels of control group were 97.95 ± 58.15 mg/dL (pretest) and 21.42 ± 14.71 mg/dL (posttest). CRP levels of treatment group were 91.20 ± 68.92 mg/dL (pretest) and 25.89 ± 21.78 mg/dL (posttest). CRP levels decreased in the posttest of both group. The reduction rate was significant in both the control group (p=0.001) and in the treatment group (p=0.001). The reduction in the control group was 78.13%, while in the treatment group it was 71.61%. The reduction in CRP levels was not significantly different between the control and treatment groups (p=0.786).




**D-dimer Levels**

D-dimer levels of control group were 607.20 ± 430.05 ng/mL (pretest) and 872.56 ± 468.02 ng/mL (posttest). D-dimer levels of treatment group were 2219.61 ± 1925.95 ng/mL (pretest) and 1377.62 ± 1153.24 ng/mL (posttest). The increase in D-dimer levels in the control group was not significantly different (p=0,200), while the reduction in D-dimer levels in the treatment group was significantly different (p=0,048). D-dimer levels increased in the control group by 43.70%, while the treatment group decreased by 37.93%. The percentage difference in D-dimer between both group was significantly different (p=0.025).




## DISCUSSION

**Effects of pine pollen on leukocytes**

Our research proves that administration of pine pollen has effect in increasing the number of leukocytes. The increase in the number of leukocytes in the control group was about 4 times that of the treatment group. Patients receiving pine pollen tended to have a slight leukocytosis, although the results were not statistically significant. Leukocytosis is the body's natural response to inflammation or infection. According to Skevaki et. al., 2020, leukocytosis is associated with inflammatory activity and is associated with disease severity, high mortality, and bacterial superinfection. The higher the leukocyte count associate with the worse prognosis.

**Effects of pine pollen on lymphocytes**

Our study proved that administration of pine pollen tends to increase the number of T-helper (CD4) and T-cytotoxic (CD8) lymphocytes. The increase in CD4 and CD8 counts in the treatment group was about 2 times that of the control group, although it was not statistically significant. According to Skevaki et.

al., 2020, reduced lymphocyte count, especially CD8, is associated with disease severity and a higher incidence of death. The lymphocyte count is useful as a prognostic marker. The increase in T lymphocytes is useful for increasing cellular immunity against SARS-CoV-2 infection and is a good prognosis.

**Effects of pine pollen on CRP**

CRP is a product that the liver produces when inflammation occurs. Administration of pine pollen showed no significant difference between control and treatment. The patients received steroid medication as a protocol for COVID-19 therapy. Possible effects of steroid drugs that reduce inflammation so that CRP levels are reduced.

**Effects of pine pollen on D-dimer**

D-dimer is a product produced in the coagulation process. Elevated D-dimer is positively associated with disease severity and mortality in COVID-19. The administration of pine pollen showed lower levels of D-dimer in the treatment group than the control group which had increased levels of D-dimer. Decreased levels of D-dimer indicate reduced coagulation activity. Hypercoagulation conditions result in blockage of blood vessels so that the tissue undergoes ischemia and death.

**Effects of pine pollen on immunity**

Pine pollen is useful for modulating immunity. Several studies have proven the effects of pine pollen for infections and tumors. The pharmacological effects of pine pollen are improving immunity, anti-aging, antioxidant, liver protection, inhibiting tumor cell proliferation, inhibiting hyperplasiaostat, anti-fatigue, lowering blood sugar levels, lowering blood lipid levels, improving intestinal function (13).

Pine pollen contains amino acids, vitamins, minerals, flavonoids, brassinosteroids, and MSM. Brassinosteroids are able to inhibit several viruses, namely poliovirus type 1, herpes simplex type 1, herpes simplex type 2, measles (14). The content of MSM is beneficial for its antioxidant, anti-inflammatory effects, reduces pain, increases energy, improves blood circulation, inhibits the release of histamine, and inhibits the proinflammatory cytokine IL-6 (15). Pine pollen still needs to be explored further regarding its effect on the SARS-CoV-2 virus and

modulation of immunity. Pine pollen is beneficial for COVID-19 patients and may be suggested as an adjuvant regimen for the therapeutic management of COVID-19. Prevention of excessive leukocytosis, increased T lymphocyte count, and decreased D-dimer are beneficial for reducing morbidity and mortality due to COVID-19.

## CONCLUSION

Pine pollen is beneficial for COVID-19 patients and may be suggested as an adjuvant regimen for the therapeutic management of COVID-19. Prevention of excessive leukocytosis, increased T lymphocyte count, and decreased D-dimer are beneficial for reducing morbidity and mortality due to COVID-19.

## ACKNOWLEDGMENT

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