Science Midwifery, Vol 14, No. 4, October 2026 ISSN 2086-7689 (Print) | 2721-9453 (Online)
Contents lists available atIOCS

Science Midwifery

journal homepage:www.midwifery.iocspublisher.org

Innovation of plant crystal-based bay leaf (Syzygium polyanthum) nanoparticle herbal medicine formulation as a candidate approach to arterial stiffness in hypertension

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ARTICLEINFO

Article history:

Received Aug 28, 2026
Revised Sep 03, 2026
Accepted Sep 14, 2026

Keywords:

Arterial Stiffness;
Bay Leaf,
Hypertension;
Plantcrystal.

ABSTRACT

Hypertension is associated with increased arterial stiffness and impaired vascular function. Bay leaf (Syzygium polyanthum) contains bioactive compounds that may support vascular function, but its delivery in conventional preparations remains limited. This study aimed to develop a PlantCrystal-based bay leaf nanoparticle herbal formulation and preliminarily evaluate its physicochemical characteristics, active compound release, and effects on mean arterial pressure (MAP) and pulse wave velocity (PWV) in a hypertensive rat model. An experimental study was conducted through the development of seven formulations, physicochemical characterization, LC-MS/MS analysis, in vitro release testing, and in vivo evaluation. The in vivo study used male Wistar rats [n = …/group], with hypertension induced using dexamethasone (0.03 mg/kgBW) and 5% NaCl administered intraperitoneally, together with monosodium glutamate (MSG) mixed in 5% NaCl solution as drinking water. The formulation designated PCXS 2 showed favorable physicochemical characteristics, with particle sizes of 48.32 nm at H1 and 43.24 nm at H30 and PDI values of 0.4087 and 0.47, respectively. Quercetin was tentatively identified by LC-MS/MS. Cumulative release of PCXS 2 reached 97.22% at 480 minutes, representing a 10.13% increase compared with bay leaf decoction, although this did not reach the predefined ≥20% target. In the in vivo study, PlantCrystal administration at 114 mg/kgBW was associated with reductions in MAP and PWV at T28, with MAP of 90.00 ± 5.16 mmHg and PWV of 390.00 ± 5.16 cm/s. One-way ANOVA showed significant differences in MAP and PWV between groups ($p < 0.001$). These findings provide preliminary evidence that the PlantCrystal-based bay leaf formulation may influence MAP and PWV in a hypertensive rat model. Further studies are required to confirm these effects and to determine the potential of this formulation for vascular function.

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INTRODUCTION

Hypertension is a major cardiovascular health problem, with approximately 1.28 billion adults aged 30–79 years living with hypertension worldwide (WHO, 2025). In Indonesia, the prevalence of hypertension among adults aged ≥18 years, based on blood pressure measurements, reached 30.8% in 2023 (SKI, 2023). Hypertension not only causes elevated blood pressure but is also associated with structural and functional changes in blood vessels, including arterial stiffness (Mills et al., 2020). Arterial stiffness reduces vascular elasticity and the ability of blood vessels to adequately buffer pressure waves, thereby increasing cardiac workload and the risk of stroke and cardiovascular disease (Segers et al., 2020). This condition can be assessed using Pulse Wave Velocity (PWV), in which higher PWV values indicate greater arterial stiffness. The Framingham Heart Study reported high PWV in 59.7% of patients with controlled hypertension and 89.9% of those with uncontrolled hypertension, and high PWV was associated with a 2.25-fold higher risk of cardiovascular events compared with normotensive individuals with low PWV (Niiranen et al., 2016). These findings highlight the need for approaches that address not only blood pressure but also vascular function and elasticity.

One natural ingredient with potential for this approach is bay leaf (*Syzygium polyanthum*). Bay leaf contains phenolic and flavonoid compounds, including quercetin, which exhibits antioxidant activity and may support vascular function through modulation of nitric oxide (NO) (Nurlely et al., 2024). Syaripudin (2025) reported that administration of bay leaf decoction reduced systolic blood pressure from 153.6 to 138.4 mmHg and diastolic blood pressure from 93.8 to 84.1 mmHg. These findings indicate the potential of bay leaf as a herbal ingredient for supporting hypertension management. However, its use in conventional herbal preparations remains limited by the stability of bioactive compounds, variations in active compound content, and suboptimal dispersion homogeneity. In addition, previous studies have primarily focused on changes in blood pressure, while the potential of bay leaf to support vascular function, particularly in relation to arterial stiffness, remains insufficiently explored.

These limitations highlight the need for a technological approach to optimize the delivery of bioactive compounds from bay leaf. One potential approach is the *PlantCrystal* technology, which reduces the particle size of powdered plant material using high mechanical energy without chemical extraction. Unlike extraction, which aims to draw active compounds from the plant matrix, *PlantCrystal* facilitates the release of active compounds from the plant matrix through particle size reduction and increased surface area, thereby supporting dissolution and potentially enhancing the bioavailability of active compounds (Jafar et al., 2022; Abraham et al., 2021). However, the application of *PlantCrystal* to bay leaf as a non-extractive approach remains limited, particularly regarding the presence of bioactive compounds after particle size reduction and its potential effects on arterial stiffness in hypertension, particularly based on PWV parameters.

Therefore, this study aimed to develop and optimize a *PlantCrystal*-based bay leaf nanoparticle herbal formulation, evaluate its physicochemical characteristics, and identify and confirm the presence of quercetin using LC-MS/MS following the *PlantCrystal* process. Furthermore, the study evaluated the active compound release profile and the biological potential of the formulation through *in vitro* and *in vivo* assessments of blood pressure and PWV as a parameter of arterial stiffness (Jafar et al., 2022; Suhandi et al., 2025; Hasimun et al., 2021). This approach is expected to yield a modern herbal formulation with optimized bioactive compound delivery while providing evidence of its potential to support blood pressure control and vascular function.

RESEARCH METHOD

Time and Place of Research

The research was conducted experimentally for four months in the Pharmaceutical Laboratory, Pharmacology Laboratory, and Pharmaceutical Chemistry Laboratory, Faculty of Pharmacy, Bhakti Kencana University, Bandung, West Java.

Research Materials and Tools

The materials used included bay leaves obtained from Manoko, Lembang, distilled water, Tween 80, HPMC, and male Wistar rats. The tools used were a drying oven, grinder, 200-mesh sieve, analytical balance, magnetic stirrer, probe sonicator, Particle Size Analyzer, Zetasizer, UV-Vis Spectrophotometer, CODA, and ECG-PPG system.

Research Variables

The research was conducted up to the in vitro and in vivo testing stages with the following variables: Independent variable: variation of Tween 80 concentration in the PlantCrystal-based nanoparticle herbal medicine formulation. Control variables: type and amount of simplicia, solvent volume, HPMC concentration, manufacturing conditions, sonication, maintenance of test animals, and testing methods. Dependent variables: particle size, PDI, zeta potential, morphology, LC-MS/MS results, in vitro release profile of active substances, and in vivo effectiveness based on blood pressure and Pulse Wave Velocity (PWV).

Research Stages

The research stages began with the collection of raw materials and the determination of bay leaf plants (Syzygium polyanthum). Next, the preparation of simplicia, the preparation of simplicia powder and its characterization, as well as phytochemical screening to identify the content of secondary metabolites, were carried out. Next, it was formulated into a nanoparticle herbal medicine based on PlantCrystal technology through a dispersion process using Tween 80 surfactant and high-energy sonication to obtain a homogeneous nanoparticle dispersion system.

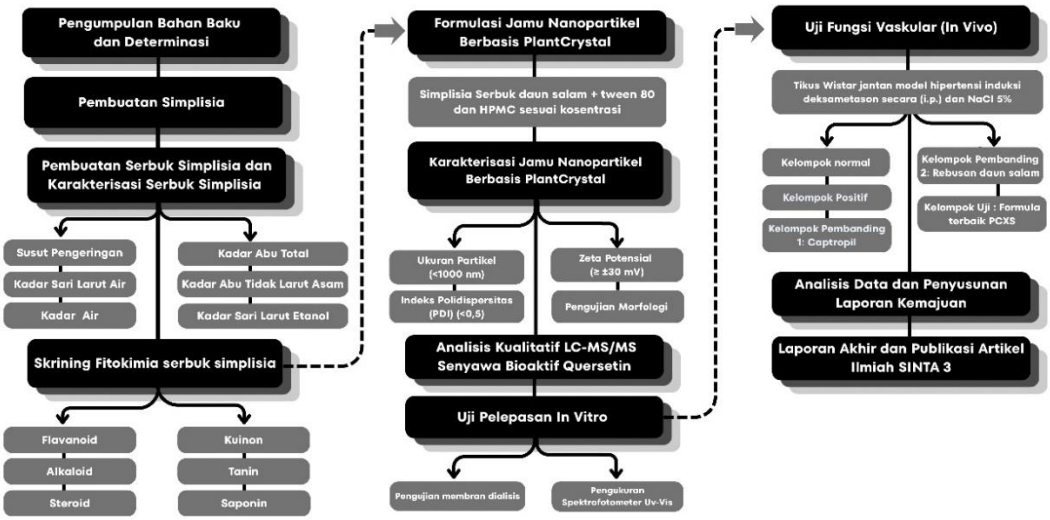


Figure 1. Research Flow

The production of nanoparticle herbal medicine based on PlantCrystal technology was carried out based on the method of Abraham et al. (2021) modified with variations in the concentration of Tween 80 surfactant as a formulation optimization factor.

Table 1. PlantCrystal-Based Nanoparticle Herbal Formula(Priana et al., 2026).

Formula	Bay leaf simplex (%)	Tween 80 (%)	HPMC (%)	Aquadest ad
PCXS F1	1.14	-	-	100ml
PCXS F2	1.14	1	-	100ml
PCXS F3	1.14	0.5	1.75	100ml
PCXS F4	1.14	0.75	1.75	100ml
PCXS F5	1.14	1	1.75	100ml
PCXS F6	1.14	1.25	1.75	100ml
PCXS F7	1.14	1.5	1.75	100ml

The powdered bay leaf simplicia that had been dispersed in hot distilled water was then mixed into the base, stirred using a magnetic stirrer until homogeneous, and continued with a sonication process using a probe sonicator for 30 minutes at 80% amplitude to form the PlantCrystal system. All the resulting formulas were then characterized by testing the particle size, polydispersity index (PDI), zeta potential, and particle morphology.

The formula with the best characteristics was subsequently analyzed for bioactive compounds using LC-MS/MS based on retention time, molecular ions, fragmentation patterns, and fit scores compared with reference data (Hidayat et al., 2026). An *in vitro* active compound release study was then conducted using a dialysis membrane, with the released compound concentration measured using a UV-Vis spectrophotometer and expressed as the cumulative release percentage. An *in vivo* vascular function study was conducted by comparing the best-performing *PlantCrystal* formulation, conventional herbal medicine, and control groups, with PWV evaluated using ECG-PPG on days 0, 14, and 28 (Hasimun et al., 2021). The achievement indicators at this stage were the identification of the target bioactive compound, attainment of the active compound release profile, and a significant reduction in PWV ($p<0.05$) toward the control value.

RESULTS AND DISCUSSIONS

Determination Test

The results of the determination test of the plant used were bay leaves with the scientific name Syzygium polyanthum (Weight) Walp from the Myrtaceae family.(Ministry of Health of the Republic of Indonesia, 2017).

Making Simple Drugs

Based on the drying results, from 3 kg of wet simplicia, 0.81 kg of dry simplicia was obtained with a dry and brittle texture and experienced a color change to brownish green (Fadhilah et al., 2025),(Purwanti & Kholifah, 2025).

Preparation of Simplisia Powder and Characterization of Simplisia Powder

The dried simplicia is ground using a grinder and sieved using a mesh sieve no. 200 to obtain finer and more uniform particle sizes (Mutia et al., 2024),(Subositi, 2014)The final results show that the resulting simple powder has characteristics of brownish green color, smooth texture, and homogeneous particle size.

Table 2. Characterization Results of Bay Leaf Simplicia

Type of determination	Bay leaf		Interpretation
	Result % (w/w)	FH1 % Requirements	
Drying Loss	5.32 ± 1.63	< 10	Qualify
Water content	5 ± 0.1	< 10	Qualify
Total Ash Content	1.5 ± 0	< 2.5	Qualify
Acid Insoluble Ash Content	1.0 ± 0	< 1.8	Qualify
Water Soluble Essence Content	16.0 ± 1.0	> 14.8	Qualify
Ethanol Soluble Essence Level	22.33 ± 1.52	>19.9	Qualify

Thus, the results of the characterization of the simple bay leaf powder show that all parameters meet the requirements of the Indonesian Herbal Pharmacopoeia (Kementerian Kesehatan RI, 2017).

Phytochemical Screening of Bay Leaf Simple Powder

Table 3. Phytochemical Screening Results

Compound Groups	Results
Flavonoid	(+)
Alkaloid	(-)
Quinone	(+)
Saponin	(+)
Tannin	(+)
Steroid	(+)

Description: + (Detected), – (Not Detected)

Phytochemical screening results showed that bay leaves positively contained flavonoids, which supports its potential as a source of bioactive compounds in hypertension research.(Maaliki et al., 2019).

Nanoparticle Herbal Formulation Based on PlantCrystal

The results of the bay leaf nanoparticle herbal medicine formulation can be seen in Figure 2.

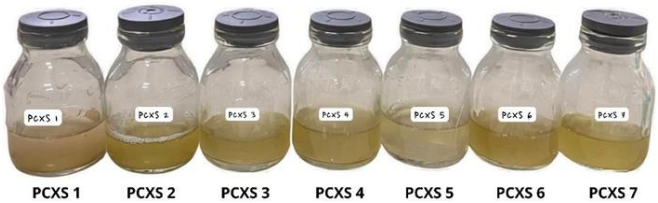


Figure 2. Results of the Formulation of Bay Leaf Nanoparticle Herbal Medicine

Based on visual observation in Figure 2, all formulas F1–F7 exhibit a light yellow to brownish yellow color with varying degrees of turbidity. All formulas appear to form a visually homogeneous liquid dispersion, although there are slight differences in clarity between formulas. F1 appears relatively cloudier, while the formulas containing Tween 80 and HPMC exhibit a more uniform dispersion. These differences in appearance are thought to be related to variations in Tween 80 concentration and the presence of HPMC, which affect the wetting and stability of the particles in the medium.(Zein, 2021),(Shabrina & Kumalasari, 2026).

Characterization of PlantCrystal-Based Nanoparticle Herbal Formula

This evaluation was conducted on all formulas during storage at room temperature (25°C) for one month, namely on day 1 (D1) and day 30 (D30). Parameters observed included particle size, polydispersity index (PdI), zeta potential, and particle morphology.(Septianti et al., 2025).

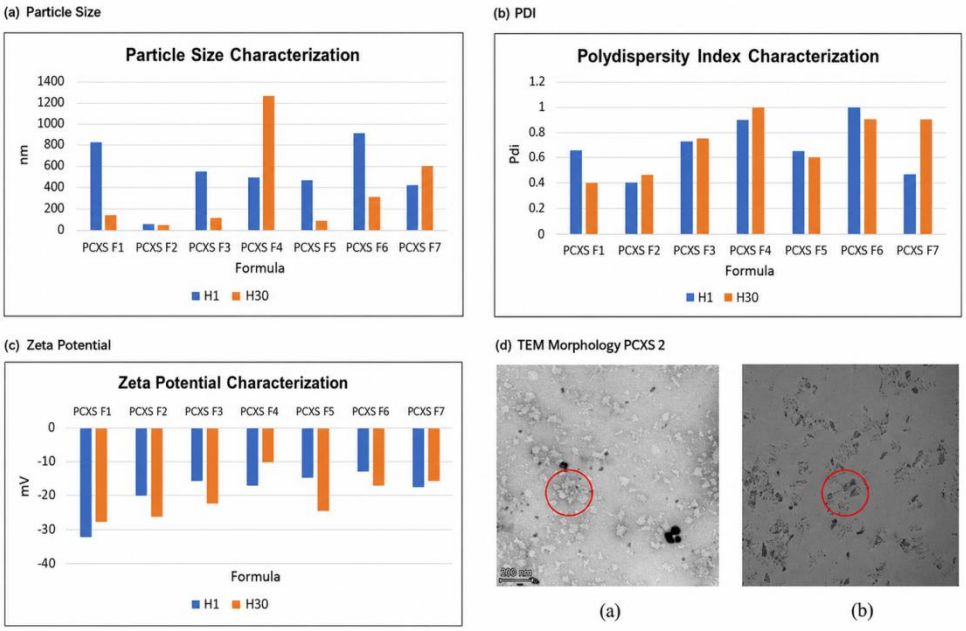


Figure 3. PlantCrystal characterization: (a) particle size, (b) PDI, (c) zeta potential, and (d) TEM morphology of PCXS 2

Particle size of 10–1000 nm indicates the formation of nanoparticles. PCXS 2 produced the smallest particle size, which was 48.32 nm at H1 and 43.24 nm at H30, while the largest size was obtained by PCXS 6 at H1 at 926.8 nm and PCXS 4 at H30 at 1244 nm. PDI values <0.5 indicate good particle size distribution, with PCXS 2 having the lowest PDI values, which were 0.4087 at H1 and 0.47 at H30, while the highest values reached 1 in PCXS 6 (H1) and PCXS 4 (H30). PCXS 2 also showed a zeta potential of −20.46 mV at H1 and −26.86 mV at H30 indicating relatively maintained electrostatic repulsion during storage. These results indicate that PCXS 2 has the best particle size, PDI, and zeta potential characteristics compared to other formulas. Morphological characterization using TEM on PCXS 2 as the optimum formula shows irregularly shaped particles in the form of small fragments on a scale of 500 nm due to the ultrasonication process. TEM results support the previous characterization and strengthen the determination of PCXS 2 as the optimum formula from the formulas tested. Based on particle size, PDI, zeta potential, and morphology, PCXS 2 is determined as the optimum formula.(Suhandi et al., 2025).

Qualitative Analysis LC-MS/MS

Based on the results of LC-MS/MS analysis, quercetin was identified in the bay leaf (Syzygium polyanthum) sample with a retention time of 4.86 minutes, a molecular ion $[M+H]^+$ of m/z 303, and a fit score of 51.09%. The fragmentation pattern showed ions at m/z 331, 303, 255, 237, 161, 155, and 44 compared with reference data. These results indicate that quercetin was tentatively identified in the bay leaf sample.(Hidayat et al., 2026).

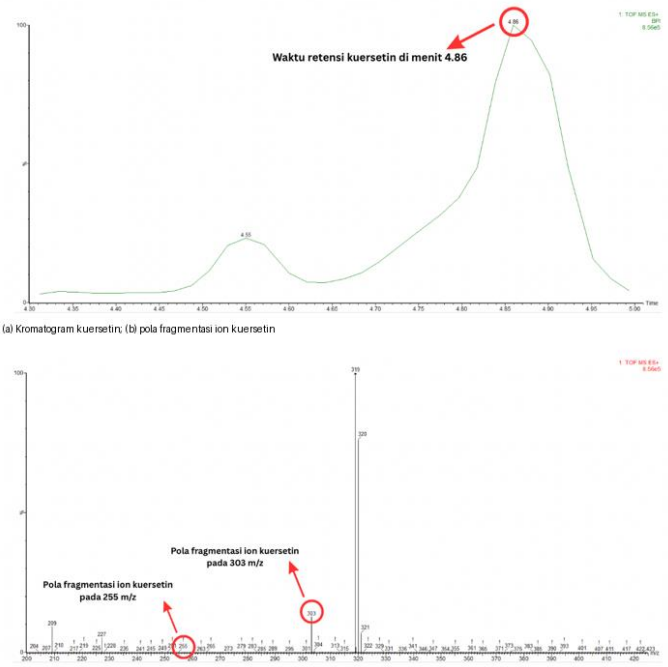


Figure 4. Results of LC-MS/MS identification of quercetin in bay leaves: (a) chromatogram and (b) ion fragmentation pattern.

Dialysis Membrane In Vitro Release Test

The release test samples were analyzed using UV-Vis spectrophotometry to measure the released flavonoid levels. The standard curve showed good linearity with an R^2 close to 1. Based on the calculation results, the release percentage of F2 nanoparticle herbal medicine increased from 64.80% at the 15th minute to 97.22% at the 480th minute. Meanwhile, bay leaf simplicia showed a relatively stable release in the range of 82.69–88.50%. The comparison curve showed that at the end of the observation, the release of F2 was higher than that of the simplicia, namely 97.22% and 88.28%, with an increase of 10.13%. Thus, there was an increase in the release profile of F2 nanoparticle herbal medicine, but it had not yet reached the indicator of an increase of ≥20%.(Hidayat et al., 2026).

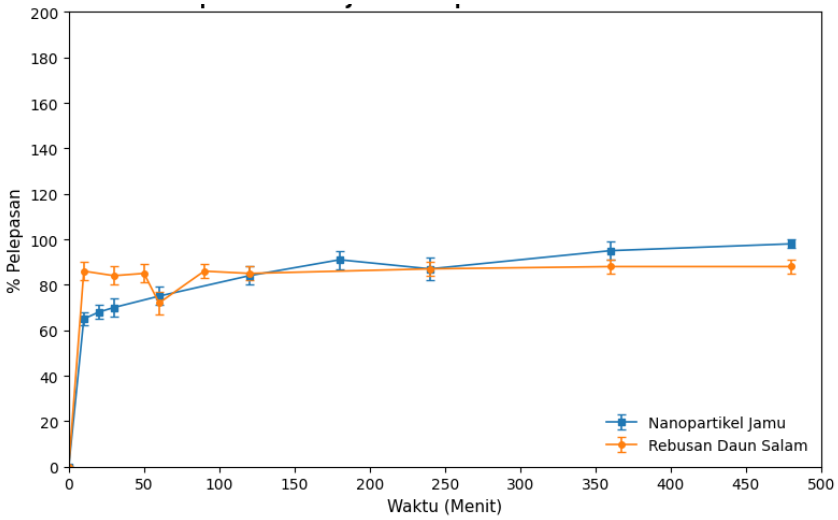


Figure 5. Release Profile of PCXS 2 Active Substance and Bay Leaf Boil

Vascular Function Test (In Vivo)

The in vivo test ethics certificate was obtained on July 14, 2026 with number 196/09.KEPK/UBK/VI/2026 before starting the in vivo test. The test animals used were male Wistar rats. Induction using dexamethasone 0.03 mg/kgBW and 5% NaCl intraperitoneally (ip) and monosodium glutamate (MSG) mixed into 250 mL of 5% NaCl solution as a drink to obtain conditions of increased blood pressure and changes in vascular parameters (Imam Syafi'i, Fadlina Chany Saputri, 2022). After the induction period, the test animals were given treatment in the form of a positive control group given captopril 4.5 mg/kgBW, a comparison group given 5 g of bay leaf decoction in 200 mL, while the test group was given 114 mg/kgBW of nanoparticle herbal medicine. Evaluation of vascular function was performed by measuring blood pressure using CODA and Pulse Wave Velocity (PWV) based on ECG-PPG at T0, T14, and T28.

Table 4. Mean Arterial Pressure (MAP) Measurement Results

Group	Mean Arterial Pressure (MAP)		
	T0 (mmHg)	T14 (mmHg)	T28 (mmHg)
Normal Control	85.00 ± 2.58	85.00 ± 2.58	83.00 ± 2.58
Negative Control (Induction)	84.00 ± 3.11	110.00 ± 5.16	122.00 ± 5.16
Positive Control (Captopril)	85.00 ± 2.58	125.00 ± 5.16	88.00 ± 5.16
Comparison (Bay Leaf Decoction)	85.00 ± 2.58	128.00 ± 5.16	96.00 ± 5.16
Test (PlantCrystal)	86.00 ± 2.58	122.00 ± 5.16	90.00 ± 5.16

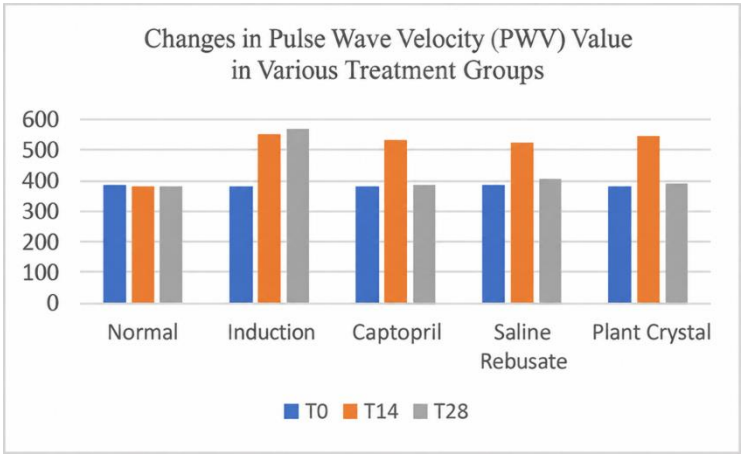


Figure 5. Mean Arterial Pressure (MAP) Measurement Results

The results of blood pressure measurements using CODA showed changes in Mean Arterial Pressure (MAP) during the observation period. After induction, the negative control group experienced an increase in MAP from 84.00 ± 3.11 mmHg (T0) to 110.00 ± 5.16 mmHg (T14). After treatment until T28, MAP decreased in the positive control group (Captopril) to 88.00 ± 5.16 mmHg, the comparison (Bay Leaf Decoction) to 96.00 ± 5.16 mmHg, and the test (PlantCrystal) to 90.00 ± 5.16 mmHg, while the negative control remained high at 122.00 ± 5.16 mmHg. The PlantCrystal MAP value at T28 was close to the normal control (83.00 ± 2.58 mmHg) and the positive control. The results of One-Way ANOVA showed significant differences in MAP between groups at all measurement times ($p < 0.001$), followed by the Tukey HSD test.

Table 5.ECG-PPG based PWV measurement results

Group	Pulse Wave Velocity (cm/s) ± SD		
	T0	T14	T28
Normal Control	386 ± 3.77	382 ± 3.87	382 ± 3.50
Negative Control (Induction)	383 ± 4.79	554 ± 5.69	570 ± 5.16
Positive Control (Captopril)	383 ± 4.40	536 ± 5.16	385 ± 5.16
Comparison (Bay Leaf Decoction)	385 ± 4.40	528 ± 5.16	405 ± 5.16
Test (PlantCrystal)	382 ± 3.87	545 ± 5.16	390 ± 5.16

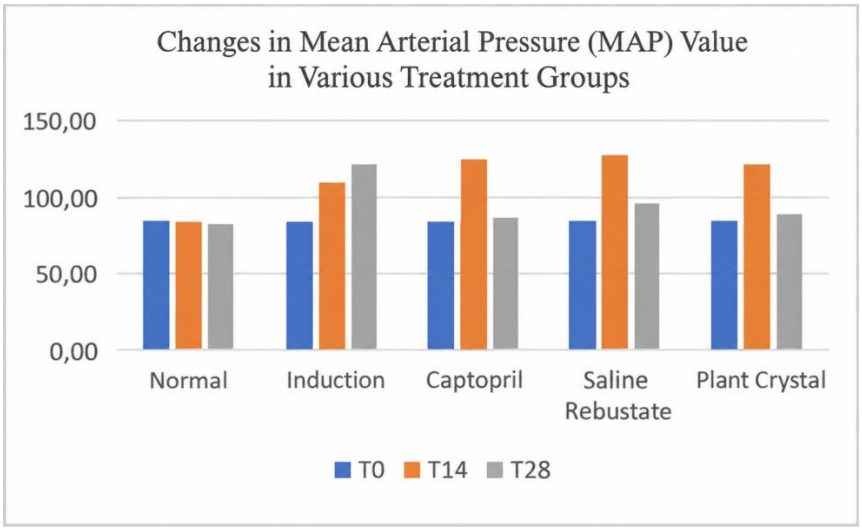


Figure 6. PWV Measurement Results based on ECG-PPG

The results of Pulse Wave Velocity (PWV) measurements showed changes in values during the observation period. After induction until T14, the negative control group (Induction) showed an increase in PWV from 383 ± 4.79 cm/s at T0 to 554 ± 5.69 cm/s at T14. After treatment until T28, the positive control group (Captopril), comparison (Bay Leaf Decoction), and test (PlantCrystal) showed a decrease in PWV to 385 ± 5.16 cm/s, 405 ± 5.16 cm/s, and 390 ± 5.16 cm/s, respectively. Meanwhile, the negative control group (Induction) continued to show high PWV values until T28, namely 570 ± 5.16 cm/s. The PlantCrystal group showed a decrease in PWV to approach the normal control group and the positive control. The results of One-Way ANOVA showed a significant difference in PWV between groups at T0, T14, and T28 ($p < 0.001$). The achievement indicator at this stage is a significant decrease in PWV ($p < 0.05$) to approach the value of the safe control.(Priana et al., 2026;Ismail et al., 2018;Hasimun et al., 2021).

CONCLUSION

The PlantCrystal-based bay leaf nanoparticle herbal formulation was successfully developed through seven formulations, with PCXS 2 showing favorable physicochemical characteristics among the formulations tested. Quercetin was tentatively identified by LC-MS/MS. PCXS 2 achieved a cumulative release of 97.22% at 480 minutes, representing a modest 10.13% increase compared with bay leaf decoction and remaining below the predefined ≥20% target. In the hypertensive male Wistar rat model, administration of the PlantCrystal formulation at 114 mg/kgBW was associated with reductions in MAP and PWV at T28, with MAP of 90.00 ± 5.16 mmHg and PWV of 390.00 ± 5.16 cm/s. The between-group differences in MAP and PWV were statistically significant ($p < 0.001$). However, these findings should be interpreted as preliminary evidence in a hypertensive rat model, and the observed association between PlantCrystal administration and reductions in MAP and PWV should be interpreted cautiously. Further studies are needed to confirm the reproducibility, efficacy, mechanisms, and safety of the PlantCrystal-based Syzygium polyanthum formulation before any implications for human hypertension or vascular function can be considered.

ACKNOWLEDGEMENTS

The author would like to thank the Directorate of Learning and Student Affairs and Bhakti Kencana University for their financial support and research facilities in implementing the Student Creativity Program for Exact Research (PKM-RE). The author would also like to thank the supervising lecturers and all parties who have assisted in the implementation of this research.

Gina Wulandari is responsible as the activity leader, the manufacture and formulation of PlantCrystal-based nanoparticle herbal medicine, the characterization of PlantCrystal nanoparticle herbal medicine, data analysis, and report preparation. Ayu Widia Ningsih is responsible for the preparation of powder and characterization of the simplicia as well as vascular function tests. Dina Kamila is responsible for the in vitro release test and the preparation of the simplicia. Sela Mustika Rohayat is responsible for the qualitative analysis of LC-MS/MS and the preparation of the simplicia. Isna Alia Rahmawati is responsible for the collection of materials, plant determination, and phytochemical screening.

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