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THE INFLUENCE OF ETHANOL EXTRACTS OF RAMBUTAN LEAVES (*NEPHELIUM LAPPACEUM* L.) AGAINST OBESITY AND INSULIN RESISTANCE IN RATS

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ABSTRACT: Ethanol extracts of rambutan leaves have been investigated for their anti-diabetes properties using the glucose tolerance method as well as insulin deficiency through alloxan induction. This study aimed to further evaluate these properties in obese and insulin resistant animals. The rat models were feeding with foods high in carbohydrates, fats, and propylthiouracil. The animal models were divided into seven groups: normal group, the positive control group, rambutan leaf extract at doses of 17.5, 35, and 70 mg/kg b.w., and the orlistat and metformin groups. The parameters evaluated during therapy were body weight, food index, feces index, and blood glucose levels. The rambutan leaf ethanol extract at a dose of 17.5 mg/kg b.w. resulted in a decrease in body weight by 2.44% compared to the initial body weight and could also decrease appetite with the amount of food intake equal to 10.71 g compared with the positive test group at 12.49 g. The rats administered 35 mg/kg b.w. rambutan leaf ethanol extract excreted 6.29g of feces and exhibited a decreased organ and fat index in the liver, spleen, and perirenal fat. In the anti-diabetic test, the blood glucose level was increased 123 mg/dL, but diabetes mellitus and insulin resistance had not yet occurred following administration of 17.5 mg/kg bw rambutan leaf ethanol extract, although the blood glucose level was lower compared with the positive test group (93 mg/dL). In conclusion, the rambutan leaf ethanol extract was shown to decrease body weight and blood glucose levels in rats.

INTRODUCTION: The incidence of overweight and obesity is increasing rapidly in different parts of the world. Obesity has become an epidemic by contributing to 35% of pain and 15–20% of deaths in developed countries. Death is not always directly caused by obesity, but obesity can cause serious health problems that can result in a metabolic disorder; cardiovascular, kidney, and prothrombin issues; as well as an inflammatory response [1].

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According to the World Health Organization (2011), obesity is characterized as excessive or abnormal fat build-up that can impair health. Complex related etiology, *i.e.*, genetic factors, metabolism, living habits, eating habits, activities, and socio-cultural and economic factors, occur in people with obesity [2].

Diabetes mellitus is one complication that can arise as a result of obesity. Diabetes mellitus is a chronic disease that occurs when the pancreas is no longer able to produce insulin, or when the body cannot use the insulin that is produced. Insulin is a hormone produced by the pancreas that functions to allow glucose from the foods we eat to pass through the bloodstream into cells in the body to produce energy.

All carbohydrates are broken down into glucose in the blood, and insulin helps glucose enter cells [3]. The prevalence of obesity in the adult population worldwide in 2005 reached 400 million people [4,] and in 2011, the American Heart Association indicated that 12 million (16.3%) children in America aged 2-19 years are considered obese. In 2013, according to the Riset Kesehatan Dasar [5], the prevalence of obese male and female adults rose 19.7% and 32.9%, respectively. The global prevalence rate of diabetes mellitus in 2012 according to the International Diabetes Federation was considered to be 8.4% of the world's population. The high prevalence of degenerative diseases that include obesity and diabetes then was undertaken therapy or treatment that can help heal and maintenance of degenerative disease itself, both pharmacological and non-pharmacological. Recommended non-pharmacological therapy includes reducing calorie intake, increasing exercise, and weight loss of 5-10% of initial weight, while pharmacological therapy can be achieved with medicines such as orlistat and metformin [6].

The use of medicines such as phentermine, lorcaserin in combination with topiramate, phentermine, and diethylpropion, which are commonly used for anti-obesity pharmacological therapy, has been limited due to significant side effects. Side effects of the drug lorcaserin include headaches, constipation, dizziness, fatigue, and dry mouth. The mechanism of action of these drugs is to control appetite through the effects of serotonin, which causes a sense of satiety so the intake of nutrients is limited [7]. The risk of severe hypoglycemia in oral therapies, as well as insulin injection in the treatment of diabetes mellitus, is high. Due to the side effects of currently available drugs, research into plants to obtain traditional medicine has been undertaken as an alternative for obesity. One herb that has shown anti-obesity properties is the leaf rambutan (*Nephelium lappaceum* L.).

One previous study reported that the inhibition of IGF-1 in obese rats can reduce body weight [8]. Rambutan has also been tested to determine the influence of skin extract concentration on lipid and rambutan accumulation in the livers of obese mice [9] and rambutan extract has been proven to reduce levels of glucose in the blood [10]. Diabetes is considered an obesity-related disease because one of the causes of obesity is the metabolic disruption of carbohydrates or glucose in the blood. Based on the highest prevalence of degenerative diseases as well as the lack of alternative treatments for these diseases, we will develop of ethanol extracts of leaves of rambutan for degenerative diseases. This study aimed to determine the effect of ethanol extracts of rambutan leaves (*Nephelium lappaceum* L.) on blood glucose levels in rats.

MATERIALS AND METHODS:

Identification of Rambutan (*Nephelium lappaceum*) Leaves: The leaves of rambutan (*Nephelium lappaceum* L.) were obtained from Kalijati-Subang, Indonesia and determination of plants was conducted in the Herbarium Plant Taxonomy Laboratory, Department of Biological FMIPA, University of Padjadjaran, Jatinangor, Indonesia. The plant authentication number is no. 069/HB/02/2017.

Preparation of Ethanol Extract of *N. lappaceum*: A total of 2 kg of dried simplicia was macerated with 10 L of 96% ethanol for 3 × 24 h at room temperature. The macerate obtained was 5 L and concentrated using a rotary evaporator.

Animals: White Wistar rats aged 2-3 months and weighing 150-250 g (University of Padjajaran) were used in this study. Before animals were tested, firstly, animals were adapted to new cage environments including feeding. Animal experiments were conducted according to the Commission of the Ethics of Health Research Faculty of Medicine, the University of Padjajaran Bandung (No. 399/UN 6. C. 10/PN/2017).

Anti-Obesity Activity Test: *In-vivo* testing of rats was performed following induction with foods high in carbohydrates, fats, and propylthiouracil (PTU), with 29 days of treatment and observation [11]. The test animals were divided into six groups, with five rats per group. The groups were as follows: normal (negative control), the positive control comparison group, orlistat (10.8 mg/kg b.w.), and rambutan leaf extract at 17.5, 35, and 70 mg/kg b.w. Induction and therapy were performed simultaneously. The parameters observed during therapy were weight, food index, and feces index. At the end of the

experimental period, the animals were sacrificed, and organs (liver, kidneys, spleen, and testicles) and fats (retroperitoneal fat, perirenal fat, and epididymal fat) were weighed.

Anti-Diabetic Activity Test: An insulin resistance hanger model was induced in 30 rats divided into six groups: negative control, positive control, comparison group using metformin (45 mg/kg b.w.), and rambutan leaf extract at 17.5, 35, and 70 mg/kg b.w. All groups, except for the negative control group, were fed foods high in carbohydrates, fats, and PTU. Orlistat, a gastrointestinal lipase inhibitor, was used to produce a weight gain standard for the measurement of body weight, metformin was used to measure blood sugar levels, and the body weights and organ index of the rats were recorded daily.

Determination of Blood Glucose Levels: A total of 10 µl of serum was added to 1000 µl hexokinase reagent (glucose) and incubated at 37 °C for 5 min. Then, UV absorption was measured at 340 nm using a UV spectrophotometer (Microlab 300®)

Insulin Tolerance Test Constant Measurements (KTTI): On day 29 of the experimental period, insulin tolerance tests were performed. Testing was performed by administering insulin by intraperitoneal injection at 0.05 U/kg b.w. and was performed as many as five times every 15 min throughout 1 h. Measurement of blood glucose levels was conducted using Easy Touch®.

Statistical Analysis: All results obtained were analyzed for statistical significance using one-way analysis of variance (ANOVA). Data were expressed as mean ± standard error of the mean for triplicate determinations or a sample size of n = 4. $P<0.05$ was considered significant.

RESULTS: In this study, we tested obesity and insulin resistance by administering rambutan leaf ethanol extract (*N. lappaceum* L.) to obese mice induced with foods high in carbohydrates and fats. The obesity test parameters observed during therapy included measurement of weight, food, and feces indices, which were obtained by comparing the weights of food and feces daily with the weights at the end period of the induction. At the end of the experimental period, animals were sacrificed, and the organs (liver, kidney, spleen, and testicles) and fat (perirenal fat, retroperitoneal fat, and epididymal fat) were measured. In terms of insulin resistance parameters, blood glucose levels were measured on day 0 and 29. Measurement of the constant insulin tolerance test (KTTI) was performed at the end of the experimental period. KTTI indicates insulin sensitivity, with a low K value indicating low sensitivity and *vice versa* [12].

Analysis of Animal Body Weight During Phase Testing: All groups (except for the negative control group, which was given normal feed) were induced with high levels of carbohydrates, fats, and PTU for 29 days. Administration of the induction foods high in carbohydrates, fat, and PTU in combination with extracts of leaves of rambutan was conducted on several animal groups to determine the effect of the rambutan extract on body weight. Data obtained using ANOVA analysis are shown in **Table 1**.

TABLE 1: COMPARISON OF THE PERCENTAGE OF BODY WEIGHT OF EACH GROUP DURING THE TEST PHASE

Test group	Average weight index ± SD			
	T8	T15	T22	T29
Negative control	0.80±9.88	2.40±12.54	5.20±10.42$^{\#}$	4.60±11.12$^{\#}$
Positive control	1.40±3.91	10.20±3.42	12.80±2.04$^{\#\wedge}$	21.20±6.68$^{*\wedge}$
Rambutan leaf ethanol extract, 17.5 mg/kg b.w.	-1.20±3.91	0.60±5.22	-2.60±0.89$^{*\wedge\#}$	-2.80±3.42$^{\#}$
Rambutan leaf ethanol extract, 35 mg/kg b.w.	1.20±4.86	5.80±3.27	7.20±4.43	7.60±3.64$^{\#}$
Rambutan leaf ethanol extract, 70 mg/kg b.w.	3.60±2.70	2.80±2.95	-0.20±4.38$^{\#}$	7.00±9.22$^{\#}$
Orlistat, 10.8 mg/kg b.w.	3.80±1.30	7.80±4.20	5.29±3.11$^{\#}$	0.40±2.40$^{\#}$

* Significantly different than negative control ($P<0.05$). # Significantly different than positive control ($P<0.05$). ^ Significantly different than comparison control ($P<0.05$).

Analysis of the Test Weight of Feces: Analysis of feces weight was performed to determine the anti-obesity effect of rambutan leaf extract on the amount of feces. Our results indicate the percentage of feces from each test group **Table 2**, based on this observation, the mechanism of weight loss by rambutan extract was suggested by inhibition of fat absorption in adipose tissue. Index comparison of

the amount of feces is the percentage of feces compared to body weight.

Analysis of Organ and Fat Index Test: Further testing of the anti-obesity effects of the rambutan leaf extract with organ index parameters (liver, kidney, spleen, and testicles) and fat (perianal, retroperitoneal, and epididymal fat). Observation of the organ index including the liver, kidneys, spleen, testicles, and fat was performed to see the distribution of fat in the sample after the end of the therapy period (29 days). The liver, kidneys, spleen, and testicles were weighed and recorded. The organ index is the percentage of the ratio of organ weight to the body weight of the test animal. Data obtained using ANOVA analysis are shown in **Tables 3** and **4**.

Analysis of Reduced Blood Sugar Levels During Therapy: Blood glucose levels obtained in this study are shown in **Fig. 1**.

TABLE 2: EFFECT OF EXTRACT OF LEAVES OF HERBS AGAINST COMPARATIVE FECES WEIGHT

Test group	Average ± SD Feces index			
	T8	T15	T22	T29
Negative control	4.20±1.30^	3.80±1.30^	2.80±1.30^	3.40±1.14^
Positive control	2.00±1.22^	2.60±0.54^	2.40±1.51^	4.20±0.83^
Rambutan leaf ethanol extract, 17.5 mg/kg b.w.	3.80 ±1.30^	3.40±1.5^	3.60±1.67	4.60±1.51^
Rambutan leaf ethanol extract, 35 mg/kg b.w.	6.20±3.42#	6.80±3.11*#	5.20±3.70	6.20±1.64*#
Rambutan leaf ethanol extract, 70 mg/kg b.w.	5.20±1.78#^	4.40±1.34^	6.20±2.16*#	4.20±0.83^
Orlistat, 10.8 mg/kg b.w.	8.40±2.51*#	8.00±2.34*#	5.80±1.92*#	7.40±0.89*#

* Significantly different than negative control (P<0.05). # Significantly different than Positive control (P<0.05). ^ Significantly different than Comparison control (P<0.05).

TABLE 3: EFFECT OF RAMBUTAN LEAF EXTRACT ON ORGAN INDEX

Test group	Average ± SD Organ index			
	Testicle	Kidney	Liver	Spleen
Negative control	5.95±1.36	1.52±0.19	6.06±1.31#^	0.70±0.30#
Positive control	8.90±1.20	5.18±7.73	10.4±0.93*	1.40±0.39*
Rambutan leaf ethanol extract, 17.5 mg/kg b.w.	6.27±2.76	1.96±0.15	9.98±1.54*	0.75±0.39#
Rambutan leaf ethanol extract, 35 mg/kg b.w.	6.74±1.50	1.40±0.25	8.64±0.79*#	0.84±0.29
Rambutan leaf ethanol extract, 70 mg/kg b.w.	5.94±0.98	1.62±0.19	9.07±0.87*	1.28±0.29*
Orlistat, 10.8 mg/kg b.w.	6.52±1.45	1.54±0.18	8.82±0.82*	0.98±0.55

* Significantly different than negative control (P<0.05). # Significantly different than positive control (P<0.05). ^ Significantly different than comparison control (P<0.05).

TABLE 4: EFFECT OF RAMBUTAN LEAF EXTRACT ON FAT INDEX

Test group	Average ± SD Fat index		
	Perirenal fat	Retroperitoneal fat	Epididymal fat
Negative control	0.20±0.14#	0.80±0.64	0.62±0.61
Positive control	0.80±0.31*^	0.82±040	0.40±0.45
Rambutan leaf ethanol extract, 17.5 mg/kg b.w.	0.23±0.15#	0.90±0.22	0.78±0.40
Rambutan leaf ethanol extract, 35 mg/kg b.w.	0.26±0.15#	0.98±0.23	0.95±0.51
Rambutan leaf ethanol extract, 70 mg/kg b.w.	0.20±0.07#	1.16±0.64	0.68±0.82
Orlistat, 10.8 mg/kg b.w.	0.31±0.22#	1.07±0.71	0.96±0.73

* Significantly different than negative control (P<0.05). # Significantly different than positive control (P<0.05). ^ Significantly different than comparison control (P<0.05).

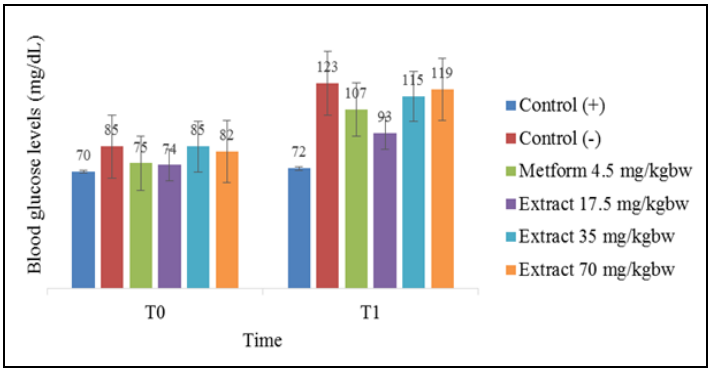

FIG. 1: REDUCED BLOOD SUGAR LEVELS DURING THERAPY

Constant Testing of Insulin Tolerance Test: This test was conducted in a preventive manner in rats induced with high-fat carbohydrate foods and PTU using different doses of rambutan leaf ethanol extract. Testing of insulin tolerance test constants (KTTI) was performed to determine whether the animal tested exhibited insulin resistance. In this study, insulin sensitivity was determined using the intraperitoneal insulin tolerance method. Blood glucose levels were measured every 15 min for 1 h following intraperitoneal administration of 0.05 U/kg bw insulin. The results of the insulin tolerance test are shown in **Table 5**.

Decreased Body Weight: We also measured overall body weight to determine the influence of body weight on blood glucose levels. Body weight data were statistically analyzed using ANOVA, and the results are shown in **Table 6**.

TABLE 5: KTTI MEASUREMENTS

Test group	KTII
Normal group	0.19±0.08*
Induction group	0.03±0.01
Metformin, 45 mg/kg b.w.	0.11±0.09*
Rambutan leaf ethanol extract, 17.5 mg/kg b.w.	0.09±0.06
Rambutan leaf ethanol extract, 35 mg/kg b.w.	0.05±0.02
Rambutan leaf ethanol extract, 70 mg/kg b.w.	0.06±0.05

*Significantly different from positive control (P<0.05).

TABLE 6: AVERAGE BODY WEIGHT (g)

Test group	Average ± SD body weight index				
	T0	T8	T15	T22	T29
Normal group	181.80±18.80	180.00±15.24	182.40±19.29	185.80±17.32	188.40±26.29
Inductio group	181.80±9.49	182.00±13.28	190.80±12.63	205.00±19.30	212.80±19.48
Metformin, 45 mg/kg b.w.	186.00±5.47	184.80±5.54	180.40±5.68	181.00±6.44	180.00±6.55*
Rambutan leaf ethanol extract, 17.5 mg/kg b.w.	196.60±37.17	191.80±34.47	196.20±39.09	193.20±42.25	188.60±27.98
Rambutan leaf ethanol extract, 35 mg/kg b.w.	174.17±15.44	178.33±16.24	178.33±16.24	187.50±18.64	186.83±20.77
Rambutan leaf ethanol extract, 70 mg/kg b.w.	197.25±18.78	196.25±19.61	188.57±20.37	196.25±19.61	198.75±21.54

*Significantly different from positive control (P<0.05).

DISCUSSION:

Analysis of Animal Body Weight During Phase Testing: Body weight was measured **Fig. 1** at the start of week 0, when animals (150-250 g) had not been induced. In the first week, body weight decreased, which was expected because the animals are adapting to the foods high in carbohydrates and fats. In week II, body weight increased in all groups, whereas in weeks III and IV, all groups except the positive control experienced weight loss. The positive control group experienced an increase in body weight of 21.45% of the initial weight, indicating the animals were obese, confirming successful induction.

ANOVA analysis with P<0.05 indicated that significant differences occurred at Time of 22 days and Time of 29 days. Multiple comparisons post-hoc Bonferroni analysis with P<0.05 revealed significant differences in the positive control at T22 and T29 compared with the negative control. Significant differences compared with the positive control were demonstrated by the negative control, rambutan leaf ethanol extract at 17.5, 35, and 70 mg/kg b.w. as well as comparators at T22 and T29. A significant difference was demonstrated by the positive control and rambutan leaf ethanol extract at 17.5 mg/kg b.w. at T22 and T29. This suggests that the rambutan leaf extract reduced overall body weight. Based on Duncan's homogenous subset analysis, the effective dose that can decrease the body weight of the test animals at day 29 is 17.5 mg/kg b.w because it is closest to the comparison.

Analysis of the Test Weight of Feces: From **Table 2**, it can be seen that the comparison group exhibited a meaningful difference compared with the positive and negative controls. The test dose of 17.5 mg/kg b.w. of 70 mg/kg b.w. also exhibited meaningful differences compared with the comparison, suggesting that at a test dose of 17.5 mg/kg b.w. and 70 mg/kg b.w. Index feces not in influence. With the test dose of 35 mg/kg b.w., there are meaningful differences compared with the positive and negative controls. Administration of orlistat at 10.8 mg/kg b.w. resulted in a large increase in feces compared with the normal and control groups.

ANOVA analysis with P<0.05 revealed a significant difference at T8, T15, T22, and T29. Based on post-hoc Bonferroni multiple comparisons analysis, a substantial difference with the negative controls was demonstrated by comparators at T8, T22, and T29; ethanol extract of 35 mg/kg b.w. of rambutan leaves at T15 and T29;

and rambutan leaf ethanol extract at 70 mg/kg b.w. at T22. Duncan's homogenous subset analysis showed that the effective dose showed by the ethanol extract of rambutan leaf group treated with 35 mg/kg b.w., it can increase the amount of fat expelled in the feces. This indicates that the rambutan leaf extract can affect the expenditure of fat released with feces but cannot significantly decrease the body weight of the test animal.

Analysis of Organ and Fat Index Test: ANOVA analysis with P<0.05 revealed a significant difference in the liver, spleen, and perirenal fat. Based on post-hoc Bonferroni multiple comparisons analysis, the significant difference of the liver compared with the negative control was shown by the positive control; ethanol extract of rambutan leaves at 17.5, 35, and 70 mg/kg b.w.; and the comparison. A significant difference in the liver compared with the positive control was indicated by the negative control, extract ethanol leaf rambutan at 17.5 mg/kg b.w., and the comparison. The negative control only indicated the difference in mean liver weight with the comparison.

In the spleen, significant differences with the positive control were demonstrated by the negative control and rambutan leaf ethanol extract at 17.5 and 70 mg/kg b.w. There was no significant difference in the spleen compared with the comparison group. In perirenal fat, a substantial difference with the negative control was demonstrated by the positive control. The negative control demonstrated a significant difference with the positive control; ethanol extract of rambutan leaves at 17.5, 35, and 70 mg/kg b.w.; and the comparison. The difference was significant with the correlation shown by the positive control. With Duncan's homogenous subset analysis, the effective dose for liver, spleen, and perirenal fat shown by rambutan leaf extract at 35 mg/kg b.w., which influence the distribution of fat in the liver, spleen, and perirenal fat, which means a dose of 35 mg/kg b.w. can effectively decrease the weight of the liver, spleen, and perirenal fat.

Analysis of Reduced Blood Sugar Levels During Therapy: Fig. 1 shows that during the 29 days of testing following induction with foods high in carbohydrates, fats, and PTU, all test groups had elevated blood glucose levels except the negative control group. The increase in blood glucose levels in the positive control group indicated that the research was successful. In the comparison group of metformin at a dose of 45 mg/kg bw, the ethanol extract groups of rambutan leave at 17.5, 35, and 70 mg/kg b.w. exhibited decreased blood glucose levels compared with the positive control group. A decrease in blood glucose levels in the comparison group with metformin therapy may be due to the presence of a metformin mechanism that can increase the insulin sensitivity of pancreatic β-cells [13]. The blood glucose data were statistically analyzed using ANOVA to determine significant differences between test groups.

Statistical analysis after 29 days showed a significant difference compared with the positive control with P<0.05 in the negative control group; metformin comparison group at 45 mg/kg b.w.; and the rambutan ethanol extract group at 17.5 mg/kg b.w. This indicates that both the metformin comparative arm and the rambutan ethanol extract test group decreased blood glucose levels, although these levels did not return to normal. In a previous study, rambutan leaf was shown to decrease blood glucose levels using an animal model of insulin deficiency with an alloxan inducer performed for 14 days [10].

Constant Testing of Insulin Tolerance Test: Table 5 indicates the state of insulin resistance that can be seen from the speed of insulin in lowering blood glucose levels. The rate at which insulin lowers blood glucose levels indicates the sensitivity of the tissue to insulin [14]. In the positive control group, decreased tissue sensitivity to insulin resulted in a reduced rate insulin-dependent lowering of blood glucose levels. This was marked by a significant difference in the negative control and metformin comparison group of 45 mg/kg bw to the positive control group with P<0.05, which indicated an improvement in tissue sensitivity to insulin. In the ethanol extract test group of rambutan leaves at 17.5, 35, and 70 mg/kg b.w. was not found insulin resistance.

Decreased Body Weights: Table 6 shows that in all test groups of ethanol extracts of rambutan leaves there was no significant difference compared with the positive control group, but at the Group's

benchmark dose of 45 mg metformin/kg bw, there is a significant difference towards the positive control group ($P<0.05$). It has been shown that metformin can also be used for sufferers of type 2 diabetes mellitus experiencing excess body weight (obesity).

CONCLUSION: Ethanol extracts of rambutan leaves (*N. lappaceum* L.) improve diabetes by reducing insulin resistance and decreasing glucose concentration. Additional studies will be important for the further analysis of this phenomenon.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

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