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Physical Stability of Binahong Leaf Extract (*Anredera cordifolia (Ten.) Steenis*) with Hydroxypropyl Methylcellulose and Hydroxyethyl Cellulose Gelling Agents

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ABSTRACT

Second-degree burns have the highest prevalence and often occur in the household environment. The healing process can be accelerated by traditional medicine. One of the many plants known to have wound-healing abilities is the Binahong plant *(Anredera cordifolia (Ten.) Steenis)*. The gel preparation is chosen because of the many benefits it can provide. The gelling agents used were *Hydroxypropyl Methyl Cellulose* and *Hydroxyethyl Cellulose*. The combination of these gelling agents was chosen because both agents are capable of producing gel preparations with good stability during storage. Therefore, the optimization was carried out to obtain the optimum formula that met the requirements. The observed responses were organoleptic, pH, spreadability, adhesion, viscosity, and homogeneity. The data obtained was optimized with the Simplex Lattice Design program in Design Expert software version 13.0.0. The results of the verification test were compared for their significance with the T-test with a 95% confidence level. The optimum gel stability of Binahong leaves *(Anredera cordifolia (Ten.) Steenis)* was tested using one-way ANOVA and post hoc. The results showed that the optimum formula for Binahong leaf extract gel *(Anredera cordifolia (Ten.) Steenis)* was obtained with a composition ratio of 0.5% HPMC and 4.5% HEC. The verification results obtained valid values for pH response, viscosity, and spreadability according to SLD predictions. The optimum formula for Binahong leaf extract gel *(Anredera cordifolia (Ten.) Steenis)* was stable during the cycling test.
Keywords: Binahong leaves; physical stability; gel

INTRODUCTION

A second-degree burn is an abnormality caused by trauma from exposure to hot water, acidic water, or anything that can cause damage to the skin layer (Effendy, 1999). Based on the literature and community experience, one of the plants that can be used to heal burns is Binahong (*Anredera cordifolia (Ten.). Steenis)*. According to Webb and Harrington (2005), the use of Binahong plants is still within limits based on experience and there is no scientific evidence based on research.

All parts of the Binahong plant can be used as medicine, from the roots, flowers, stems, and leaves. However, until the present day, the part that is most often used for health is the leaves (Manoi, 2019). Binahong leaves can be used to treat various diseases. An administration of fresh mashed Binahong (*Anredera cordifolia (Ten.) Steenis*) leaves can speed up the wound healing process in rabbits (Ariani, 2014).

The formulation chosen for Binahong leaves in this study is gel formulation. The gel preparation was chosen based on the many advantages such as easy application, higher penetration power when compared to cream preparations, better absorption in the skin when compared to cream preparations, ease of application to the skin, and ease to wash off.

The physical properties and stability of a gel are largely determined by the gelling agent and humectants used. The greater the amount of gelling agent used, the higher the viscosity produced (Zats and Kushla, 1996).

The formulation of the Binahong leaf extract gel in this study used the Hydroxypropyl Methylcellulose and Hydroxyethyl Cellulose gelling agent.

The optimization of the Binahong leaf extract gel formula used the Simplex Lattice Design method with Design Expert software version 13.0.0 in the mixture design program with various components of HPMC and HEC so that it was expected to produce preparations with good physical stability during storage.

METHODOLOGY

Materials and Instruments

Binahong leaf extract (IdoBio China), HPMC (pharmaceutical grade), HEC (pharmaceutical grade), propylene glycol (pharmaceutical grade), methylparaben (pharmaceutical grade), propylparaben (pharmaceutical grade), ascorbic acid (pharmaceutical grade).

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Glassware (Iwaki), pH meter (Boeco PT-320), stopwatch (Alba Digital), ultra turrax T25 (JANKE & KUNKEL IKA®-Labortechnik) digital weighing balance (Adventurer™,ohaus), Brookfield viscometer (DV-I Prime Japan), spreadability test kit (Faculty of Pharmacy UGM), adhesive test kit (Marchaban et al. 2015).

Gel Formulation

Materials were weighed according to the formula. HPMC was added to hot water at 70-80°C and then stirred until a transparent gel mass was formed. HEC was added with distilled water and stirred until a transparent gel mass was formed in different mortars at room temperature. The gel was mixed in one mortar and stirred homogeneously. The extract was put into the mortar, then methyl paraben, propyl paraben, ascorbic acid, and propylene glycol were mixed and stirred at 35°C into a beaker glass until dissolved. This mixture was put into the gelling agent and added with distilled water up to 100 mL and homogenized with ultra turrax at 3-8 rpm without heating. The preparation was left until it was homogeneous (Angelia et al, 2022).

Testing the physical properties of the gel

The physical properties of 8 Binahong leaf extract gel formulas combined with HPMC and HEC were tested and observed for organoleptic, homogeneity, viscosity, spreadability, adhesion, and pH.

Determination of optimum gel formula

Determination of the optimum formula was carried out by processing data from the results of testing the physical properties of the HPMC and HEC combination gel using the Design Expert version 13.0.0 software. The physical parameters used were viscosity, spreadability, and pH. Target response and degree of importance were adjusted to obtain the optimal combination of HPMC and HEC.

Verification of optimum gel formula

The optimum gel formula was then tested for its physical properties at week 0 and compared with the predicted value of the physical properties of the Design Expert software version 13.0.0. The parameters of physical properties tested include viscosity, spreadability, and pH. Statistical analysis for verification used one sample t-test with a 95% confidence level which aims to determine whether the predictions and experimental results differ significantly or not.

Determination of the optimum physical stability of the HPMC and HEC combination gel formula

Testing the physical stability of the optimum formula of Binahong leaf extract gel included organoleptic, homogeneity, pH, viscosity, spreadability, and adhesion through 3 cycles of cycling test.

Organoleptic Test

The organoleptic examination included the examination of the taste, color, and smell of Binahong leaf extract gel (Ansel, 1989).

pH Testing

pH testing was carried out with a calibrated pH meter. Then, the gel preparation was taken and the electrode was dipped. After that, the pH meter was left to show a constant number (pH value of the preparation) (Tranggono, 2007).

Spreadability Test

A sample of 1 gram was placed on a transparent glass. Above it, a transparent glass was placed and left for 1 minute. Then, the diameter of the gel spread was measured. Loads added respectively were 50 grams, 100, 150, 200, to 250 loads, and were left for 1 minute. Then, a constant diameter was measured. A spread of 5-7 cm indicated a semisolid consistency which indicated comfortability in using this preparation (Garg *et al.*, 2022).

Adhesion Test

As much as 0.25 grams of the gel was placed on top of two glass objects, then pressed with a load of 1 kg for 5 minutes. After that, the glass object was put on the test equipment and was added a load of 80 grams on the test equipment. The release time from the object glass was recorded (Garg *et al.*, 2022).

Viscosity Test

The viscosity test was carried out by dipping the spindle into the gel preparation and then the viscosity value was seen (Voight, 1995).

Homogeneity Test

The homogeneity test was carried out by observing visually by applying the gel to the surface of the object glass. The observed object was the presence of coarse grains or parts that were not mixed properly. If there were no coarse granules in the preparation, then it could be concluded that the preparation was homogeneous (Barel *et al.*, 2009).

Stability Test at Extreme Temperatures

This test was carried out using the cycling test method (freeze-thaw test). Each formula was stored at 4^{o} ±2^{o}C for 24 hours. Then, it was stored at 40^{o}±2^{o}C for the next 24 hours (1 cycle). Tests were carried out for 6 cycles and at the end of each cycle, pH, organoleptic, spreadability, adhesion, viscosity, and homogeneity were observed using the same test method on the physical properties test (Zulkarnain et al, 2022).

RESULT AND DISCUSSION

Gel Physical Properties

The physical properties test of Binahong leaf extract gel was carried out on 8 run formulas obtained from Design Expert version 13.0.0. The physical properties tested were the organoleptic test, pH, spreadability, and viscosity. The test was carried out 48 hours after the preparation of the gel. The aim was to minimize the bias caused by the influence of mechanical energy when making the gel.

The organoleptic test aimed to see the quality of the preparation because the organoleptic test was an indicator to see the quality of the semisolid preparation. The organoleptic tests performed included color, odor, and consistency of the preparation. Based on the observations made, the 8 runs of the Binahong leaf extract gel formula had a transparent yellow gel, a distinctive odor of Binahong leaf extract, and was homogeneous. The color and smell of this gel were influenced by the Binahong leaf extract used. Runs 6 and 8 had a rather thick consistency therefore the HPMC component had a greater influence, because HPMC formed a gel base by absorbing solvent so that the liquid was retained and increased the resistance of the liquid by forming a compact mass.

Homogeneity test aimed to determine the homogeneity aspect of the gel preparations that had been made. The 8 runs of Binahong leaf extract gel preparations had good homogeneity where the color of the preparation was even and there were no coarse grains in the texture.

The pH test aimed to determine the degree of acidity of the preparations made. A pH that is too alkaline can cause dry skin and a pH that is too acidic can irritate the skin. In consequence, the pH of preparation needs to be adjusted to the pH of the skin, which is in the range of 4.5-6.5 (Walters and Roberts, 2008). The pH test results for the 8 run formulas showed that run 7 had the highest pH, which was 5.033, while run 6 had the lowest pH, which was 4.628. The pH value of each run of this formula corresponded to the required pH range.

The results of ANOVA analysis with a 95% level of confidence obtained a p-value of 0.0015 (p-value <0.05), meaning that variations in the levels of the gelling agent used caused changes in pH responses that were significantly different. The results of the analysis of lack of fit showed a p-value of 0.6868 (p-value > 0.05), meaning that there was no significant difference between the observed pH response and the pH response predicted by the mathematical equation.
Based on the approach with SLD, the resulting pH response equation was:

$$\mathbf{Y = 4.73A + 5.03B - 0.8176AB + 0.916AB\,(A\text{-}B)}$$

Legend : Y = pH response; A = HPMC level (%b/v); B = HEC level (%b/v)

Based on this equation, each gelling agent gave a positive response, meaning that each addition of HPMC and HEC concentrations could increase the pH of the preparation. The gelling agent that affected the pH the most was HEC which was shown to have a higher positive response value compared to HPMC. HEC affected the increase in pH because HEC can form a solution with a high pH when dissolved in water, therefore it can increase the pH of gel preparations (Laverius, 2011). Based on the results obtained, the pH of the preparation was still within the required range due to the interaction between HEC and HPMC which gave a negative response. Hence, the interactions that occurred between these components could lower the pH of the preparation.

Viscosity

Viscosity is a quantity that expresses resistance to a preparation to flow. According to Langenbucher and Lange (2007), an acceptable viscosity for semisolid preparations is 50-1000 dPas with an optimum value of 200 dPas. The results of the viscosity test of the 8 run formulas showed that run 8 had the highest viscosity, namely 294.80 dPas, while run 7 had the lowest viscosity, namely 243.20 dPas. The viscosity value of each run formula corresponded to the required viscosity range.

The results of the ANOVA analysis with a 95% level of confidence obtained a p-value of 0.0256 (p-value <0.05), meaning that variations in the levels of the gelling agent used caused changes in the viscosity response that differed significantly from each run formula. The results of the analysis of lack of fit showed a p-value of 0.702 (p-value > 0.05), meaning that there was no significant difference between the observed viscosity response and the scattering response predicted by the mathematical equation.

Table I. Results of Statistical Analysis of pH Response

Source	*p-value*	Description
Model *(cubic)*	0.0015	*Significant*
Lack of fit test	0,6868	*Not Significant*

Table II. Results of Model Statistical Analysis of the Viscosity Response

Source	*p-value*	Legend
Model *(cubic)*	0,0256	*Significant*
Lack of fit test	0,7019	*Not Significant*

Table III. Statistical Analysis Results of Spreadability Response

Source	*p-value*	Description
Model *(linear)*	0,0169	*Significant*
Lack of fit test	0,3872	*Not Significant*

Based on the approach with SLD, the resulting pH response equation was:

Y=273.1A+249.3B+122.59AB-202.13AB(A-B)

Description : Y = spreadability response; A = HPMC level (% b/v); B = HEC level (%b/v)

Based on this equation, each gelling agent gave a positive response, meaning that each addition of HPMC and HEC concentrations could increase the viscosity of the preparation. The gelling agent that affected the viscosity most was HPMC which was shown to have a higher positive response value compared to HEC. There was an increase in viscosity with the addition of HPMC because HPMC can form a gel base with a compact matrix by absorbing solvent so that the solvent is retained and can increase fluid resistance (Martin *et al.*, 1993). Based on the results obtained, the viscosity of the preparation was still within the required range due to the interaction between HEC and HPMC which gave a positive response. Therefore, the interactions that occurred between these components could increase the viscosity of the preparation.

Spreadability Test

Spreadability is one of the things that determine the effectiveness in the release of active substances and consumer acceptance of semisolid preparations. Spreadability is inversely proportional to viscosity. The greater the spreadability, the more viscosity will decrease.

The spreadability test results of the 8 run formulas showed that run 7 had the highest spreading power, namely 24.341 cm2, while run 8 had the lowest spreading power, namely 18,848 cm2. Run 8 had the lowest spreadability with a diameter less than the required range of 4.9 cm. This is because the run 8 formula had the highest viscosity, namely 294.80 dPas, thus making the spreadability of the preparation smaller.

The results of ANOVA analysis with a 95% level of confidence obtained a p-value of 0.0169 (p-value <0.05), meaning that the variation in the level of gelling agent used caused a change in the response power that differed significantly from each run formula. The results of the analysis of lack of fit showed that the p-value was 0.387 (p-value > 0.05), meaning that there was no significant difference between the observed scatter power response and the scatter response predicted by the mathematical equation. Another study (Elya Zulfa, *et al.,* 2018) showed that the cream preparations obtained decreased the spreadability when the levels of binahong extract were increased. The spreadability is good when it is between 5-7 cm in diameter (Yati *et al.*, 2018).

Based on the simplex lattice design approach, the resulting pH response was the following equation:

Y= 18,95A + 23,48B………………… (10)

Description : Y = spreadability response; A = HPMC level (% b/v); B = HEC level (%b/v)

Based on this equation, each gelling agent gave a positive response, meaning that each additional concentration of HPMC and HEC could increase the spreadability of the preparation.

The gelling agent that most influenced the spreadability of the preparation was HEC, which was shown to have a higher positive response value compared to HPMC. Another study by

Table IV. Independent and Bound Variables in SLD to Determine the Optimum Formula

Trial Variables	**Limitation**		
Free Variables	**Low Composition**	**Composition High**	**Target**
HPMC	0,5%	2%	*In Range*
HEC	3%	4.5%	*In Range*
Bound Variables	Lower Limit	Upper Limit	Target
pH	4,628	5,033	*Maximize*
Viscosity	243.2 dPas	294.8 dPas	*In Range*
Spreadability	18.85 cm^2	24.34 cm^2	*Maximize*

Sari et al., (2021) showed that the variations in emulsifiers in binahong extract scrub cream preparations did not change during the experiment.

Determination of the Optimum Formula of Binahong Leaf Extract Gel

The optimum formula for Binahong leaf extract gel was determined using the Design Expert with the SLD method. The parameters used were pH, viscosity, and spreadability. These parameters provided a significant response to each formula run. The concentration of HPMC and HEC was used as a factor that affects the parameters or is called the independent variable. The goal for the pH response is to maximize, the viscosity in range and the spreadability to maximize. The degree of importance used was four stars (++++) in terms of pH and spreadability, while the chosen default for viscosity was (+++).

Software DE provides solutions according to the desired optimization target. The solution chosen is the formula with the highest desirability value.

The range of desirability values is 0 – 1. The greater the desirability value, the more response variable for formula optimization can reach the optimum point according to the desired target.

The desirability value chosen was the highest value, namely 0.957 with a proportion of 0.5% HPMC, and 4.5% HEC.

Verification of the Binahong Leaf Extract Optimum Gel Formula

The results of the analysis with the one-sample t-test on the response to the prediction with the response to the optimum formula test results can be seen in Table V.

The formula obtained through optimization using design experts was replicated 3 times to produce 4 preparations of Binahong leaf extract gel. The analysis results in Table VI show that the viscosity, spreadability, and pH responses are not significantly different from the predicted responses. This shows that the design used can provide the right response prediction.

Physical Stability Test of Binahong Leaf Extract Gel Optimum Formula with the Cycling Test Method

The optimum formula for Binahong leaf extract gel was tested for physical stability, which included organoleptic, pH, viscosity, dispersion, and adhesion. The method used was a cycling test that aimed to determine the stability of preparation in extreme conditions in the form of temperature changes.

Organoleptic after Cycling Test

The organoleptic stability testing during the cycling test did not change either the color of the gel, the odor, or the homogeneity of the Binahong leaf extract gel. These results indicate that the use of HPMC and HEC can produce organoleptically stable gels.

Homogeneity Test

The results of the homogeneity test of the optimum formula of the Binahong leaf extract gel that had been formulated met the requirements for good homogeneity, namely the absence of coarse grains or inhomogeneous materials in the preparation.

pH Stability Test

The pH test is carried out to determine the pH of the preparation obtained at a safe distance (4.5-6.5) so that the preparation feels comfortable and does not irritate the skin (Naibaho *et al.,* 2013; Zulkarnain *et al.,* 2022).

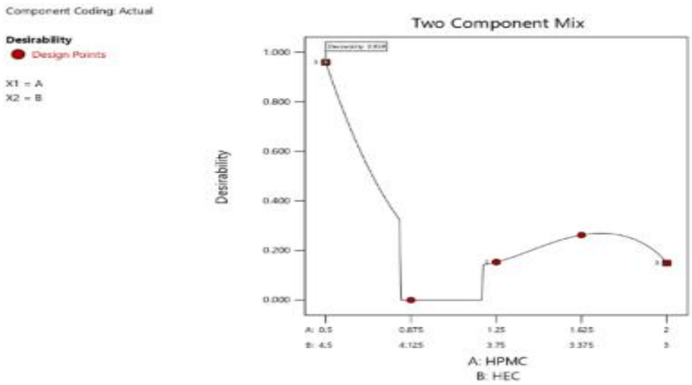

Figure 1. Desirability chart based on *Simplex Lattice Design*

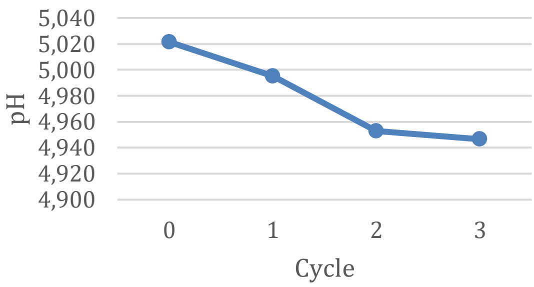

Figure 2. Binahong Leaf Extract Gel pH Test Results during the Cycling Test

Table V. Prediction of the Physical Properties of Binahong Leaf Extract Gel Optimum Formula

Response	Predictive Value
pH	5.029
Viscosity (dPas)	249.302
Spreadability (cm^2)	23.485

Table VI. Optimum Formula Verification

Parameter Response	Prediction	Test	Sig *(2-tailed)*	Description
Viscosity	249,302	248,586	0,705	Not significantly different
Spreadability	23,485	23,142	0,299	Not significantly different
pH	5,029	5,010	0,566	Not significantly different

The optimum formula pH test results during storage can be seen in Figure 2. The pH value of Binahong leaf extract gel is always within the required range.

Based on the Shapiro-Wilk test, a significance value of > 0.05 was obtained. These results indicate that the pH of the Binahong leaf extract gel is normally distributed. After carrying out the normality test, it is continued with the homogeneity of variance test to examine the homogeneity of the data variations. The homogeneity test results obtained a significance value of > 0.05. The results show that the test data population has a homogeneous variant.

Based on the results of the ANOVA test, a significance value of 0.051 was obtained (significance value > 0.05). The results of this analysis indicate that there is no significant difference in the pH of the preparations during the test. Meanwhile, based on the results of the post hoc test, the pH of the preparations from the first

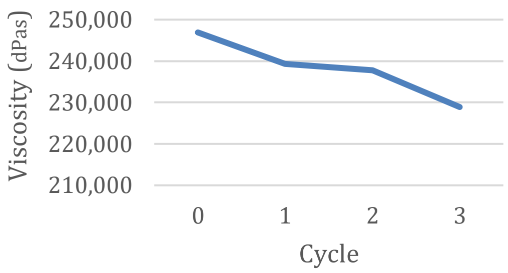

Figure 3. Binahong Leaf Extract Gel Viscosity Test Results during the Cycling Test

to the third cycle was not significantly different. The results of the analysis showed that the pH of the Binahong leaf extract gel preparation was stable during storage.

Viscosity Test

The optimum formula viscosity test results during storage can be seen in Figure 3. The viscosity value of the Binahong leaf extract gel is always within the required range.

The viscosity test is performed to determine the thickness of a fluid. The viscosity of the gel preparation should not be too high because it will make it difficult for the gel to be removed from the container.

Based on the Shapiro-Wilk test, a significance value of > 0.05 was obtained. The homogeneity test results obtained a significance value of > 0.05. These results indicate that the data population is normally distributed and homogeneous.

Based on the results of the ANOVA test, a significance value of 0.209 was obtained (significance value > 0.05). These results indicate that there is no significant difference in the viscosity of the preparations during the test. Based on the results of the post hoc test, the viscosity of the preparation from the first to the third cycle was not significantly different or the viscosity of the gel preparation was stable during storage. The gel preparation obtained from the experimental results had a viscosity of 248,586 dPaS which is good because it is still in the range of 150-300 dPas (Tambunan & Sulaiman, 2018).

Spreadability Stability Test

The optimum formula spreadability test results during storage can be seen in Figure 4. The spreadability value of Binahong leaf extract gel is always in the required range.

Based on the Shapiro-Wilk test, a significance value of > 0.05 was obtained. The homogeneity test results obtained a significance value of > 0.05. The test data population has variants that are normally distributed and homogeneous.

Based on the results of the ANOVA test, a significance value of 0.051 was obtained (significance value > 0.05). The results of this analysis indicate that there is no significant difference in the spreadability of the preparations during the test. Based on the results of the post hoc test, the spreadability of the preparations from the first to the third cycle was not significantly different or the spreadability of the preparations was stable during storage. The spreadability was inversely proportional to the viscosity; if the viscosity increases, the spreadability will decrease.

Adhesion Spreadability Stability Test

The optimum formula adhesive test results during storage can be seen in Figure 5. The adhesive value of Binahong leaf extract gel is always in the required range.

Based on the Shapiro-Wilk test, a significance value of > 0.05 was obtained. The homogeneity test results obtained a significance value of > 0.05. These results indicate that the data population is normally distributed and homogeneous.

Based on the results of the ANOVA test, a significance value of 0.0588 was obtained (significance value > 0.05). These results indicate that there is no significant difference in the adhesion of the preparations during the test. The post hoc test results show that the adhesion of the preparations from the first to the third cycle is not significantly different. The results of the analysis show that the adhesion of the Binahong leaf extract gel is stable during storage. The adhesion is

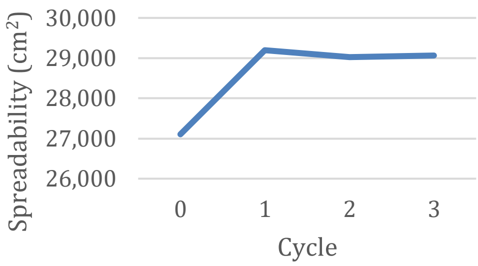

Figure 4. Results of the Spreadability Test of Binahong Leaf Extract Gel during the Cycling Test.

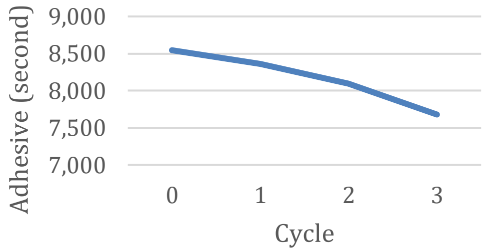

Figure 5. Binahong Leaf Extract Gel Adhesive Test Results during the Cycling Test.

inversely proportional to the spreadability, i.e. if the adhesive power goes down, the spreading power will go up.

CONCLUSION

The optimum formula obtained is the Binahong extract gel preparation with the proportion of gelling agent HPMC 0.5% and HEC 4.5%. Binahong leaf extract gel is stable and has physical properties that meet the required criteria. Increasing the concentration of HPMC affects the increase in viscosity while increasing the concentration of HEC affects the increase in pH and spreadability. Based on the results of the ANOVA test, the composition of HPMC and HEC has a significant effect on the viscosity of the preparation.

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