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Article

The Combination of Bay Leaf (*Syzgyum polyanthum*) and Noni Fruit (*Morinda citrifolia*) in Lowering Cholesterol Levels in Balb/C Hypercholesterolemia Mice

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Abstract. Central Kalimantan is rich in natural resources of potential medicinal plants, such as bay leaf and noni. These medicinal plants have been used traditionally. However, there is minimal scientific evidence about their use as a medicine due to limited research. The current research aims to identify the influence of applying a combination of bay leaf and noni fruit extract in lowering cholesterol levels in Balb/c hypercholesterolemic mice. The research employs a mixed method, namely explorative and experimental research. The research subjects are 28 female Balb/c mice in a hypercholesterolemic condition. The research consists of 7 treatments, namely positive control, negative control, P1 (20%), P2 (30%), P3 (40%), P4 (50%), and P5 (60%) with 4x repetitions. It combines the extract of bay leaf and noni fruit to lower cholesterol levels in the research subjects. Data analysis uses one-way ANOVA. The research results indicate that the application of a combination of bay leaf and noni fruit extract has a significant influence on the reduction of cholesterol levels in hypercholesterolemic mice with a p-value α (α 0.05) of 0.000. The concentration effective in lowering the cholesterol levels in hypercholesterolemic mice is in concentration P7 (60%) with a reduction of 59.25 mg/dL.

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1. Introduction

Central Kalimantan has potential forests rich in natural resources in the form of medicinal plants. Moreover, the native Dayak tribe in Central Kalimantan is also rich in traditional knowledge about treatment by using various plants in their surroundings [1]. People in Central Kalimantan have long relied on medicinal plants as an alternative treatment for generations. These medicinal plants include bay leaf (*Syzgyum polyanthum*). Bay leaf is easy to grow in the Central Kalimantan province due to its environmental and climate conditions suitable for bay leaf cultivation; therefore, many people cultivate the plant for cooking ingredients and traditional medicine. This is in line with research results [2] stating that bay leaf is a medicinal plant mostly used by people in Kalimantan to treat various illnesses, such as hypercholesterolemia.

Another medicinal plant is noni (*Morinda citrifolia*) which is not widely cultivated by people in Central Kalimantan and only grows wild. This is in line with research results [3] explaining that in 2018, there were 42,655 trees in Central Kalimantan with productivity of 2.78 Kg fruits/tree. However, only 100 trees in Palangka Raya city with productivity of 1.75 Kg fruits/tree. This is related to its limited utilization as a yard plant and is seldom used as a commercial plant although it has been used as a traditional medicinal plant by several communities to cure some diseases.

Traditionally, bay leaf has been widely used as an alternative medicine to treat gout, high cholesterol, gastritis, and stroke, and improves blood circulation [4]. Likewise, the noni plant is efficacious for curing some diseases, such as liver disease, gastritis, hypertension, diabetes, diuretics, and as a roundworm medicine. Additionally, the plant can reduce total blood cholesterol levels, LDL, triglycerides, increase HDL, and improve the histological structure of the vessels (thickening of the tunica media) of the aorta of mice given a high-fat diet [5-6]. However, there is no scientific research that combines both plants to enhance their efficacy in treating various diseases. Therefore, further efforts are needed to document and scientifically prove the potential of the combination of bay leaf and noni fruit for optimal use. Based on the research results of [7], combining two plants can have better potential and increase effectiveness due to their flavonoid content that can reduce cholesterol levels.

The public tends to consider these plants as wild plants and sometimes a waste without any effort to cultivate them widely, especially for noni plants [8]. The minimum documentation and scientific proof on these plants as a medicine is due to limited research conducted regarding their content and benefits as a medicine. Moreover, research on medicinal plants is mostly conducted partially without proof in certain combinations. Therefore, this current research combines medicinal plants of bay leaf and noni plants to reduce cholesterol levels in the blood (hypercholesterolemia).

Hypercholesterolemia is a disease caused by a buildup of fat in the blood, causing blockage of blood vessels. It is caused by an increase in consumption of calorie-dense foods, such as fast foods that are considered more practical compared to balanced foods [9]. Changes in dietary habits and physical activities lead to imbalance and can cause hypercholesterolemia [10]. Hypercholesterolemia is an increase in cholesterol levels in blood plasma that are above the normal threshold [11]. One of the methods for reducing hypercholesterolemia and cardiovascular diseases is by reducing total blood cholesterol levels using medicines.

Many cholesterol-lowering drugs are available in the market from natural to modern or synthetic medicines. Non-pharmacological therapy can also be used to lower cholesterol levels in the blood, such as dieting and exercising. If the non-pharmacological therapy fails, pharmacological therapy is an option using natural, modern, or synthetic medicine [12]. However, the use of modern or synthetic medicines has side effects with high doses and long-term consumption. Therefore, to reduce the side effects, many people use alternative treatment by utilizing medicinal plants or herbals including bay leaf and noni plant.

Bay leaf has advantages in several secondary metabolite compounds, such as flavonoids, alkaloids, terpenoids, steroids, tannins, and saponins [13]. In addition to its considerable content of

secondary metabolite, bay leaf is believed to have the capability to lower cholesterol levels in blood because of its flavonoid content which can indicate antioxidants and is able to control HDL cholesterol in mice, based on research [14]. In line with research [15] stating that the application of bay leaf extract can prevent an increase in LDL cholesterol levels that is assumed to be related to its content of active substances, which is flavonoid. One of the active substances of the flavonoid group contained in bay leaves is quercetin. Quercetin with a strong antioxidant property can prevent an increase in cholesterol levels by inhibiting the occurrence of LDL oxidation.

Another plant, noni, has an advantage in parts that contain efficacious compounds, such as roots, skin, leaves, flowers, and fruits. These parts bear various secondary metabolites beneficial for human health, namely anthraquinone, alkaloids, flavonoids, scopoletin, terpenoids, octanoic acid, Vitamin C, Vitamin A, carotene, amino acids, caproic acid, caprylic acid, ursolic acid, aucubin, routine, and proxeronin [16-17]. It is the flavonoid content in noni fruit that can lower cholesterol levels in the blood with its high antioxidant property that reduces cholesterol levels [18-19]. Research [20] states that the content of scopoletin compounds in noni fruits that are rich in antioxidants can lower cholesterol levels in hypercholesterolemic sufferers. Therefore, it is necessary to prove the potential of bay leaf and noni plants scientifically by combining both plants in an effort to utilize natural ingredients.

The research aims to identify the influence of applying the combination of bay leaf and noni fruit extract in lowering cholesterol levels in Balb/c hypercholesterolemic mice. The research results are expected to be used as scientific evidence that is beneficial for society and as basic information and finding or updating information for further, more specific research.

2. Experimental Section

2.1. Tools and Materials

Tools used in the research included mice cages, syringe, mouse oral probe, easy touch cholesterol checker, orbital shaker, blender, measuring cup, Erlenmeyer flask, test tube, beaker, spatula, micropipette, analytical balance, PCR tube, hotplate, funnel, stationery, and cellphone camera. The research materials consisted of bay leaf and noni fruit simplicia, bay leaf and noni fruit extract, 70% alcohol, quail egg yolk, kara coconut milk, simvastatin, distilled water, ethanol, filter paper, and cholesterol test strip.

2.2 Method

The research was conducted at the Integrated Laboratory of Palangka Raya in August - November 2024. The method used was mixed methods, namely exploratory and experimental research. The exploratory research aimed to identify the secondary metabolite compound content of bay leaf (*Syzgyum polyanthum*) extract and noni fruit (*Morinda citrifolia*) extract through phytochemical and antioxidant tests. The experimental research at the laboratory aimed to identify the influence of the application of bay leaf and noni fruit extract on the reduction of cholesterol levels in hypercholesterolemic mice. The research flow chart can be seen in Figure 1.

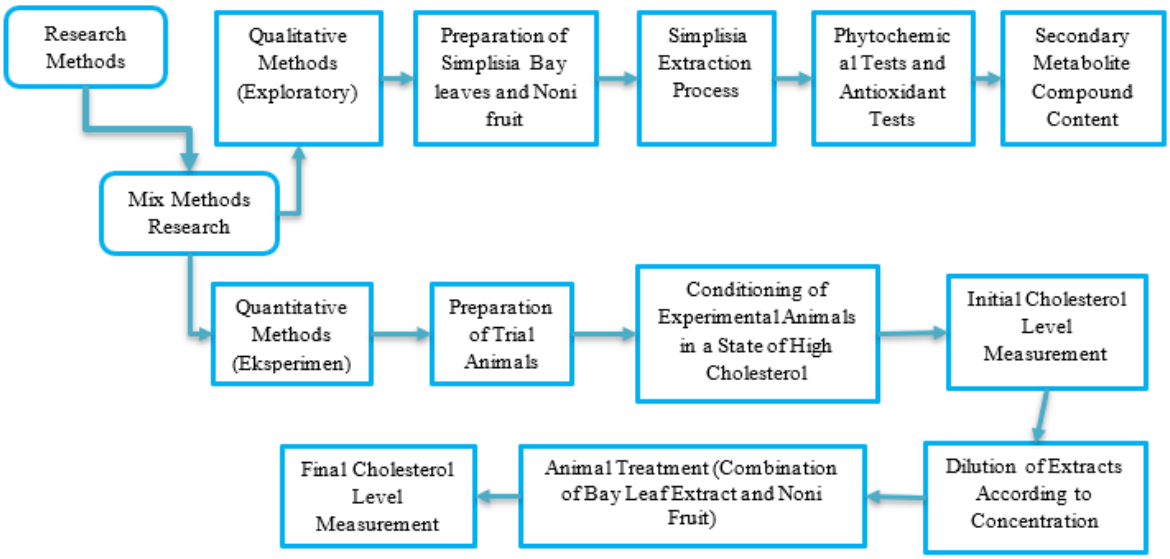

Figure 1. Research flow chart

2.2.1 The Making of Bay Leaves and Noni Fruit Extract

The working procedure in the making of bay leaf and noni fruit extract used the maceration method because the sample maceration method has the advantage of using 95% ethanol solvent due to its properties which can dissolve almost all substances, whether polar, semi-polar, and non-polar compared to other methods [21]. According to [22] there were 7 steps in this stage. First, prepare and wash bay leaves and noni fruits until clean and chop the noni fruits into small pieces, then dry them in direct sunlight until completely dry. Second, chop bay leaves into small pieces and blend until smooth like powder. Third, blend dried noni fruit and chop it into small pieces to allow the blending process until smooth like powder. Fourth, simplisia of bay leaves and noni fruits can be soaked in ethanol and left for ± 6 hours. Fifth, filter the suspension using a clean cloth and filter it again using filter paper. Sixth, the filtered results are put into a Becker glass. The next process is the evaporation of the extract in a simple way using a hot plate at a controlled temperature. The evaporation process is carried out until there is no more alcohol in it. The last step is to store the produced extract of bay leaves and noni fruit and make them as parent stock of the extract formulation.

2.2.2 Preparation of the Combination Formulation of Bay Leaf and Noni Fruit Extract

The working procedure in the making of the combination formulation of bay leaf and noni fruit extract consisted of 3 steps. First, prepare the bay leaf and noni fruit extract from the parent stock and put each extract in a Becker glass separately. Second, take the bay leaf and noni fruit extract by following the combination formulation designed in Table 1. Third, make dilutions of each combination formulation of extracts in several levels of research treatment dilution, namely 20%, 30%, 40%, 50%, and 60%. The selection of the concentrations in this research was adjusted and referred to previous relevant research. Based on the research [23] indicated that giving bay leaf infusion with a concentration of 20% is effective in lowering total blood cholesterol levels in dyslipidemia model mice and the potential is equal to simvastatin with a reduction in cholesterol levels of 27 mg/dl.

Research [24] suggested that the application of noni fruit extract at a concentration of 60% is effective in lowering cholesterol levels in quails and there was a significant difference compared to before the application of noni fruit extract. In the research, a concentration of 60% provided a more

significant influence on the reduction of cholesterol levels compared to other concentrations. This indicates that noni fruit can reduce total cholesterol levels in the blood.

Table 1. Combination formulation of 1:1 of bay leaf and noni fruit extract

No	Material	Formulation
1	Bay leaf extract	50 %
2	Noni fruit extract	50 %

Note: Bay leaf extract: 50 gr of bay leaf extract + 50 ml of distilled water
Noni fruit extract: 50 gr of noni fruit extract + 50 ml of distilled water

2.2.3 Preparation of Experimental Animals

Experimental animals used in the research were 28 female Balb/c mice. Balb/c mice were selected as research subjects due to their superiorities, namely relatively short life cycle, easiness in handling, small size, and similarity to humans in anatomy, physiology, and genetics [25]. Prior to the research, the experimental animals received a period of adaptation to the cage environment for ±1 weeks and were given standard food and drink every day in ad libitum. Then, they were weighted and grouped randomly [26]. The purpose of the adaptation period is to prevent the experimental animals from stress and to make them able to adapt to their new environment [27]. Several things need to be considered in preparing experimental animals. First, the experimental animals will be given BR 1 feed once a day and enough drink. Second, the experimental animals will be put in a cage according to their size and numbers with the following set criteria, namely a cage with a size of 46 x 32 x 15 cm^3, with 2 mice per cage, and will be coated with sawdust husks which are replaced once a week to make the experimental animals more comfortable and stay warm. The sawdust husks absorb mice's urine and feces so the cage remains dry and odorless.

2.2.4 Quail Egg Feeding

Quail egg feeding was carried out orally to 7 experimental animal treatment groups with a dose of 0.5 ml for a week. Previously, the mice were given standard foods and measured for their initial cholesterol levels. The cholesterol level measurement used a Cholesterol Test Strip. The use of quail eggs as experimental animal feeding was due to its content of cholesterol levels of 2138.17 mg/100 g [28]. The safe fat intake for humans is ≤ 300 mg per day.

In this research, the experimental animals would be given fat intake twice the recommended safe limit for fat intake, then multiplied by the conversion factor (humans to mice), namely 600 mg x 0.0026 = 1.56 mg lemak. If 100 g (100000 mg) quail egg yolk is equal to 2138.17 mg cholesterol, then the feed intake given would be 73 mg quail egg yolk per day. The quail egg yolk feeding was also adjusted to the capacity of the mice's stomach, which is 0.5 ml; therefore, suspension made was by mixing 7.3 g of quail egg yolk with coconut milk and distilled water up to 15 ml. The volume given to the mice was 0.5 ml/day [29].

2.2.5 Experimental Animal Treatments

The procedure of experimental animal treatments in the research referred to the research by [30] consisted of four steps. First, conducted initial weighting of mice and checked initial cholesterol levels before the application of the research treatment. Second, research treatments were carried out by giving a high-fat feed, which was quail egg yolk and coconut milk, orally with a tube 2x a day routinely with a dose of 0.5 ml. Third, mice with high cholesterol in treatment groups that were made as a research sample were all given a combination of bay leaf and noni fruit extract, while the control group was not given a combination of bay leaf and noni fruit extract. The positive control group, however, was given a cholesterol-lowering drug, which was simvastatin, whereas the negative control group

was given with merely sterile distilled water. The treatments were conducted orally to mice once a day for a week. The last step was measuring cholesterol levels in mice every 2 days for a week; therefore, the measurement of cholesterol levels in mice was 3 times a week.

2.3 Data Analysis

The data analysis technique employed to test the hypotheses in this stage was one-way ANOVA (Analysis of Variance) with a significance level of 95% using SPSS software. The use of SPSS software was to facilitate the data calculation process so that the data produced was more accurate and reliable. Data generated from the data analysis will be used to interpret and answer the problem formulation, which is the influence of the application of the combination of bay leaf and noni fruit extract in lowering cholesterol and effective concentration that could lower cholesterol levels.

3. Results and Discussion

The results of the secondary metabolite test of bay leaf and noni fruit based on the phytochemical and antioxidant tests can be seen in Table 2.

Table 2. Results of secondary metabolite test of bay leaf and noni fruit

No	Compound Identification	Parameter	Result	
			Bay Leaf	Noni Fruit
1	Flavonoid	Olive green, orange	(+)	(+)
2	Alkaloid:		(+)	(+)
	Meyer	Cloudy brown, Dark brown		
	Dragendorf	Orange, Light brown		
	Bouchardat	Light brown, Dark Brown		
3	Tannin/Phenol	Black	(+)	(+)
4	Steroid	Cloudy yellow, Cloudy brown	(-)	(-)
5	Triterpenoid	Cloudy yellow, Cloudy brown	(+)	(+)
6	Saponin	Orange, Cloudy yellow	(+)	(+)
7	Antioxidant test	-	2.9199 ppm	8.6411 ppm

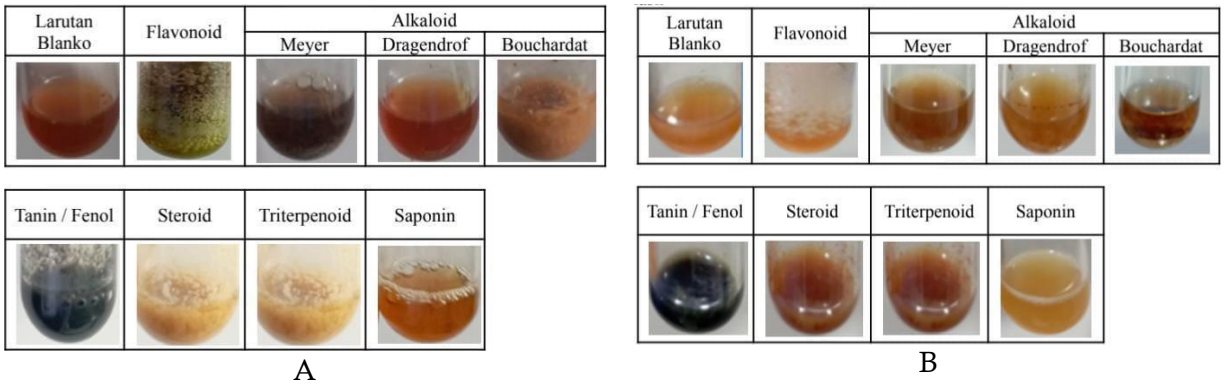

Figure 2. A) Results of Secondary Metabolite Content Test of Bay Leaf, B) Results of Secondary Metabolite Content Test of Noni Fruit

The results of the secondary metabolite compound content test on bay leaf and noni fruit in Table 2 indicate that both natural ingredients contain flavonoid compounds with parameters of olive green and orange. The results suggest that both materials have an influence in lowering cholesterol levels. This is based on the research of [12] indicating that the presence of active ingredients in the forms of flavonoids, one of which is quercetin, is able to prevent an increase in cholesterol levels. In addition to containing flavonoid compounds, bay leaf, and noni fruit also contain other compounds such as alkaloids, tannins, triterpenoids, and saponins, all of which are known to have medicinal properties for several human diseases. According to [31], secondary metabolite compounds are chemical compounds that generally have bioactivity capabilities and function to defend themselves from unfavorable environments, such as temperature, climate, pest disturbance, and plant diseases, and can be used to treat various human diseases.

The results of the antioxidant content test in bay leaf and noni fruit indicate that bay leaf had an antioxidant content of 2.9199 ppm, which means that it has an active and high antioxidant content. According to [32-33], bay leaf extract has a strong antioxidant activity indicated by a value of 4.08 ppm. This suggests that bay leaf extract has a very active antioxidant activity. Therefore, bay leaf can be considered as a promising source to develop products with high antioxidant content [34] and has the potential as a cholesterol drug [35]. Moreover, the antioxidant content test in noni fruit resulted in a value of 8.6411 ppm indicating that noni fruit has a very strong, active, and high antioxidant activity. According to [36], noni fruit extract has a very high antioxidant activity indicated by a value of 10.4734 ppm. This result suggests that noni fruit has a very active and strong antioxidant activity.

The experimental research conducted was orally testing the combination of bay leaf and noni fruit extract using a gastric tube method in hypercholesterolemic mice with a dose of 0.6 ml/mouse once a day for a week. Simvastatin was used as a positive control in this research. Simvastatin is a commonly used antibiotic drug that could lower cholesterol levels [37-38]. Data from the experimental research results are presented in Table 3.

Table 3. Recapitulation of cholesterol level data before and after treatment

Treatment	Before	After	Reduction
P1 (+)	146	108.25	37.75
P2 (-)	144.75	143.25	1.5
P3 (20%)	139.25	104.5	34.75
P4 (30%)	152	106.5	45.5
P5 (40%)	152	104.75	47.25
P6 (50%)	155.75	107	48.75
P7 (60%)	163.25	104	59.25

Based on Table 3, the application of a 1:1 combination of bay leaf and noni fruit extract has a significant influence in lowering cholesterol levels in hypercholesterolemic mice. After the application of 1:1 combination of bay leaf and noni fruit extract, data analysis was conducted statistically using one-way ANOVA with SPSS Software to interpret the influence of the application of the combination of bay leaf and noni fruit extract on the reduction of cholesterol and effective concentration that could lower the cholesterols. The SPPS software was used to facilitate the data calculation process thus data produced are more accurate and reliable [39]. Data are presented in Table 4.

Table 4. Data of ANOVA test results

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	21567.875	1	21567.875	173.031	.000
Within Groups	6730.964	54			
Total	28298.839	55			

Table 4 indicates that the results of variance analysis of cholesterol level reduction generated F-statistics with p-value = 0.000, where p-value < α (α = 0.05) at a significance level of 95%. Based on the data, it can be interpreted that the application of bay leaf and noni fruit extract in lowering the cholesterol levels in hypercholesterolemic mice has a significant influence. To determine the most suitable and efficient concentration to lower cholesterol levels in hypercholesterolemic mice, the data were presented in a percentage of comparison between the average cholesterol levels of mice before and after the research treatments as illustrated in Figure 3.

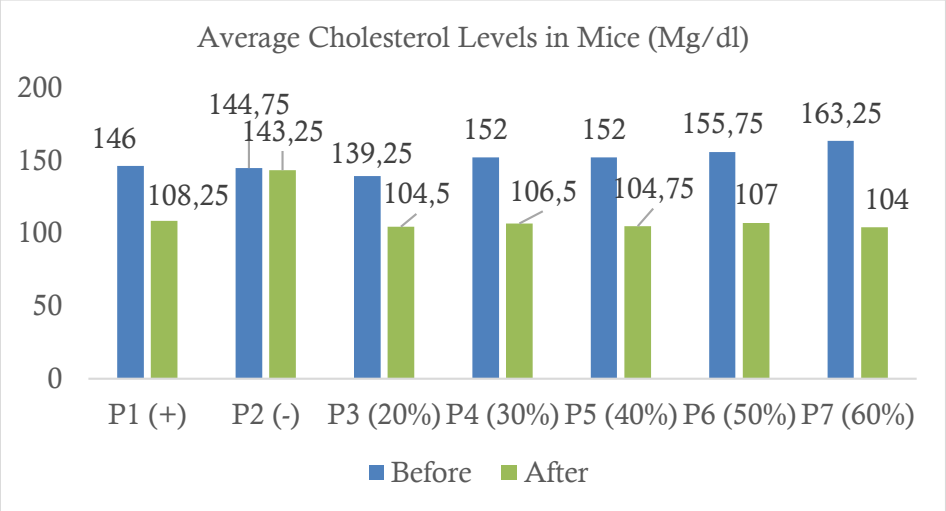

Figure 3. Comparison average number of cholesterol levels before and after treatment

Figure 3 shows the results of before and after application of the combination of bay leaf and noni fruit extract in hypercholesterolemic mice. The results of the data on the average decrease of cholesterol levels in mice before and after the treatments indicate that the highest was given by the combination of bay leaf and noni fruit extracts at a concentration of P7 (60%) with an average decrease of 59.25 mg/dL and the lowest average decrease in mice cholesterol levels was at a concentration of P2 (negative control) with a decrease of 1.5 mg/dL.

The results of the ANOVA test indicate that the application of the combination of bay leaf and noni fruit extract has a significant influence in lowering cholesterol levels in Balb/c hypercholesterolemic mice with a p-value = 0.000 < α (α = 0.05). This is supported by the results of phytochemical and antioxidant tests conducted, which showed that both plants contain flavonoid compounds and high antioxidants thus they can lower cholesterol levels in mice. According to research [5] stating that the application of noni fruit extract has an effect in lowering cholesterol levels due to the flavonoid content in the fruit and high antioxidant sources. However, the research only used one plant; therefore, a combination of two types of plants can increase the effect.

The application of bay leaf and noni fruit extract in the current research had the most effective concentration in lowering cholesterol levels in treatment P7 with a concentration of 60% with an average reduction of 59.25 mg/dL. Research [18] states that the application of 60% of noni fruit extract is able to prevent an increase in cholesterol levels and has a significant influence in lowering cholesterol levels with a p-value < α (α = 0.05).

Data of the decrease in cholesterol levels in hypercholesterolemic mice in Table 4 after the research treatment were analyzed for normality and homogeneity as a requirement for further ANOVA statistical tests. The results of the data normality can be seen in Table 5.

Table 5. Results of normality test of post-treatment cholesterol levels in mice

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
P	.162	4	-	.989	4	.952
P	.210	4	-	.982	4	.911
P	.185	4	-	.972	4	.855
P	.155	4	-	.998	4	.995
P	.218	4	-	.920	4	.538
P	.250	4	-	.927	4	.577
P	.250	4	-	.953	4	.734

The normality test results in Table 5 indicate a significance value based on Shapiro-Wilk of > 0,05, therefore data were normally distributed. This is supported by research [40] arguing that if the significance value based on Shapiro-Wilk > 0.05, then the data are normally distributed. If the generated data were normally distributed, then a homogeneity test can be carried out. The results of the homogeneity test on mice cholesterol level data are presented in Table 6.

Table 6. Results of homogeneity test of post-treatment cholesterol levels in mice

	Levene Statistic	df1	df2	Sig.
Based on Mean	1.769	1	54	.189
Based on Median	.093	1	54	.761
Based on Median and with adjusted df	.093	1	34.059	.762
Based on trimmed mean	.743	1	54	.393

The results of the homogeneity test in Table 6 indicate a significance value of 0.189 > p-value α (α = 0.05); therefore, the generated data were homogeneous. The data were supported by the value of the Levene Statistic of 1.769 which can be interpreted that the smaller the value, the greater the homogeneity of the data. This is also supported by research [41] that the significance value of a homogeneity test that is greater than 0.05 (p > 0.05) indicates that the data variance is homogeneous.

4. Conclusion

Based on the research results, it can be concluded that the application of the combination of bay leaf and noni fruit extract has a significant influence in lowering cholesterol levels in hypercholesterolemic mice with a p-value < α (α = 0.05) of 0.000. Additionally, the effective concentration in lowering cholesterol levels in hypercholesterolemic mice is in concentration P7 (60%) with a decrease of 59.25 mg/dL. The research results are expected to be used as basic information and a finding or updating information for further specific research.

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