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Phytochemical Profiling and Granule Formulation of Green Betel Leaf (*Piper betle* L.) Extract for Potential Bio-Larvicidal Application

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Abstract

Background: *The increasing spread of Aedes aegypti as a vector of dengue disease has encouraged the exploration of safer, plant-based larvicidal materials. This study aimed to identify the phytochemical constituents of green betel leaf (Piper betle L.) extract and to develop a bio-larvicidal granule formulation as a modified dosage form. Phytochemical screening was conducted to identify bioactive compounds potentially associated with larvicidal activity.* **Methodology:** *Granules were prepared using the wet granulation method, employing polyvinylpyrrolidone (PVP) as a binder and lactose as a filler. The formulated granules were further evaluated through physical characterization tests, including flow rate, angle of repose, and dispersion time, to assess their suitability as a granular dosage form.* **Findings:** *The results demonstrated that all formulations exhibited acceptable flow properties, appropriate angles of repose, and rapid dispersion in water, indicating favorable handling and application characteristics. The flow rate test results showed that granules with concentration variations of 25%, 50%, 75%, and 100% exhibited flow rates of 71.4 g/s, 62.5 g/s, 50 g/s, and 45.5 g/s, respectively. Physical evaluation demonstrated that the granules had acceptable angles of repose (31°–36°) and dispersion time (20–25 seconds).* **Contribution:** *This study was conducted as a step toward developing an environmentally safe, natural-material-based biolarvicide.*

Keywords: *Bio-larvicidal granules; Granule characterization; Phytochemical screening; Piper betle L.*

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INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is an acute viral disease caused by dengue virus and transmitted to humans through the bites of infected *Aedes* mosquitoes, primarily A*edes aegypti* and *Aedes albopictus*. Dengue virus consists of four serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), all of which are capable of causing infection in humans. DHF remains a major global public health problem, particularly in tropical and subtropical regions. The World Health Organization (WHO) estimates that approximately 2.5 billion people, or 40% of the world's population, are at risk of dengue infection, with around 390 million cases occurring annually worldwide. Indonesia is classified as a hyperendemic country for dengue, with cases reported in almost all provinces and districts, and daily reports reaching hundreds of cases accompanied by dengue-related mortality (World Health Organization, 2012).

Indonesia's tropical climate, characterized by high humidity and abundant rainfall, provides favorable conditions for the proliferation of *Aedes aegypti*, which predominantly breeds in clean water containers found both indoors and outdoors. Female *Aedes aegypti* mosquitoes act as the main vector of dengue transmission (Soegijanto, 2012). Morphologically, this species is distinguished by its dark body with distinctive silvery-white markings on the legs and a lyre-shaped pattern on the thorax (Service, 2012). Vector control strategies targeting the larval stage are considered one of the most effective approaches to reducing dengue transmission, as they prevent the emergence of adult mosquitoes.

Current dengue control programs, such as space spraying (fogging), have shown limited effectiveness and often rely on synthetic insecticides that may induce resistance in mosquito populations. One of the most commonly used chemical larvicides is temephos (commercially known as abate). Although effective, improper or prolonged use of chemical larvicides can lead to resistance development and pose potential health risks to humans, including neurological and dermatological effects (Ahmad et al., 2007). These concerns highlight the urgent need for safer, environmentally friendly, and sustainable alternatives. WHO has recommended the development of biological and plant-based vector control methods as safer options for environmental and human health (World Health Organization, 2012).

Green betel leaf (*Piper betle L.*) is a widely available plant in Indonesia, including Lampung Province, and has been reported to possess larvicidal properties. Previous studies have demonstrated that *Piper betle* leaves contain various bioactive compounds such as phenols and their derivatives (e.g., chavicol and eugenol), alkaloids, tannins, flavonoids, and saponins, which contribute to their insecticidal activity (Mustofa, 2010). Additional reports indicate that *Piper betle* extract exhibits larvicidal effects against *Aedes aegypti*, supported by phytochemical screening results showing the presence of steroids, quinones, and essential oils with antibacterial and antiseptic properties (Aulung, 2010).

Despite its promising bioactivity, the practical application of *Piper betle* extract requires appropriate formulation to ensure stability, ease of handling, and effective release of active compounds. Granule dosage forms produced via wet granulation offer several advantages, including improved flow properties, reduced dust formation, and controlled dispersion in water. Therefore, this study focuses on phytochemical

profiling of green betel leaf extract and the development of a bio-larvicidal granule formulation, followed by comprehensive physical characterization to evaluate its suitability as an alternative plant-based larvicidal product.

METHOD

This study employed an experimental study of the formulation development type, which begins with the analysis of the phytochemical profile of the extract, followed by the formulation of granules, and then the characterization of the physical properties of the resulting granules.

Sample

The research material used in this study was green betel leaf (*Piper betle* L.), which was collected from Trimurjo District, Central Lampung, Indonesia. The leaves were selected as the plant part for extraction based on their reported bioactive properties.

Instrument

The instruments used in this study included laboratory glassware, analytical balance, blender, mesh sieve (60 mesh), rotary vacuum evaporator, drying oven, granulate flow tester (Erweka®), and pH meter. Reagents used for phytochemical screening included magnesium powder, concentrated hydrochloric acid, Mayer's reagent, Dragendorff's reagent, Bouchardat's reagent, ferric chloride ($FeCl_3$), and distilled water. General laboratory tools are not described in detail.

Data collection

Data were collected through experimental observations during the extraction process, phytochemical screening, granule fabrication, and physical evaluation of the granules. Phytochemical data were obtained qualitatively based on color changes, precipitate formation, and foam stability during screening tests. Granule characterization data included flow rate, angle of repose, and dispersion time measurements, which were recorded for each formulation containing different extract concentrations.

Procedure

Preparation of Green Betel Leaf Simplicia

Green betel leaves were cleaned, sorted to remove damaged parts, washed, sliced, and dried under direct sunlight for 3–4 days until a constant weight was achieved. The dried leaves were ground into powder using a blender and sieved through a 60-mesh sieve to obtain uniform simplicia.

Extraction of Green Betel Leaf

Extraction was performed using the maceration method, in which 1000 g of simplicia powder was soaked in 10.000 mL of 96% ethanol for 3 × 24 h with occasional stirring to enhance the extraction of bioactive compounds (Harborne, 1998). The mixture was filtered to separate the filtrate from the residue

(Departemen Kesehatan Republik Indonesia, 2000). A second maceration was conducted using fresh solvent, and the combined filtrates were concentrated using a rotary vacuum evaporator at 40–45°C to obtain a viscous extract (Sarker et al., 2006). The total extract obtained was then calculated to determine the extraction yield (%).

Fabrication of Bio-Larvacidal Granule

Bio-larvicidal granules were fabricated using a wet granulation method with four extract concentrations (25%, 50%, 75%, and 100%), along with a 0% extract granule formulation used as the control. This method was selected to improve flowability, reduce dust formation, and prevent powder segregation (Lachman et al., 1994). The dried extract was mixed with lactose as a filler and polyvinylpyrrolidone (PVP) at a concentration of 2% as a binder. PVP was dissolved in distilled water and blended with the extract and excipients until a homogeneous mass was obtained, with the total formulation adjusted to 100 g. Ethanol (96%) was added dropwise to facilitate granule formation (Aulton, 2007). The wet mass was dried in an oven at 40°C for approximately 30 min and sieved through a 22-mesh sieve to obtain uniform granules.

Table 1. Granulated Biolarvicide Formulation design

Materials	**F1**	**F2**	**F3**	**F4**	**F5**
P. betle Leaf extract	0%	25%	50%	75%	100%
PVP 2%	5 ml	5 ml	5 ml	5 ml	5 ml
Lactose	Add to 100g	Add to 100g	Add to 100g	Add to 100g	Add to 100g

Phytochemical screening

Phytochemical screening was conducted to identify the presence of major secondary metabolites in the extract. Flavonoids were detected using magnesium powder and concentrated hydrochloric acid, indicated by the formation of red or yellow–orange coloration (Harborne, 1987). Alkaloids were identified using Mayer's, Dragendorff's, and Bouchardat's reagents based on precipitate formation (Farnsworth, 1996). Tannins were detected using ferric chloride solution, indicated by a dark green or bluish-green color change (Evans, 2009). Saponins were identified based on the formation of stable foam after vigorous shaking and acid addition (Kokate, 1994). Information on phytochemical screening methods is presented in Table 2.

Table 2. Phytochemical Screening Testing Method

Phytochemical compound	**Test methods**
Flavonoid	2 ml of extract solution is added with 0.5 g of magnesium and five drops of concentrated HCL
Alkaloid	- Tube I : 1 ml of extract and add Mayer's reagent - Tube II : 1 ml of extract and add Dragendorff's reagent - Tube III : 1 ml of extract and add bouchardat's reagent

Tanin	Add 1 ml of extract to 2 ml of distilled water, then add two drops of 1% FeCl solution
Saponin	1 ml of extract is added to 10 ml of distilled water, then shaken and observed to see if there is any foam

Evaluation of Granule Characteristics

Granule characteristics were evaluated through flow rate, angle of repose, and dispersion time tests. Flow rate was measured using a granulate flow tester (Erweka®), with values greater than 10 g/s indicating good flow properties (US Pharmacopeia, 2018). The angle of repose was calculated from the height and diameter of the granule pile, where values ≤ 30° indicated excellent flowability (Aulton & Taylor, 2018). Dispersion time was determined by dissolving 10 g of granules in 1 L of water and recording the time required for complete dispersion. The test was conducted in triplicate at room temperature with manual agitation.

Data analysis

Data obtained from phytochemical screening were analyzed descriptively based on qualitative observations. Granule characterization data were presented as numerical values and evaluated descriptively to assess the physical quality and suitability of the formulated granules as a bio-larvicidal dosage form.

RESULT AND DISCUSSION

Preparation of Simpicia and Extraction Yield

Green betel leaves (*Piper betle* L.) were processed into simplicia through sun-drying for 3–4 days to minimize thermal degradation of heat-sensitive phenolic compounds. Controlled drying without high temperature is known to preserve phenolic stability and improve extraction efficiency (Chan et al., 2007; Naczk & Shahidi, 2004). The dried leaves were milled and sieved using a 50-mesh screen to obtain uniform particle size (~500 µm), facilitating solvent penetration and mass transfer during extraction (Yunus et al., 2013).

Table 3. Total Percentage Yield of Green Betel Leaf (*Piper betle* L.) Extract

Category	Amount
Solvent volume (mL)	10.000
Sample weight (g)	1.000
Total viscous extract (g)	87,46
Extrcation yield (%)	8,74

Extraction was performed using maceration with 96% ethanol due to its semi-polar nature, which is suitable for dissolving major bioactive compounds such as flavonoids, alkaloids, and tannins (Cowan, 1999; Azmir et al., 2013; Dai & Mumper, 2010; Stalikas, 2007; Markham, 1982). Maceration was selected because it avoids thermal stress that may degrade bioactive compounds. Occasional stirring enhanced solvent–matrix interaction and improved metabolite diffusion (Rostagno et al., 2003). Concentration of the combined filtrates using a rotary evaporator at 45 °C yielded 87.46 g of viscous extract from 1 kg of simplicia, corresponding to a rendement of 8.74%. Rotary evaporation at low temperature

effectively preserves compound integrity while increasing extract concentration (Sarker & Nahar, 2012; Chemat et al., 2012).

Phytochemical Screening of *Piper betle* Leaf Extract

Phytochemical screening revealed the presence of flavonoids, alkaloids, tannins, and saponins in the extract. Flavonoids were confirmed by the formation of orange-brown precipitates, while alkaloids were detected using Dragendorff's and Bouchardat's reagents.

Table 4. Phytochemical Screening Results of Green Betel Leaf (*Piper betle* L.) Extract

Compounds	Identification Result	Phytochemical Test Result
Flavonoids	Formation of brownish-orange precipitate	+
Alkanoids	White precipitate (mayer reagent)	-
	Brown precipitate (dragendorff reagent)	+
	Brown precipitate (bouchardat reagent)	+
Tanins	Bluish-black precipitate	+
Saponins	Foam formation	+

Note: symbol (+) indicates a positive qualitative reaction showing the presence of the tested phytochemical compounds; symbol (−) indicates no observable reaction based on visual reaction criteria.

Tannins and saponins were identified by characteristic color changes and stable foam formation, respectively. These secondary metabolites are widely reported to exhibit insecticidal properties through disruption of enzymatic activity, digestive systems, and membrane integrity of insect larvae (Sukandar et al., 2006; Ghosh et al., 2012; Isman, 2006). The coexistence of these compounds suggests a synergistic bioactivity profile of *P. betle* leaf extract.

LC-MS Identification of Bioactive Compounds

LC–MS analysis further confirmed the complexity of bioactive compounds in the extract. Hydrocinnamic acid was identified as the dominant compound, indicated by the largest peak area (5.73×10^{10}), highlighting its potential contribution to biological activity. Phenolic derivatives such as hydrocinnamic acid are known to induce oxidative stress and damage larval integument structures (Pavela, 2015). Several nitrogen-containing compounds consistent with alkaloid or alkaloid–peptide structures were also detected, aligning with reports that Piperaceae alkaloids interfere with acetylcholinesterase activity and neural transmission in insect larvae (Regnault-Roger et al., 2012).

Table 5. Compounds with larvicidal potential identified by LC–MS analysis of green betel leaf (*Piper betle L.*) extract

No.	Name of Compund	Formula	Area
1.	Hydrocinnamic acid	C9 H10 O2	5.73×10^{10}
2.	Alkaloid	C30 H36 N6 O7	1.39×10^{10}
3.	Alkaloid/Peptide	C31 H38 N6 O7	6.56×10^{9}
4.	Tetrapirol	C35 H36 N4 O6	5.86×10^{9}

5.	Fenolic glicoside	C34 H40 O9	5.17×10^{9}

Additional compounds, including tetrapyrrole-like structures and phenolic glycosides, further support the potential of the extract as a bioactive agent through phototoxic and digestive disruption mechanisms (Duke et al., 2002; Nerio et al., 2010). The detected metabolite profile supports a synergistic mode of action commonly observed in botanical insecticides (Pavela & Benelli, 2016).

Granule Formulation Using Wet Granulation

Granules were formulated using wet granulation to improve flowability, minimize dust formation, and ensure uniform distribution of the extract. Polyvinylpyrrolidone (PVP) was used as a binder due to its chemical stability, non-toxicity, and resistance to enzymatic biodegradation (Rowe et al., 2009; Kibbe, 2000), while lactose served as a filler to enhance mechanical strength and dispersibility (Sa'dah & Fudholi, 2011).

Table 6. Formulation of Biolarvicidal Granules Containing Green Betle Leaf Extract

Materials	F1	F2	F3	F4	F5
P. betle Leaf extract	0 g	3,5 g	7,2 g	10,7 g	14,2 g
Aquades	15 ml	11,5 ml	7,8 ml	4,3 ml	0,8 ml
PVP 2%	5 ml	5 ml	5 ml	5 ml	5 ml
Lactose	80g	80g	80g	80g	80g

Four formulations containing increasing concentrations of the extract and one formulation without the extract were successfully made fabricated, producing granules with uniform size and characteristic green coloration that intensified with extract concentration.

(a) **(b)** **(c)** **(d)**

Figure 1. Granule (a) F1; (b) F2; (c) F3; (d) F4

Differences in color were observed among the granules from the four formulations. Granules F1 (Figure 1) exhibited a lighter green color compared to granules F2, F3, and F4. Granules F2 showed a darker green color than F1, but were less intense than those of F3 and F4. Granules F3 and F4 displayed a more intense green coloration than the two preceding formulations. The intensity of the granule color was influenced by the concentration of extract used in each formulation. The granules exhibited the characteristic color of green betel leaf extract, namely brownish green, with a relatively compact texture that facilitates storage and further testing.

Physical Characterization of Biolarvacidal Granules

Flow Rate

Physical characterization demonstrated that extract concentration significantly influenced granule properties.

Table 7. Flow Rate Test Result of Biolarvacidal Granule

No.	Formula	Flow rate (g/s)
1.	I (Extract *Piper betle* granule 25%)	71.4
2.	II (Extract *Piper betle* granule 50%)	62.5
3.	III (Extract *Piper betle* granule 75%)	50.0
4.	IV (Extract *Piper betle* granule 100%)	45.5

Flow rate decreased from 71.4 g/s at 25% extract concentration to 45.5 g/s at 100 %, indicating increased interparticle cohesion at higher extract loads. Increased cohesion reduces gravitational dominance and restricts free flow, as previously reported for herbal granules with high active content (Andriani et al., 2023; Astuti & Maesaroh, 2020). Although all formulations exceeded 10 g/s, indicating very fast flow, excessive flowability may promote segregation and reduce application efficiency (Murtini & Elisa, 2018).

Angle of Repose

Angle of repose values ranged from 31° to 36°, corresponding to good to moderate flow properties (Carr, 1965; Geldart et al., 2006). Lower angles observed at lower extract concentrations reflected reduced friction and cohesion between particles, consistent with higher flow rates. Increasing extract content resulted in larger angles, confirming the inverse relationship between flowability and interparticle interaction (US Pharmacopeia, 2018; Carr, 1965).

Table 8. Angle of Repose Test Result of Biolarvacidal Granule

No.	Formula	Angle of Repose (º)
1.	I (Extract *Piper betle* granule 25%)	31
2.	II (Extract *Piper betle* granule 50%)	34
3.	III (Extract *Piper betle* granule 75%)	35
4.	IV (Extract *Piper betle* granule 100%)	36

Dispersion Time

Dispersion time increased proportionally with extract concentration, ranging from 20.14 s (25%) to 25.02 s (100%). All formulations met the acceptable dispersion criterion (<5 min), indicating satisfactory release behavior in aqueous media (Astuti & Maesaroh, 2020). The prolonged dispersion observed at higher extract concentrations is attributed to denser granule structure and reduced water penetration, a phenomenon consistent with previous reports on herbal granules containing high extract loads (Marfu'ah et al., 2024).

Table 9. Dipersion Time Test Result of Biolarvacidal Granule

No.	Formula	Dipersion Time (s)
1.	I (Extract *Piper betle* granule 25%)	20.14
2.	II (Extract *Piper betle* granule 50%)	22.92
3.	III (Extract *Piper betle* granule 75%)	24.84
4.	IV (Extract *Piper betle* granule 100%)	25.02

CONCLUSION

Green betel leaf (*Piper betle* L.) extract was confirmed to contain bioactive secondary metabolites, including flavonoids, alkaloids, tannins, and saponins, supported by LC–MS identification of dominant phenolic and alkaloid-related compounds. The extract was successfully formulated into biolarvicidal granules using a granulation-based method with polyvinylpyrrolidone as a binder and lactose as a filler. All granule formulations exhibited acceptable physicochemical characteristics, including adequate flow properties, angle of repose, and rapid dispersion in water. The flow rate test results showed that granules with concentration of 25%, 50%, 75%, and 100% exhibited flow rates of 71.4 g/s, 62.5 g/s, 50 g/s, and 45.5 g/s, respectively. The angle of repose values increased with extract concentration, ranging from 31° for the 25% formulation, 34 for 50%, 35 for 75%, and 36 for the 100% formulation, indicating acceptable flow behavior. Dispersion testing revealed rapid dispersion in water, with dispersion times of 20.14 seconds (25%), 22.92 seconds (50%), 24.84 seconds (75%), and 25.02 seconds (100%). Increasing extract concentration influenced granule cohesiveness and flow behavior but did not compromise dispersion performance.

These findings indicate that *Piper betle* leaf extract can be successfully formulated into stable granules with suitable physical characteristics, providing a promising basis for further development of plant-based biolarvacidal formulations. Increasing extract concentration influenced granule cohesiveness and flow behavior but did not compromise dispersion performance. These results indicate that *Piper betle* leaf extract can be formulated into stable granules with suitable physical characteristics, providing a promising basis for further development of plant-based biolarvicidal formulations.

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