

# Liposome Preparation of Tekelan Leaf (*Chromolaenaodorata* L.) Extract: Manufacturing and Evaluation

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## ABSTRACT

**Background:** Liposomes are biocompatible, biodegradable, and non-immunogenic due to their phospholipid composition which is similar to cell membranes. Active chemicals that are contained in liposomes preparation has a goal in improving solubility, minimizing adverse effects, extending release, protecting drugs, targeting drugs, and increasing efficacy. **Objective:** The purpose of this study was to formulate the ethanol extract of tekelan leaves into liposome preparations and to determine differences in particle size, polydispersity index (PI) and stability. **Materials and Methods:** This research begins with making extract by maceration. The extract formed was then formulated into liposome preparations with the composition of F1 (30 mmol), F2 (40 mmol) and F3 (50 mmol) ingredients. The formulation was carried out by thin layer hydration with variations in sonication time of 10 minutes, 20 minutes and 30 minutes. Evaluation of liposomes was carried out organoleptically, testing pH, particle size, polydispersity index (PI), and physical stability at room temperature. Data analysis was carried out statistically using SPSS 20.0 One Way ANOVA method to see if there were differences in each group. The average pH test results of the three formulations were 6.2±0.3. The particle size results in the 30th minutes obtained particle sizes of F1 (293.63±1.6 nm), F2 (201.9±1.5 nm) and F3 (143.17±0.6 nm). **Results:** The results of the polydispersion index (PI) were F1 (0.307±0.03), F2 (0.275±0.06) and F3 (0.229±0.02). The results of the observation of room temperature stability obtained that the organoleptic results formed two layers, namely a clear layer and a cloudy layer. In the One-Way ANOVA test, a significance value of p>0.05 (0.068) was obtained. **Conclusion:** Liposomes produced from ethanol extract of tekelan leaves are stable when stored at low temperatures (4±0.5°C) with an organoleptic state of odorless, dark green color and thick consistency. **Key words:** Liposomes, Tekelan, pH, Stability, Particle size.

## INTRODUCTION

Tekelan (*Chromolaena odorata* L.) is an Asteraceae plant that contains active substances such as alkaloids, flavonoids (auron, chalcone, flavones, and flavonols), saponins, tannins, high amino acid content, and other phenolic content in the form of extracts.<sup>1</sup> Previous research has extracted and discovered flavonol compounds containing quercetin (3'-4'-dihydroxyflavones) in tekelan leaves.<sup>2</sup> Quercetin in a tekelan leaf ethanol extract is classed as Biopharmaceutical Classification System (BSC) II due to its limited water solubility and high permeability.<sup>3</sup> Because of the low solubility and permeability of quercetin, a formulation that can increase its bioavailability is needed to achieve the desired therapeutic effect. The drug delivery system refers to a group of medicine delivery systems that are intended to improve therapeutic effect through controlled release. In addition to improving bioavailability and therapeutic impact, it is used for targeted pharmaceutical release.<sup>4</sup>

Liposomes are one of the drug delivery techniques that is currently being developed. Liposomes are an excellent carrier for increasing the solubility and penetration of the chemicals they transport. Liposomes have both hydrophilic and lipophilic structures, which trap hydrophilic medications in the water core and lipophilic drugs in the lipid bilayer.<sup>5</sup> Along with their good solubilizing power, their manufacture is easier and makes liposomes an attractive drug carrier system.<sup>6</sup> Liposomes are biocompatible, biodegradable,

and non-immunogenic due to their phospholipid composition (which is similar to cell membranes). Pharmaceuticals (active chemicals) are contained in liposomes with the goal of improving solubility, minimizing adverse effects, extending release, protecting drugs, targeting drugs, and increasing efficacy.<sup>7</sup> The researcher is interested in employing the thin layer hydration approach to formulate the ethanol extract of tekelan leaves into liposome dosage forms with the goal of enhancing the bioavailability and therapeutic impact of the ethanolic extract of tekelan leaves.

## MATERIALS AND METHODS

### Materials

The materials used in this study were tekelan leaves, 96% ethanol, distilled water (Ikapharmindo), Lipoid S75, Lipoid DMPG-Na, Span-60, Cholesterol (Sigma Aldrich), methanol (Merck), chloroform (Merck) and PBS (Phosphate). Saline Buffers) (Merck).

### Preparation of Tekelan leaves

Fresh tekelan leaves are washed, then separated from the branches, and dried in a drying cabinet at a temperature of 30-40°C for 5 days or until the leaves are dry enough. The dried leaves are then ground into powder.<sup>8</sup>

### Extraction of Tekelan leaves

A total of 2000 g of Tekelan leaf powder was extracted using 96 percent ethanol as the solvent. The maceration procedure employed up to 15000

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ml of 96 percent ethanol. The maceration procedure was carried out by placing 7.5 parts of the liquid into a vessel containing 10 parts of simplicia with an appropriate degree of fineness, then covering and leaving for 5 days, protected from light, stirring regularly. The pulp is pressed with a flannel cloth and then filtered using filter paper after 5 days of screening. The dregs were rinsed with the remaining 96 percent 5000 ml ethanol solvent before being filtered again. The filtrate obtained was concentrated with a rotary evaporator at a temperature of 50°C until a thick extract were obtained.<sup>8</sup>

### Preparation liposomes by thin layer hydration method

The composition of the liposome formulation of tekelan leaf ethanol extract was 50 mmol. The preparations are divided into two mixtures in the formulation. A mixture (consisting of lipoid S75, lipoid DMPG-Na, cholesterol and span 60). B Mixture (consisting of methanol, chloroform, ethanol extract of tekelan leaves). Each material's specific gravity is used to compute its density. The entire amount of substance is 50 mmol. The extract was dissolved in methanol and chloroform in a concentration of 100 mg (5:5) after being dissolved and homogenized in mixture. A rotary evaporator was used to evaporate the contents of a round tool flask, then heated to a temperature of 60°C at a pressure of 200 mBar for 1 hour, repeated it until a thin film formed on the round bottom flask's walls, then added PBS to the flask. Extracted Liposomes were purified using a PD 10 column, placed in a container, and shrunk using ultrasonic with a 30 minute sonication duration.<sup>9</sup>

### Liposome particle size observations

The purified liposomes were analyzed by Particle Size Analyzer (PSA). Note the change in particle size. The formulation of liposomes can be seen in Table 1.

### Characteristics of liposomes

Determination of Characteristics of Liposomes was conducted by determine the color and odor of liposomes by visually, Then continue to Measuring pH using a pH meter at a temperature of 25°C±2 by replication of three times.<sup>9,10</sup> Measurement of particle size and zeta potential was carried out using a particle size analyzer (Horiba SZ 100), the sample was put into a cuvette after 100x dilution. The stability of the liposome preparation was evaluated organoleptically in the form of color changes and the formation of particulates dispersed into the PBS carrier liquid.<sup>11</sup>

### Storage stability at room temperature (25±0.5°C)

The preparations were stored at room temperature (25±0.5°C) for 12 weeks, then observed for 12 weeks. Observations were made in the form of organoleptic observations (change in color, odor, phase separation and clarity). In addition, particle measurements of each formulation were carried out.<sup>12</sup>

### Liposomal morphology test

Liposomal morphology was carried out using TEM (Transmission Electron Microscopy) and PSA (Particle Size Analyzer) tools. In

addition, stability and percent adsorption efficiency tests (% EE) were carried out.

### TEM (Transmission Electron Microscopy)

TEM was conducted at the Chemistry Laboratory, Gadjah Mada University. TEM was performed to analyze the inner morphology of liposome particles, crystal structure and specimen composition. The liposome sample of tekelan leaf extract was diluted with dilutions of 20x and 50x, and then the sample was dripped onto the formvar coated copper grid as much as one drop and dried at room temperature. After drying, it was analyzed by TEM. The sample was put into a container and analyzed at a temperature of 25°C.<sup>11</sup>

### Determination of percent adsorption efficiency

A total of 1 mL of liposome suspension was dissolved in phosphate buffer saline pH 6.0 in a ratio of 1:10. The aqueous suspension was centrifuged at 3000 rpm for 30 min. The supernatant obtained was pipette 1.0 mL and put into a 10 mL volumetric flask, then the volume was filled with saline phosphate buffer pH 6.0 to the limit line. Then 1.0 mL pipette was added and 6.0 saline phosphate buffer was added in a 10 mL volumetric flask, then filtered with filter paper. The absorbance of the solution was measured at a wavelength of 368 nm.

The efficiency of vesicle entrapment was determined by separating the free drug from the drug absorbing vesicle using the ultracentrifugation technique. The liposome suspension was centrifuged for 30 minutes at 3000 rpm and a temperature of 4°C in order to separate the non-adsorbed drug. The amount of drug (FD) was determined on the supernatant. The concentration of the centrifuged supernatant was determined using UV-VIS spectrophotometry.<sup>13</sup>

The adsorption efficiency of 9%EE) is calculated by the formula:

$$\% EE = \frac{TD - FD}{TD} \times 100\%$$

Information:

TD = Total compounds contained in the formula

FD = The number of compounds detected in the supernatant

### Data analysis

Determination of the size and distribution of liposomes was observed with PSA (Particle Size Analyzer) to determine the size of liposomes and particle distribution or polydispersity index (PI). TEM (Transmission Electron Microscopy) to analyze the inside morphology of liposome particles, crystal structure and specimen composition. Stability test to see the stability of liposome preparations in storage. The data obtained were then analyzed descriptively and presented in the form of tables and figures.

**Table 1: Tekelan leaf ethanol extract liposome formulation (*C. odorata* L.).**

Ingredients	F1 (30 mmol)	F2 (40 mmol)	F3 (50 mmol)
Tekelan leaf ethanol extract	100 mg	100 mg	100 mg
Chloroform	5 mL	5 mL	5 mL
Methanol	5 mL	5 mL	5 mL
Lipoid S75	258.97 mg	345.33 mg	431.68 mg
Lipoid DMPG-Na	6.815 mg	9.09 mg	11.36 mg
Cholesterol	5.8 mg	7.74 mg	9.67 mg
Span-60	1.83 mg	2.44 mg	3.05 mg
PBS	10 mL	10 mL	10 mL

## RESULTS AND DISCUSSION

### Result of dried sample characteristic examination

The results of dried sample characterisation are used to determine the Dried Sample's specifications. Because the origin of the growing environment impacts the content of the active component, this specification is used to determine the clarity of the material under investigation. The water content, total ash content, acid insoluble ash content, water soluble extract content, and ethanol soluble extract content of Tekelan leaves were all determined. Table 2 shows the findings of the investigation of these parameters.

The water content of tekelan leaf dried powder was 6.62 percent, which was less than the Ministry of Health of The Republic of Indonesia's requirement of less than 10%. The water content test is used to determine the maximum amount of water that can be present in the material. The amount of water in traditional medicines is related to microbial development and accelerates the hydrolysis of chemical ingredients, resulting in a reduction in their quality.<sup>14</sup> The amount of chemicals that could be extracted with water from a dried samples was determined by determining the amounts of water soluble extract. The amount of water soluble extract in tekelan leaves was 21.11 percent, which met the Ministry of Health of the Republic of Indonesia's standard of not less than 5%. The number of chemicals that could be extracted with ethanol from a dried samples was determined by determining the ethanol soluble extract content. The ethanol soluble extract level at the tackle was 16.89%, which met the Ministry of Health of the Republic of Indonesia's guideline of not less than 3.5 percent.<sup>14</sup>

The ash content of a product is determined to assess how much non-volatile material remains. Ash can arise from the plant tissue itself or additional impurities like sand or dirt when the total ash concentration is high. The acid insoluble ash content test is used to detect how much impurity is present in sand or silicate soil.<sup>14</sup> The total ash content obtained was 7.92 percent, which met the standards of the Ministry of Health of the Republic of Indonesia, which were not to exceed 13 percent. Despite the fact that the acid insoluble ash content obtained was 1.2 percent, it did not fulfill the Ministry of Health of the Republic of Indonesia's standards of not more than 1%.

### Results of identification of chemical compounds in Tekelan leaves

Identification of chemical compounds in tekelan leaves aims to prove the presence or absence of compounds such as alkaloids, flavonoids, tannins, steroids and saponins. The identification results can be seen in Table 3 below.

### Liposomal pH measurement results

Measurement of pH is carried out to find out what the pH of the preparation is because pH can affect the availability of drugs in molecular form. Drugs in molecular form can penetrate easily. The results of the measurement of the pH of the liposomes were seen before and after being purified. These results can be seen in Table 4.

**Table 2: Results of examination of the characteristics of dried tekelan leaves (*C. odorata* L.).**

No	Parameter	Results
1	water content	6.62%
2	water soluble essence	21.11%
3	Ethanol soluble extract content	16.89%
4	total ash content	7.92%
5	acid insoluble ash content	1.2%

**Table 3: Identification results of chemical compounds of tekelan leaves.**

Compound	Powder	Extract
Alkaloids	+	+
Flavonoids	+	+
Tanins	+	+
Saponins	+	+
Steroids/Triterpenoids	+	+
Glycoside	+	+

**Table 4: Results of measurement of liposomal pH ethanol extract of tekelan Leaves (*C. odorata* L.).**

Formula	Replication	pH	Average±SD
I	1	6.2	6.1±0.1
	2	6.1	
	3	6.0	
II	1	6.1	6.2±0.6
	2	6.2	
	3	6.2	
III	1	6.3	6.2±0.1
	2	6.1	
	3	6.2	

The liposome formulation of the ethanol extract of tekelan leaves has a pH close to neutral, according to the pH measurements. It's important that the pH level isn't overly acidic or basic. Because the pH level must be adjusted to match the pH of the body's fluids. An acidosis phase will occur if the body fluids become overly acidic due to the use of liposomes with an acidic pH, with symptoms such as an increase in heart rate, a characteristic sour-smelling breath that shows the presence of ketoacidosis, decreased hunger, and others. However, if the pH is too alkaline, the body's potassium mineral balance and blood calcium levels would be disrupted. Alkalosis is the medical term for this illness.<sup>15</sup>

### Observation of particle size and zeta potential

The results of the measurement of liposome particles from the ethanol extract of tekelan leaves using the PSA (Particle Size Analyzer) tool. The results of the particle size readings can be seen in Table 5.

Table 5 reveals that the smallest particle size and polydispersity index of niosomes at 30 minutes at F3 (50 mmol) is 143.170.55 nm, with a polydispersity index of 0.2290.02. Because the particle size was still in the region of 100-400 nm, F3 was chosen as the best condition. The particles will be able to pass through the Langerhans islets in the pancreas up to 69 percent of the follicular depth (2000-4000m) at this size. A low polydispersion index value, on the other hand, suggests that liposomes have superior particle size homogeneity.<sup>16</sup> According to previous study, increasing the surfactant concentration in a liposome formulation can increase particle size. This is due to the increasing number of surfactants that combine to form vesicles, causing the liposome particle size to increase.<sup>17</sup>

The significant value of homogeneity based on the difference in particle size of the liposomes of the ethanol extract of tekelan leaves was  $p > 0.05$  using the One Way ANOVA approach (0.069). The liposome formulation is homogeneous, as evidenced by this. A significant value of  $p > 0.05$  (0.068) was found in the One Way ANOVA test. This demonstrates that there is no discernible change in particle size across the formulations.

The statistical observation of the One Way ANOVA approach obtained a significant value of  $p > 0.05$  when examined based on the difference in sonication time (0.045). It is claimed that the modulation of sonication time in the liposome formulation of ethanol extract of tekelan leaves

**Table 5: Particle size observation results.**

Formula	Sonication Time								
	10 minutes			20 minutes			30 minutes		
	Particle Size (nm±SD)	PI±SD	Zeta Potential (mV±SD)	Particle Size (nm±SD)	PI±SD	Zeta Potential (mV±SD)	Particle Size (nm±SD)	PI±SD	Zeta Potential (mV±SD)
I	385.5 ± 1.1	0.419 ± 0.058	-62.7 ± 0.17	313.6 ± 1.3	0.345 ± 0.04	-35.2 ± 0.9	293.6 ± 1.6	0.307 ± 0.03	-42.9 ± 0.6
II	343.6 ± 1.6	0.392 ± 0.05	-55.4 ± 1,1	275.7 ± 1.2	0.260 ± 0.04	-34.67 ± 0.64	201.90 ± 1.54	0.275 ± 0.06	-45.37 ± 0.85
III	357,4 ± 0.9	0.377 ± 0.05	-64.23 ± 1.0	267.07 ± 1.6	0.320 ± 0.01	-35.93 ± 0.64	143.17 ± 0.55	0.229 ± 0.02	-42.2 ± 1.0

**Table 6: Observation results of liposomal organoleptic ethanol extract of tekelan leaves at room temperature storage (25±0.5°C) for 12 weeks.**

Formula	Inspection	Condition	
		Before Observation	After Observation
F1	Smell	No smell	No Smell
	Color	Deep green	Deep green
	Consistency	Thick	two layers are formed
F2	Smell	No smell	No smell
	Color	Deep green	Deep green
	Consistency	Thick	Two layers are formed
F3	Smell	No smell	No smell
	Color	Deep green	Deep green
	Consistency	Thick	Two layers are formed

**Table 7: Observation results of liposomal organoleptic ethanol extract of tekelan leaves (*C. odorata* L.) at low temperature storage (4±0.5°C).**

Formula	Inspection	Condition	
		Before	After
F1	Smell	No smell	No smell
	Color	Deep green	Deep green
	Consistency	Thick	Thick
F2	Smell	No smell	No smell
	Color	Deep green	Deep green
	Consistency	Thick	Thick
F3	Smell	No smell	No smell
	Color	Deep green	Deep green
	Consistency	Thick	Thick

**Table 8: Results of ethanol extract of tekelan leaves liposome adsorption efficiency.**

Formula	Replication	Absorbance	%EE	Average±SD
1	1	0.0044	97.92	97.52±1.51
	2	0.0075	95.85	
	3	0.0031	98.79	
2	1	0.0033	98.66	98.55±1.24
	2	0.0017	99.73	
	3	0.0054	97.25	
3	1	0.0019	99.59	99.66±0.18
	2	0.0015	99.86	
	3	0.002	99.53	

is significant. When this is combined with the Tukey HSD test, two distinct groups emerge. At the 20th and 30th minutes, both groups had a significance value of  $p > 0.05$  (0.693). Meanwhile, a significant value of  $p > 0.05$  (0.199) was achieved at the 10 and 30 minutes. This demonstrates that based on differences in sonication duration between the 20 and 30 minutes, as well as between the 10 and 15 minutes.

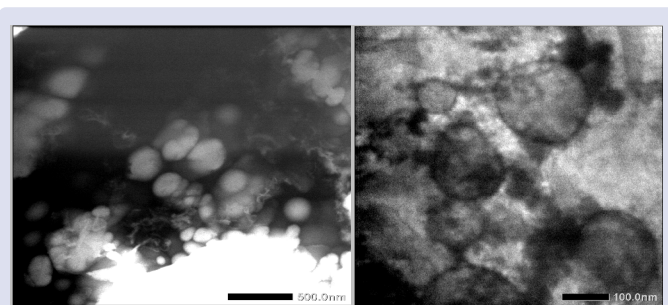
### Determination of physical stability test

The organoleptic data of ethanol extract of tekelan leaves liposomes was evaluated during the course of 12 weeks of storage, with observations every week. Changes in color, odor, shape, particle size, and phase separation were found in liposomes maintained at room temperature. Table 6 shows the findings of the liposome preparations examination.

### Storage stability results at low temperatures (4±0.5°C)

Evaluation of organoleptic observations of the preparation was carried out during 12 weeks of storage with observations every 1 week, the liposome preparation of ethanol extract of tekelan leaves (*C. odorata* L.) was stored at low temperature (4±0.5°C) and observed changes in color, odor, shape, particle size, and phase separation. The results of the evaluation of the stability of the liposome preparations can be seen in Table 7.

Table 7 shows the stable ethanol extract of tekelan leaves liposomes during storage. color, odor and shape did not change from the beginning of observation until storage for 12 weeks. Phase separation is also not formed. The lower the storage temperature, the higher the



**Figure 1:** TEM results at 10,000 times magnification of liposome ethanol extract of tekelan leaves (*C. odorata* L.) formulation-3 with sonication time 30 minutes (a) before purification, (b) after purification.

stability of the drug. This is related to the decomposition of active substances and complementary substances in the drug will be smaller so that the resulting levels will be even greater.<sup>18</sup>

### Liposome morphology

The liposome morphology of the ethanol extract of tekelan leaves (*C. odorata* L.) was observed by Transmission Electron Microscopy (TEM). The selection of the TEM instrument was made because this instrument is best used to show the morphology of nanometer-scale liquid preparations.<sup>19</sup> The working principle of TEM is that electrons are fired and passed through the specimen object by focusing the electrons by the condenser lens. Then the electrons will hit the fluorescent screen, where the screen will emit light when exposed to electrons.<sup>20</sup> The results of TEM observations of liposomes from tekelan leaf extract (*C. odorata* L.) can be seen in Figure 1 above.

Before and after purification, TEM (Transmission Electron Microscope) images of liposomes from tekelan leaf extract revealed a somewhat rounded form with various particle sizes. The TEM size of the liposomes of tekelan leaf extract before purification was 500 nm, however after purification, the TEM size was reduced to 100 nm. The amount of lipid, the solvent, and the surfactant used to generate the vesicle all had an impact on its diameter, according to the researchers.<sup>21</sup> The particle size after purification was less than before purification, according to the researchers.<sup>18</sup>

### Adsorption efficiency

The efficacy of vesicle entrapment was assessed using an ultracentrifugation technique to separate the free drug from the drug absorbing vesicle. To separate the medicine that is not adsorbed from the lipid vesicles that have formed, they were centrifuged for 30 minutes at 3000 rpm and 4°C. The quercetin molecule in the centrifuged supernatant was not adsorbed, and its absorbance could be determined using UV-VIS spectrophotometry. Table 7 shows the results of the adsorption efficiency test.

The amount of extract adsorbed in the liposome crosslinker is expressed as a percentage of entrapment efficiency. Because its value can indicate the ability of the crosslinker to transfer the active component to the therapeutic target, adsorption efficiency is mostly used in drug delivery systems. The solubility of the medication in the matrix or polymer, as well as the amount of polymer utilized, determine the entrapment efficiency of a particle. The medicine is strongly adsorbed in the polymer/matrix since the ethanol extract of Duan Tekelan is freely soluble in it.<sup>22</sup>

### CONCLUSION

The thin layer hydration method can be used to synthesize ethanol extract of tekelan leaves into liposome formulations. Liposomes made

from tekelan leaf ethanol extract are odorless, dark green in color, and thick in consistency and are stable when stored at low temperatures (40±5°C). It is, however, unstable at room temperature (25±5°C), with an organoleptic condition devoid of odor, a dark green color, and a consistency consisting of two layers: a clear layer and a cloudy layer.

### ACKNOWLEDGEMENT

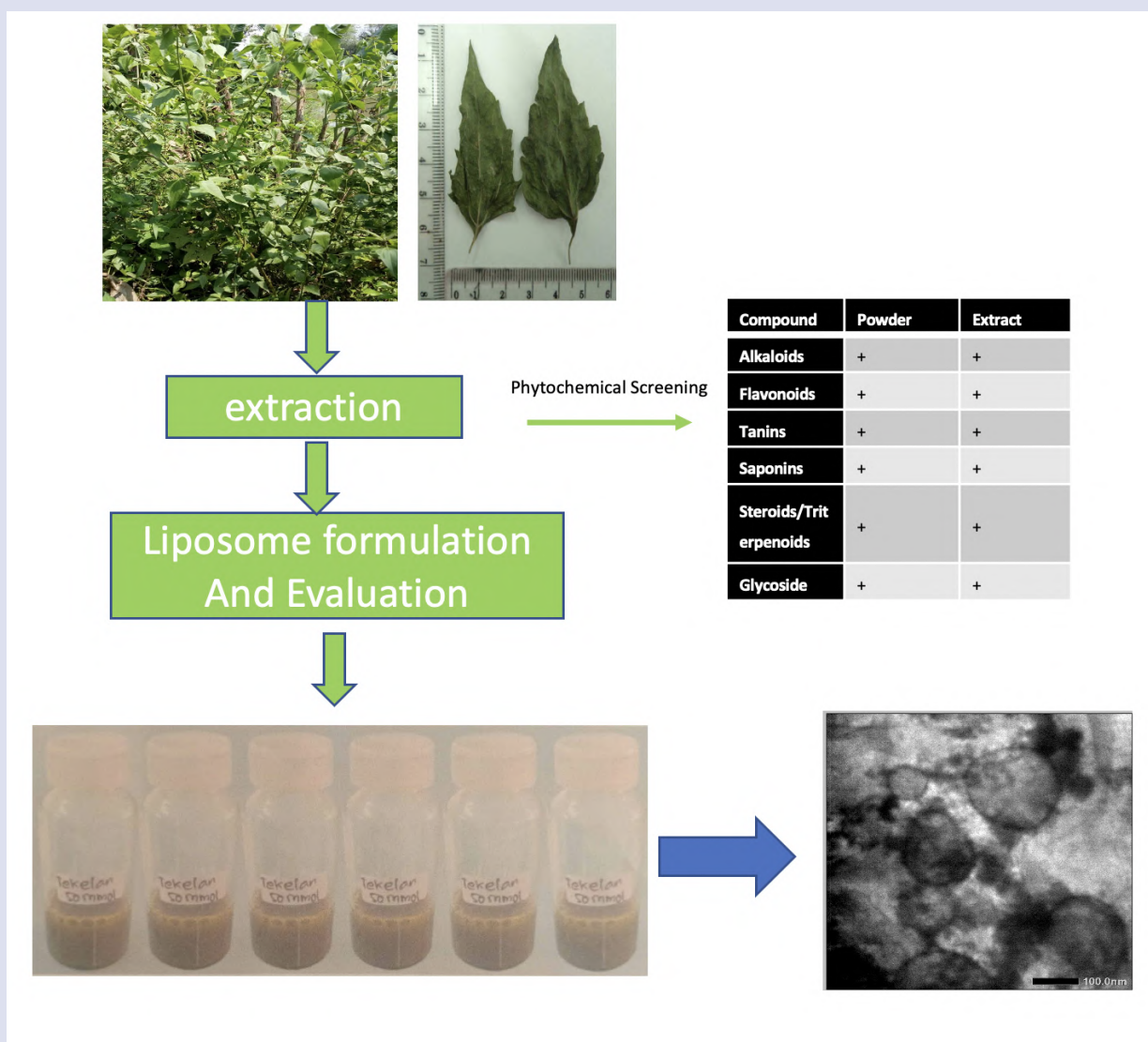
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## GRAPHICAL ABSTRACT



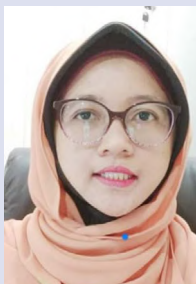
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