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Determination of Total Flavonoid Content and Characterization of Nanoparticles of Kecombrang Leaf Extract (*Etlingera elatior* (Jack) R.M.Sm.)

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Abstract: Kecombrang (*Etlingera elatior* (Jack) R.M.Sm.) is one of Indonesia's potential plants that contain such bioactive compounds as polyphenols, alkaloids, flavonoids, steroids, saponins, and essential oils; it has pharmacological activity. This study aims to determine the total flavonoid content of kecombrang leaf extract. It also defines the characteristics of the nanoparticles of kecombrang leaf extract. Kecombrang leaves were extracted through maceration. The determination of the total flavonoid content by spectrophotometry used quercetin p.a. as a comparison. The preparation of nanoparticles used ionic gelation with 0.1% sodium alginate and 0.01% calcium chloride crosslinkers. The characteristic parameters of the nanoparticles of kecombrang leaf extract included the visual, transmittance, adsorption efficiency, particle size distribution, polydispersity index, and zeta potential. The yield value of kecombrang leaf extract was 46.55%. The total flavonoid content was 88.11 mgQE/g with a regression standard curve Y = 0.1022x + 0.0745 and correlation coefficient (r) = 0.9922. The nanoparticle solution provided a clear visual with a particle size and PI of 108.2 nm and 0.311, a transmittance and adsorption efficiency of 94.76% and 93.76%, and a zeta potential of -36 mV. The total flavonoid content of kecombrang leaf extract with 3 replication examined was 88.06 mgQE/g, 87.91 mgQE/g, 87.81 mgQE/g. The nanoparticle solution of kecombrang leaf extract has the characteristics that qualify as a nanoparticle preparation.

Keywords: Kecombrang (*Etlingera elatior* (Jack) R.M.Sm.), flavonoids, nanoparticles.

Introduction

The many side effects caused by synthetic drugs have made people start switching to natural drugs that are known to have lower side effects. The use of natural medicine is growing because it has been empirically proven to be able to cure various diseases [1]. The widespread use of herbal medicine in developing countries is not only due to the minimum side effects but also because of culture as one of the factors in the development of herbal medicine use [2]. Antioxidants play a role in protecting the body from the invasion of reactive oxygen species. It has been reported that 56% medicinal plants spread across Asia and Africa. The pharmacological activity is related to the content of chemical compounds, such as phenolics, alkaloids, flavonoids, terpenoids, coumarins, and glycosides, that produce positive effects [3].

Kecombrang is one of the potential plants originating from Indonesia. [4]. The kecombrang plant contains bioactive compounds in the form of polyphenols, alkaloids, flavonoids, steroids, saponins, and essential oils, which are suspected to have the potential as an anti-inflammatory [5], wound healer [6], antidiabetic [7], antibacterial [8], and antioxidant. The flavonoids in kecombrang leaves have high antioxidant activity, protecting against ROS through the accessible radical release pathway [9]. Flavonoids can act as an antimicrobial, antioxidant, antidiabetic, and anti-inflammatory agent [10]. However, the low solubility of secondary metabolites in water also reduces their oral bioavailability. A particular drug delivery system can improve the bioavailability and effectiveness of secondary metabolites. Research shows that the

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use of nanostructured lipid carriers can enhance the solubility and bioavailability of secondary metabolite compounds [11].

Nanoparticles are particles with one dimension ranging between 1 and 1000 nm. They exhibit different properties depending on their surface size and function. Their small size and large surface area have led to their extensive use in various fields, such as cosmetics, electronics, as well as diagnostic and therapeutic medical applications [12]. In this study, the synthesis of the nanoparticles of kecombrang leaf extract uses the polymer-based ionic gelation method. Polymer nanoparticles are used extensively as drug carriers for controlled and sustained release. The encapsulated entity can be attached to the surface of a nanosphere or nanocapsule or inserted into a polymer matrix or shell [13]. The two polymers used are sodium alginate and calcium chloride, both of which have been approved by the FDA for clinical use as they are both biocompatible and biodegradable [14]. Alginate is a natural brown seaweed polymer with extraordinary potential because alginate is biocompatible and cheap. The disadvantages of alginate use include low solubility, unstable solution stability, and low viscosity. However, the addition of $CaCl_2$ (a multivalent cation compound) can increase the viscosity of alginate, thereby improving the ability of alginate in matrix formation [15]. This study aims to measure the total level of flavonoids in kecombrang leaf extract and determine the characterization of the nanoparticles of kecombrang leaf extract for topical preparations.

Materials and Methods

Materials

The equipment used in this study was an analytical balance (Fujitsu FSR-0220), beaker glass (Pyrex), measuring cup (Pyrex), measuring flask (Herma), PSA (Horiba: nanoPartica SZ-100V2), oven (DHG-9053 A), blender (Cosmos), magnetic stirrer (HJ-3 Magnetic Stirrer), spectrophotometer (Shimadzu UV-1280), and rotary evaporator (R-1001VN).

The materials used in this study were kecombrang leaves (*Etlingera elatior* (Jack) R.M.Sm.), 96% ethanol, sodium alginate (Sigma Aldrich), calcium chloride (Merck), quercetin (Sigma Aldrich), AlCl3 (Merck), and Potassium Acetate (Kanto Chemical).

Extraction of Kecombrang Leaves

The sample of kecombrang leaves (*Etlingera elatior* (Jack) R.M.Sm.) was taken from Kadomas Village, Pandeglang District, Pandeglang Regency, Banten. The sample was cleaned and washed under running water. After that, the sample was dried using an oven at 50°C and then mashed using a blender. The dried simplicia of kecombrang leaves (*Etlingera elatior* (Jack) R.M.Sm.) was weighed for 500 g and put into maceration, and then 96% ethanol was added at a ratio of 1:10 until the simplicia was submerged. The maceration was carried out for three days, with stirring every day for 10 minutes. On the third day, the macerate was filtered and accommodated in dark glass bottles. Next, the filtrate was evaporated to remove the solvent by using a rotary evaporator until a thick extract was obtained [16].

Determination of the Total Flavonoid Level of Kecombrang Leaf Extract

Preparation of the Reagent Solution

To manufacture the 10% $AlCl_3$ reagent, 10 mg of $AlCl_3$ powder was weighed and then dissolved using aquadest to the limit of 10 mL mark. To manufacture the potassium acetate, 1 g of potassium acetate was weighed and dissolved using aquadest to the limit of 10 mL mark [17].

Determination of the Standard Curve of Quercetin

As much as 10 mg of standard quercetin was weighed and dissolved in 10 mL of Ethanol p.a. The stock solution (1000 ppm) was pipetted as much as 1 mL, and the volume was made to 10 mL with ethanol p.a. to obtain a concentration of 100 ppm. Several concentration series were made from the standard solution of 100 ppm quercetin, including 2 ppm, 4 ppm, 6 ppm, 8 ppm, and 10 ppm. Each series of the standard solution concentrations of quercetin was pipetted for 0.2 mL (2 ppm), 0.4 mL (4 ppm), 0.6 mL (6 ppm), 0.8 mL (8 ppm), and 1 mL (10 ppm). Then, for each concentration series, 3 mL of ethanol p.a., 0.2 mL of $AlCl_3$ 10%, and 0.2 mL of potassium acetate were added, and the volume was made to the limit of the mark with aquabidest using a 10 mL measuring flask. After that, it was incubated for 30 minutes at a room temperature. The absorbance was determined by using the UV-Vis spectrophotometry method at maximum wavelengths [17].

Determination of the Maximum Wavelength in Quercetin Standard Solution

The determination of the maximum wavelength of quercetin was carried out by *running* the quercetin solution in the wavelength range of 300-800 nm. The maximum wavelength was used to measure the absorption of the sample [17].

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Determination of the Total Flavonoid Level of Kecombrang Leaf Extract

A total of 0.5 mL (500 µl) of kecombrang leaf extract (*Etlingera elatior* (Jack) R.M.Sm.) was put into a 10 mL measuring flask, and then 3 mL of ethanol p.a., 0.2 mL of 10% $AlCl_3$, and 0.2 mL of potassium acetate were added and made to the limit of the mark by using aquabidest. After that, the mixture was incubated for 30 minutes at a room temperature. The absorbance was determined by using the UV-Vis spectrophotometry method at maximum wavelengths. The sample was made in three replications for each analysis to obtain the average value of absorbance, and the flavonoid level was calculated using the following equation [17]:

$$F = \frac{c \times V \times f}{m}$$

Information:
F : Percent Flavonoid
c : Quercetin Equivalence
V : Total Volume of the Extract
f : Dilution Factor
m : Sample Weight

Nanoparticle Preparation

The manufacture of the kecombrang leaf extract nanoparticles used the cross-linking of 0.1% sodium alginate polymer with 0.01% $CaCl_2$. As much as 0.1% sodium alginate solution was added to 1 mg/mL of kecombrang leaf extract solution and stirred using a magnetic stirrer at a speed of 1500 rpm for 30 minutes, and then 0.01% $CaCl_2$ solution was added and stirred again for 60 minutes. The nanoparticle solution was further characterized for the visual, transmittance, adsorption efficiency, particle size distribution, polydispersity index, and zeta potential value [18].

Characterization of the Nanoparticle Solution of Kecombrang Leaf Extract

Visual Test

The visual test was performed by observing the nanoparticle preparation directly with the eyes. A visual test aims to determine the presence of particles formed by the extract with cross-splicing agents, especially a residue in the preparation.

Transmittance Test

Transmittance measures the clarity of a solution or dispersed system quantitatively. The transmittance test was carried out by adding 100 µL of the nanoparticle extract solution plus aqueous solution until a final volume of 5 mL, and the mixture was vortexed for 1 minute; the transmittance value was measured by using the UV-Vis spectrophotometry at a wavelength of 670 nm. The parameter of the transmittance value is the absorbance value, which is close to 100% [19].

Entrapment Efficiency

The determination of the total flavonoid content of the kecombrang leaf extract nanoparticles for the entrapment efficiency was carried out by using the UV-Vis spectrophotometer method. The entrapment efficiency was achieved by centrifugating the nanoparticle solution at 12,000 rpm for 4 minutes to precipitate the nanoparticles perfectly. The supernatant was measured by using a UV-Vis spectrophotometer with a wavelength of 365.5 nm. The percentage of entrapment efficiency can be calculated using the following equation [20] :

$$\text{Entrapment Efficiency (\%)} = \frac{W - w}{W} \times 100\%$$

Information:
W : Flavonoid levels of the extract
w : Supernatant flavonoid levels (Undigested)

Particle Size Distribution

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The particle size was measured using a Particle Size Analyzer (PSA). Particle size distribution is used to estimate the distribution of drugs *in vivo*, the toxicity, and the biological and aiming ability of a nanoparticle system [21].

Polydispersity Index

A polydispersity index describes the homogeneity of a colloidal solution. The polydispersity index has a value range from 0 to 1 where a value close to 0 produces a homogeneous dispersion while a value of >0.5 indicates high heterogeneity [18].

Zeta Potential Value

The zeta potential was measured using a zeta sizer tool. The test was used to characterize the charge properties of the nanoparticles. Nanoparticles with zeta values smaller than -30 mV and more than +30 mV have higher stability [20].

Results and Discussions

Kecombrang Leaf Extraction

The extraction process was carried out by the maceration method, in which the kecombrang leaf powder was soaked in 96% ethanol at a ratio of 1:10. The extract obtained was then calculated as the yield, which was based on the percentage of the final weight to the initial weight.

Table 1 The Extraction Processes and Rendemen of Maceration of Kecombrang Leaf

Sample	Initial Weight (g)	Final Weight (g)	Rendement (%)
Extract	200	93.1	46.55

Based on **Table 1,** 200 g of kecombrang leaf powder was macerated with 96% ethanol until the solution was almost colorless. The filtrate was obtained and then concentrated with a rotary evaporator, and 93.1 g of thick extract was obtained; the yield value obtained was 46.55%. The yield obtained from the extraction process using a 96% ethanol solution formed a thick and dark brown paste. The yield obtained was better than the study by [22] in which the yield of kecombrang leaves produced from an extraction with 96% ethanol solvent was 26.6%. The length of maceration used can affect the yield value because the longer the contact between the sample and the solvent, the greater the number of compounds extracted [23]. The type of solvent greatly influences the yield and the total secondary metabolites extracted due to the ability of the solvent type to filter different active substances. The higher the level of polarity of the solvent, the higher the yield obtained; the more polar the solvent is, the better the extraction power will be. This is because the flow of solvent into the cell of the material will cause the protoplasm to swell, and the cell content in the material will be dissolved according to its solubility. The polarity of the solvent and the polarity of the extracted material are associated with high solubility [24].

Determination of the Total Flavonoid Level of Kecombrang Leaf Extract

The quantitative test began with the manufacture of the quercetin standard. Quercetin was used as a standard raw material because quercetin is a flavonoid of the flavonol group that has a hydroxyl group neighboring the flavones and flavonols [25].

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Table 2 Total Flavonoid Analyses of Kecombrang Leaf Extract

Sample	Quercetin Standard (mg/L)	Total Flavonoid Level (mgQE/g)
Kecombrang leaf extract	8.811	88.11

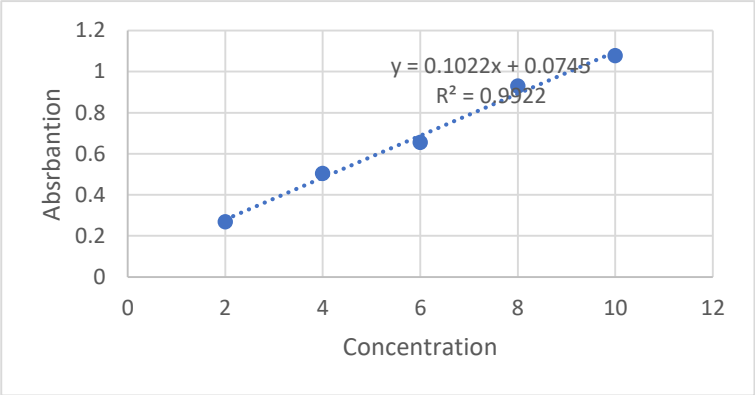

Figure 1 Linear Regression Equation of Quercetin Standard Curve

The results of the measurement of the quercetin standard absorbent in **Figure 1** obtained the maximum wavelength, which was received with a result of 365.5 nm, and the value of the linear regression equation between the quercetin absorbent and the concentration was y = 0.1022x + 0.0745 with the value of r = 0.9922. The linear regression equation of quercetin can be used to determine the total concentration of flavonoid compounds in the kecombrang leaf extract. **Table 2** shows the total flavonoid level obtained in kecombrang leaf extract, which is 88.11 mgQE/g. The flavonoid level obtained is better than the findings of the research conducted by Kusuma *et al.*, (2024) which showed that the total flavonoid content of kecombrang leaf water extract was 5.45 mgQE/g.

Nanoparticle Preparation of Kecombrang Leaf Extract

The preparation of the nanoparticles of kecombrang leaf extract used 0.1% sodium alginate crosslinkers and 0.01% calcium chloride ($CaCl_2$). Ionic gelation-based synthesis uses electrostatic forces to connect polymer units to form nanoparticles. Negatively charged alginates are used as polymers while calcium ions are added as cross-linkers [27].

Table 3 Characterization of the Nanoparticles of Kecombrang Leaf Extract

Sample	Visual Test	Transmittance Test (%)	Entrapment Efficiency (%)	Particle Size Distribution (nm)	Zeta Potential (mV)	Polydispersity Index
Nanoparticle Solution of Kecombrang Leaf Extract	Clear	94.76	93.76	108.2	-36.2	0.311

The physical characteristic test of the nanoparticles of kecombrang leaf extract aims to determine the influence of the combination of sodium alginate and calcium chloride in nanoparticles. Based on **Table 3,** it is known that the nanoparticle solution of kecombrang leaf extract provides a clear visual. This shows that the combination of sodium alginate polymer and calcium chloride cross-linking agent exerts an effect on the visual enhancement of nanoparticles [20].

The transmittance value of the nanoparticles of kecombrang leaf extract was 94.76% and produced a clear and transparent dispersion. The transmittance value was close to 100%, indicating that the droplet size was estimated to reach nanometers [28]. Transmittance testing on nanoparticles of kecombrang leaf extract aims to measure the clarity of nanoparticles quantitatively. The high percent value of transmittance means that the particle size is getting smaller [29]. Sodium alginate increases the transmittance value. The use of calcium chloride also increases the transmittance value. This can be due to the large number of bonds

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formed between Ca^{2+} ions and carboxyl groups from alginate that are not excessive. In the alginate dissolution process, decomplexity occurs because Na+ ions are released and ionic alginates are formed. When the alginate solution interacts with calcium chloride, there is a complex of carboxylate groups in alginate with a divalent cation Ca^{2+}, which, when in excess, forms a precipitate [18].

The entrapment efficiency of the kecombrang leaf extract nanoparticle solution was 93.76%. This indicates that the amount of flavonoid level adsorbed in the nanoparticle solution is getting larger [30]. Sodium alginate increases the value of entrapment efficiency. Sodium alginate affects the degree of cross-linking because the ratio of mannuronic acid and guluronic acid block determines the availability of active sites for forming 3-dimensional tissue structures and affects the adsorption of drugs in the matrix. Calcium chloride also increases the value of adsorption efficiency, but the effect is lower than that of sodium alginate. The interaction between sodium alginate and calcium chloride increases the value of entrapment efficiency [18]. The combination of sodium alginate and calcium solution forms a polymer chain that crosses with each other slowly. This accelerates the process of diffusion of calcium ions into the extruded polymer droplets so that the inner polymer chain produces better cross-linking than the polymer chain that is far from the surface [31].

The nanoparticles of kecombrang leaf extract had a particle size of 108.2 nm with a polydispersity index value of 0.311. The particle size corresponds to the nanoparticle size range of 1 – 1,000 nm [29]. The result of the zeta potential test of the nanoparticle solution of kecombrang leaf extract was -36 mV. The zeta potential yield is not good because the value is more than -30 mV. This describes the condition of the particle surface charge that is sufficient to cause a repulsive force between particles but has low stability. The factor that affects the poor zeta potential value is the change in pH. The low pH value can be influenced by the mixed components in the nanoparticle preparation, especially the surfactant at the interface of the two unmixed liquids [32]. The polydispersity index shows the particle size distribution where the polydispersity index ranges between 0 and 1. A polydispersity index value close to zero indicates a homogeneous or uniform particle distribution. In contrast, a polydispersity index value that exceeds 0.5 suggests that the particles have a high level of heterogeneity. The value of the polydispersity index in **Table 3** is less than 0.5, indicating that the resulting nanoparticle formula has a homogeneous particle size distribution; therefore, it tends to be physically and does not cause the particles to aggregate [33].

Conclusion

Based on the results of the study, the total flavonoid content of kecombrang leaf extract (Etlingera elatior (Jack) R.M.Sm.) with 3 replication examined was 88.06 mgQE/g, 87.91 mgQE/g, 87.81 mgQE/g. The nanoparticle solution of kecombrang leaf extract (*Etlingera elatior* (Jack) R.M.Sm.) were prepered with sodium alginate and $CaCl_2$ polymers has quite good characteristics and is qualified as a nanoparticle preparation. Some obstacles are factors that can be considered for future researchers in perfecting the research, in this study SEM/TEM testing has not been carried out.

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