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Original Research Article

The Effect of Indonesian Anti-Hyperglycemic Herbal Formula on Fasting Blood Glucose and Quality of Life of Diabetic Patients: A Randomized, Open-Label Clinical Trial

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ABSTRACT

Diabetes mellitus is a non-communicable disease that is still a crucial health problem in Indonesia. Recently, the Indonesian communities has now considered using medicinal plants based on ancestral knowledge. The study aimed to evaluate the Indonesian anti-hyperglycemic herbal formula (AHHF), focused on fasting blood glucose (FBG) and quality of life (QoL) of hyperglycemia patients. A total of 242 volunteers participated in the study and were divided into the AHHF and metformin groups. Every subject was given an infusion of AHHF or oral metformin 500 mg twice a day for six weeks. The observation of FBG and QoL using the 36-item Short-Form Health Survey (SF-36) was performed on day-0, 21, and 42 of the study. The study used the subject's symptoms and liver-kidney function in the safety analysis. The FBG level of subjects in both groups on day-21 (AHHF: 155.36 mg/dL; metformin: 154.87 mg/dL) and 42 (AHHF: 149.14 mg/dL; metformin: 153.07 mg/dL) was significantly decreased compared with day-0 (AHHF: 162.92 mg/dL; metformin: 164.37 mg/dL). There was no significant difference in FBG level between the two groups on day-0 and 21. However, the FBG level of the AHHF group on day-42 was lower than the metformin group. Both groups experienced a significant increase in SF-36 scores from 74.34 to 80.78 in the AHHF group and 77.29 to 80.64 in the metformin group. There was no side effect reported, and all subjects' liver-kidney function was in the normal range. In conclusion, AHHF reduced FBG levels of diabetic patients and improved their QoL.

***Keyword*:** Anti-hyperglycemic herbal formula, Clinical study, Fasting blood glucose, Quality of life

Introduction

Diabetes is characterized by hyperglycemia, a condition of excessive blood glucose levels.[1] There were 463 million people diagnosed with diabetes worldwide in 2019. In 2045, these numbers were predicted to increase to 700 million.[2] Across Asian countries, the variation of prevalence depends on the differences in health care quality and the prevalence of obesity and hypertension.[3] Indonesia has a 13% prevalence of diabetes growing year by year and becoming a massive problem in the national health care system.[4]

A large number of cases and the gap of health care services, especially in remote areas, stimulate people to find alternative therapy. Recently, the Indonesian communities have looked at phytotherapy as an alternative treatment for hyperglycemia. They believe it is relatively safe without significant side effects.[5] As a country with incredible biodiversity, Indonesia has many potential medicinal plants used for generations.[6] Indonesian traditional herbal called *jamu* has been usedfor over generations for treating diseases and maintaining health.[7] Several stages ranging from animal testing to humans are needed to strengthen the evidence of medicinal plants for diabetes.[8]

A polyherbal formula with an anti-hyperglycemia effect (AHHF) has been developed by Medicinal Plant and Traditional Medicine Research and Development Center (B2P2TOOT in Bahasa).

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In an experimental study on animals, anti-hyperglycemic formulas' infusion had no harm against liver, kidney, stomach, heart, lymph, and lung function. A phase 1 study of AHHF on 45 volunteer subjects showed that these formulas are safe for hyperglycemia therapy without any significant side effects.[9] The study evaluated the effect of AHHF on patients' fasting blood glucose (FBG) and quality of life compared with metformin.

Materials and Methods

The study was conducted at 50 primary health facilities and the *Jamu* Research Center from March to December 2017. The method of study was purposive randomization, open-label with end blinded observation. The study had received ethical approval (NO. LB.02.01 / 5.2 / KE 238/2017) from the Ethics Commission of the Indonesian Ministry of the Health Republic of Indonesia.

The patients who voluntarily participated were requested to sign the informed consent approval form. The patients aged 20-60 years, diagnosed with type 2 diabetes mellitus, FBG level > 126 mg/dL,[10] and have not received any treatment, or last take anti-diabetes drugs for more than four weeks were included in the study. Patients who were pregnant or breastfeeding, have cancer or severe illness, and were hypersensitive with remedy were excluded. A computer program generated the randomization sequence. The patients were randomly divided into two groups: the AHHF and the metformin group.

Materials preparation

The *Syzygium polyanthum* leaves, *Andrographis paniculata* herbs, *Cinnamomum burmani* barks, and *Curcuma xanthoriza* rhizomes were harvested from the gardens of Medicinal Plant and Traditional Medicine Research and Development Center. All samples of collected plants were determined and stored in the Herbarium *Tawangmanguense*. The harvested plants were dried into simplicia in an oven at a temperature of 60^{o}C until the water content was less than 10%. The standardization of

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simplicia were carried out by performing quality control checks (drying shrinkage, fungus number, total plate number, total ash content, acid insoluble ash content, soluble alcohol extract, water-soluble extract, and chemical content using Thin Layer Chromatography). The standardized simplicia were packed in the sterile packaging plastics. One package of AHHF consisted of 5 g *Syzygium polyanthum* leaves, 5 g *Andrographis panic*ulata herbs, 7 g *Cinnamomum burmani* barks, and 10 g *Curcuma xanthoriza* rhizomes. The package was equipped with the instruction on how to make an infusion. The preparation of infusion was started by boiling 1 L of water, followed by adding one package of AHHF, and boiling for 15 minutes with gentle heat. After being collected and filtered, the next step was to divide the infusion into two portions. One portion had to be taken in the morning, while the other in the afternoon. The oral tablets of metformin 500 mg were ordered and purchased from the accredited pharmacy in Central Java, then packed into small clipped plastic packs. One plastic pack consisted of two tablets of metformin that had to be taken in the morning and afternoon. During the study, every subject was asked to visit the research doctor every week. On every visit, the research doctor gave seven packages of AHHF or metformin according to their group. They also examined all symptoms and possible adverse events of the subject involved in the study. The AHHF or metformin was administered to the subject for 42 days.

Parameter of efficacy and safety

The measurement of FBG level was performed on day-0, 21, and 42 of the study. The assessment of the subject's quality of life (QoL) using the 36-item Short-Form Health Survey (SF-36) was also carried out on day-0, 21, and 42. SF-36 is a questionnaire form containing 36 questions which already been widely used in Indonesia.

The adverse events' recording was performed during the treatment. Any probable side effect was observed from interview report and laboratory tests. The laboratory tests were conducted in order to determine the liver-kidney function on day 0 and 42, including blood urea nitrogen (BUN), creatinine, Serum Glutamic Oxaloacetic Transaminase (SGOT), and Serum Glutamic Pyruvic Transaminase (SGPT). The normal values of the parameter are: BUN = 15-38 mg/dL (men), 7-18 mg/dL (women); creatinine = 0.7-1.4 mg/dL (men), 0.6-1.2 mg/dL (women); SGOT = 0-45 mg/dL; SGPT = 0-35 mg/dL.[11,12] All biochemical parameters were performed by International Organization for Standardization (ISO) accredited laboratories.

Statistical analysis

After collection, data analysis was done using a statistical program version 18.0. The descriptive data were calculated and presented. The paired T-test was performed to determine the difference between day-0, 21, and 42. While the difference between the two groups was analyzed using the Independent T-test. Differences at $P < 0.05$ were considered to be statistically significant.

Results and Discussion

A total of 242 subjects met the criteria. Two subjects resigned from the study, and one subject relocated from the town in the AHHF group. On the other hand, four subjects in the metformin group resigned from the study, and one subject could not be contacted (Figure 1). At baseline, there was no significant difference ($p>0.05$) in demographic data between the two groups (Table 1). The AHHF and metformin groups had the same baseline before treatment.

Figure 2 shows that after 21 days of treatment, the average FBG level of the AHHF group was decreased. The decrease continued to 149.144 mg/dL on day-42. The paired sample T-test results compared between FBG levels on day-21 and 42 with day-0 measurement showed $p<0.05$ (significant). On day-21 in the metformin group, The average FBG level was significantly decreased compared with day-0. However, there was no significant FBG reduction on day-42 compared with day-21 ($p>0.05$).

The comparison of FBG levels between the AHHF and metformin groups is shown in Table 2, and there was no significant difference ($p>0.05$) between the two groups on day-0 and 21. However, on the 42nd day of the study, the average FBG level of the AHHF group was significantly lower than the metformin group ($p<0.05$).

The FBG level of more than 126 mg/dL was defined as hyperglycemia, while the FBG of less than 126 mg/dL was considered normal. In the beginning, the FBG levels of all subjects were > 126 mg/dL. After 21 days of treatment, 29 subjects in the AHHF group showed normal FBG levels, five subjects more than metformin. However, on day 42, 30 subjects in each group had a normal value of FBG. Figure 3 shows a similar result on Kaplan–Meier survival curves for having normal FBG levels between two groups. Both groups had the same average time of having normal FGS levels on day 39.

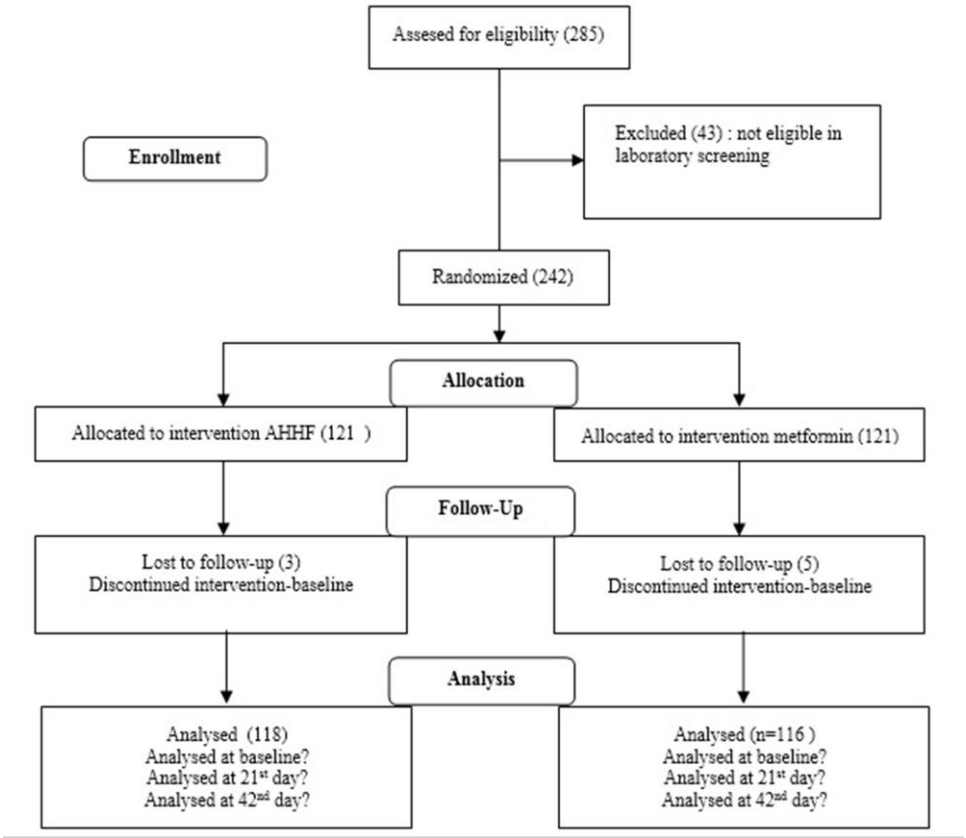

Figure 1: Enrollment, randomization, allocation, follow-up, and analysis.

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The average scores of SF-36 study subjects are shown in Figure 4. The result shows an increase in the average SF-36 score gradually in both groups. The statistical analysis result shows that the increase was statistically significant ($p<0.05$). As shown in Table 3, the average SF-36 score of the AHHF group on day-0 was lower than the metformin group. However, the difference was not statistically significant ($p>0.05$). The results of the analysis on measurements day 21 and 42 also showed p values >0.05. It can be concluded that the difference in the ability to improve SF-36 scores in the two groups was not statistically significant.

During and after the treatment, there was no side effect complained from the subjects. Also, no unwanted severe events were found. The laboratory result of liver and kidney function showed no abnormalities in the two groups (Table 4). In the AHHF group, there was a significant difference in SGPT and BUN on day-42 and day-21 compared with baseline. A significant difference also was found in the SGPT level of the metformin group on day-21 compared with baseline. However, the differences did not have clinical significance because all of the subjects' values were still in the normal range.

The majority of plants with a hypoglycemic effect work through inhibition of the enzymes *α-amylase* and *α-glucosidase*. While other plants play a role in restoring pancreatic cells, improving insulin secretion and sensitivity, and exerting antioxidant and hepatoprotective functions. The phytochemical agents responsible for those mechanisms are varied from saponins, polyphenols, ellagitannins, triterpenes, and mineral elements.[13]

AHHF has a composition of *S. polyanthum* leaves, *A. paniculata* herbs, *C.burmani* barks, and *C. xanthoriza* rhizomes. These medicinal plants have evidence of the effect of lowering blood sugar. A previous study showed that the ability of bay leaf extract (*Syzygium polyanthum*) to inhibit *α glucoside* was equivalent to glibenclamide.[14]

Table 1: The demographic characteristics of the studied groups.

Characteristics	AHHF group n (118)	metformin group n (116)	Total	p*
Age				
- 26 – 35 year	12 (57.14%)	9 (42.86%)	21 (100%)	0.194^{ns}
- 36 – 45 year	25 (41.67 %)	35 (58.33%)	60 (100%)	
- 45 – 55 year	46 (51.69%)	43 (48.31%)	89 (100%)	
- > 55 year	35 (54.69%)	29 (45.31%)	64 (100%)	
Sex				
- Men	39 (45.35%)	47 (54.65%)	86 (100%)	0.079 ^{ns}
- Women	79 (53.38%)	69 (46.62%)	148 (100%)	
Education (finished)				
- Elementary School	32 (42.14)	25 (43.86)	60 (100%)	0.296 ^{ns}
- Junior High School	18 (52.94)	16 (47.06)	34 (100%)	
- Senior High School	25 (38.46)	40 (61.54)	65 (100%)	
- University	41 (55.41)	33 (44.59)	74 (100%)	
Occupation				
- No Occupaton	27 (49.09%)	21 (50.91%)	55 (100%)	0.108 ^{ns}
- Military/Police/Officer	24 (61.54%)	15 (38.46%)	39 (100%)	
- Private employee	20 (50.00%)	20 (50.00%)	40 (100%)	
- Enterpreneur	16 (42.11%)	22 (57.89%)	38 (100%)	
- Labour/farmer	20 (64.52%)	11 (35.48%)	31 (100%)	
- Others	11 (42.31%)	15 (57.69%)	27 (100%)	
BMI				
- underweight	6 (100%)	0 (0%)	6 (100%)	0.061 ^{ns}
- normoweight	41 (51.25%)	39 (48.75%)	80 (100%)	
- overweight	52 (49.52%)	53 (50.48%)	105 (100%)	
- obesity I	12 (36.36%)	21 (63.64%)	33 (100%)	
- obesity II	7 (70%)	3 (30.00%)	10 (100%)	

*) Independent T-test, significant at $p<0.05$; ns = not significant ($p>0.05$).AHHF = Anti-hyperglycemic herbal formula

Table 2: Analysis of FBG level between AHHF and metformin group

Measurement day	AHHF group	metformin group	p*
	mean (mg/dL) ± SD	mean (mg/dL) ± SD	
0	162.92 ± 25.542	164.37 ± 33.554	0.333^{ns}
21	155.36 ± 32.113	154.87 ± 39.108	0.457^{ns}
42	149.14 ± 28.657	153.07 ± 40.419	0.023^{s}

Values expressed as mean ± SD; n = 118 (AHHF group) and n = 116 (metformin group); *) Independent T-test, significant at $p < 0.05$; ns = non significant; s = significant

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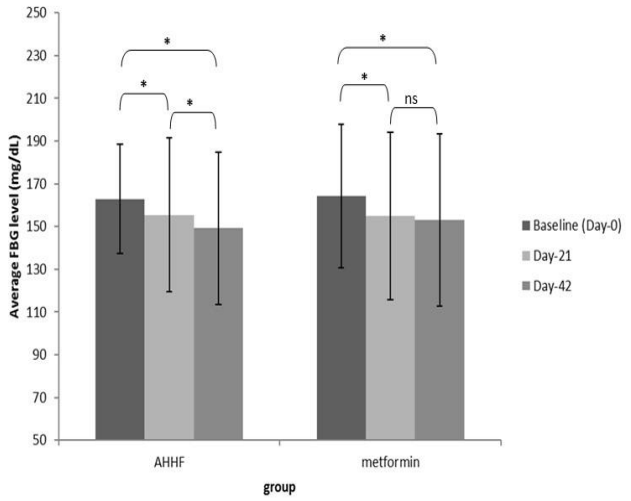

Figure 2: Comparison of the average of FBG in the AHHF group and metformin group. *Paired t-test, significant at $p \leq 0.05$; ns = not significant ($p > 0.05$). AHHF = Anti-hyperglycemic herbal formula

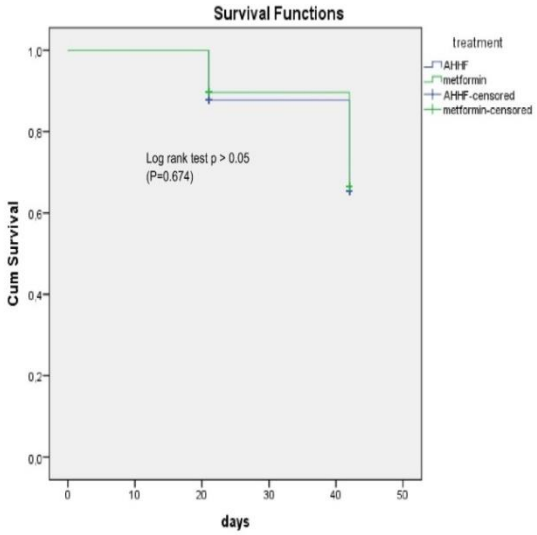

Figure 3: Kaplan–Meier Survival Curves for having normal FBG levels. (Primary Outcome)

Table 3: Analysis of SF-36 score between AHHF and metformin group

Measurement day	AHHF group	metformin group	p*
	mean ± SD	mean ± SD	
0	74.34 ± 16.386	77.29 ± 16.637	0.066[ns]
21	78.38 ± 13.206	79.39 ± 12.144	0.254[ns]
42	80.78 ± 11.518	80.64 ± 12.604	0.461[ns]

Values expressed as mean ± SD; n = 118 (AHHF group) and n = 116 (metformin group); *) Independent T-test, significant at $p < 0.05$; ns = non significant; s = significant

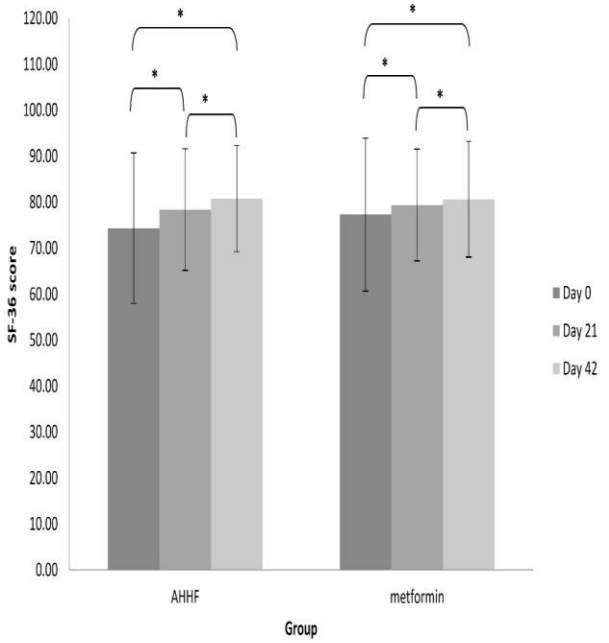

Figure 4: Comparison of SF-36 score in AHHF group and metformin group. *Paired t-test, significant at $p \leq 0.05$; ns = not significant ($p > 0.05$). AHHF = Anti-hyperglycemic herbal formula

Table 4: Analysis of SGOT, SGPT, BUN, and creatinine of AHHF and metformin group

Parameter	AHHF group (Mean + SD)			metformin group (Mean + SD)		
	Day 0	Day 21	Day 42	Day 0	Day 21	Day 42
SGOT	20.52 ± 6.89	20.25 ± 6.48	20.21 ± 7.36	19.43 ± 6.4	19.40 ± 6.20	19.29 ± 5.73
SGPT	20.75 ± 9.09	21.07 ± 9.27	19.96 ± 8.03[a]	20.13 ± 8.27	19.17 ± 7.74[b]	20.03 ± 8.06
BUN	24.69 ± 9.37	23.87 ± 8.94[c]	24.11 ± 8.55	22.48 ± 8.77	22.87 ± 8.24	22.35 ± 7.91
Creatinin	0.74 ± 0.24	0.74 ± 0.25	0.73 ± 0.25	0.84 ± 0.30	0.85 ± 0.29	0.83 ± 0.28

a: Significant difference between day 42 compared to day 0 in the same group(Paired t-test, significant at $p \leq 0.05$)
b: Significant difference between day 21 compared to day 0 in the same group(Paired t-test, significant at $p \leq 0.05$)
c: Significant difference between day 21 compared to day 0 in the same group (Paired t-test, significant at $p \leq 0.05$)

The antidiabetic effect of bay leaf extract was indicated from its activity in increasing uptake of glucose in peripheral tissues and restraining glucose ingestion in the digestive system.[15]
The primary active compound of *A. paniculata*, which has been studied for reducing blood sugar, is andrographolide.[16] The mechanisms of andrographolide's action are including increasing glucose utilization, enhancing the expression of glucose transporter subtype 4 (GLUT4), improving Langerhans islet condition, and increasing pancreatic insulin levels.[16,17]Andrographolide also played an essential role in reversing the CAT, GPx, and SOD activities back to a normal level. The action occurs mainly in the hippocampus, hypothalamus, and cerebral cortex cerebellum of the DM rat brain.[18,19]
The study of aqueous extract *Cinnamomum burmani* showed an inhibitory effect against the α-glucosidase enzyme equal to glucobay (Acarbose) 1%. Cinnamon is enriched with *Methylhidroxy Calcone Polymer*, a flavonoid that can stimulate translocation of GLUT-4 in adipose tissue.[20] Polyphenol of cinnamon extract has the potential effect for improving insulin sensitivity lead to upregulated glucose uptake.[21,22] Also, cinnamon is widely known as an insulin-mimetic because it enhances the enzymatic reaction of phosphorylation and dephosphorylation.[23] Other study showed a combined bioactive fraction derived from *Cinnamomum burmanii* and *Lagerstroemia speciosa* have the capability for preserving β-cell performance and improving insulin resistance in patients with impaired glucose tolerance.[24] A study reported that several traditional medicinal plants might be combined to improve pharmacological activities.[16] The progressivity and incidence of diabetes mellitus are related to reactive oxygen species (ROS) due to high exposure of free radicals compounds.[25,26] Accordingly, enriched antioxidant compounds of AHHF can be a potential therapy for type 2 diabetic patients. Besides, The diversity of active compounds in AHHF may have a synergistic effect as an anti-hyperglycemic agent. This mechanism is similar to previous research. Fatmawati *et al.* showed complementary effects, which occur with different mechanisms towards one indication between *Moringa oleifera* leaves and *Andrographis paniculata*.[27] Based on previous research, the preparation of AHHF using boiled water had a positive effect because it did not affect nondiabetic animals' fasting blood glucose levels.[28] It may minimize the risk of hypoglycemia which is the neglected complication of therapy in type 2 diabetic patients.[29] This study showed that the anti-hyperglycemic effect of AHHF is equal to metformin after 21 days of treatment. Another finding on day 42 of treatment was that the average of FBG in the AHHF group was lower than in the metformin group. The normal values of liver and renal function during and after treatment indicate that AHHF is safe for consumption.

Conclusion

The AHHF effectively reduces fasting blood sugar levels and improves the quality of life (SF-36) of type 2 diabetic patients compared to metformin. The use of AHHF for treatment is also categorized as clinically safe.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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