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Formulation and Evaluation of *Typhonium flagelliforme* Tuber Extract Tablets with Cytotoxic Activity Against MCF-7 Breast Cancer Cells

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Abstract

Cancer is the leading cause of death. Data from the Global Cancer Observatory shows that in 2022, Breast cancer in women ranks second and is the leading cause of death. Because of the limited cancer treatments available, medicinal plants are an alternative because they have anticancer properties. The indigenous Indonesian medicinal plant *Typhonium flagelliforme* has been widely used in various studies for its potential as an anticancer. Currently, medicinal plants are generally used in capsules, which are more sensitive to moisture and temperature that can affect drug stability compared to tablets. The aim of this research was to produce tablets containing active extract from *Typhonium flagelliforme* that meet physical quality requirements as anti-breast cancer tablets with cytotoxic activity against MCF-7. The research method is in vitro test of cytotoxic activity against MCF-7 cells. The results of the research show that ethanol extract from *Typhonium flagelliforme* tubers can be formulated into tablets that have potential as a breast cancer treatment. Ethanol extract is the most active extract with an IC50 value of 16.04 µg/mL in MCF-7 cells. The physical parameters extract granules from Formulas 1 to 3 meet the requirements. The physical parameters of tablets in Formulas 1 to 3 meet the requirements, but the disintegration time of Formula 3 tablets does not meet the requirements.

Keywords: Breast cancer, MCF-7, Tablet, Typhonium flagelliforme, Physical parameters of the tablet

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Kanker merupakan penyebab utama kematian. Data dari *Global Cancer Observatory* menunjukkan bahwa pada tahun 2022, kanker payudara pada wanita berada di urutan kedua dan merupakan penyebab utama kematian. Karena keterbatasan terapi kanker yang tersedia, tanaman obat menjadi alternatif karena mempunyai aktivitas sebagai antikanker. *Typhonium flagelliforme* merupakan tanaman obat yang telah digunakan dalam penelitian antikanker. Umumnya penggunaan tanaman obat dimasukkan kedalam kapsul, yang sensitif terhadap kelembaban dan suhu yang dapat mempengaruhi stabilitas obat dibandingkan sediaan tablet. Tujuan penelitian ini untuk menghasilkan tablet dengan zat aktif ekstrak aktif umbi keladi tikus yang memenuhi persyaratan mutu fisika sebagai tablet anti kanker payudara yang mempunyai aktivitas sitotoksik sel kanker payudara MCF-7. Metode penelitian yang digunakan metode eksperimental berupa uji invitro aktivitas sitotoksik terhadap sel MCF-7. Hasil penelitiannya ekstrak etanol umbi keladi tikus bisa diformulasikan menjadi sediaan tablet yang berpotensi sebagai antikanker payudara. Ekstrak etanol merupakan ekstrak yang paling aktif dengan nilai IC_{50} 16,04 µg/mL pada sel MCF-7. Parameter fisik granul ekstrak umbi keladi tikus dari Formula 1 sampai 3 memenuhi persyaratan. Parameter fisik tablet pada Formula 1 sampai 3 memenuhi persyaratan tetapi waktu hancur tablet Formula 3 tidak memenuhi persyaratan.

Kata Kunci: Kanker payudara, MCF-7, Tablet, Typhonium flagelliforme, Parameter fisik tablet

INTRODUCTION

Cancer is the leading cause of death, with morbidity rates currently increasing in every country around the world. Data from the Global Cancer Observatory (GLOBOCAN) shows that in 2022, breast cancer in women ranked second with 2.3 million cases, and was the fourth leading cause of cancer deaths worldwide with 666,000 deaths, or 6.9% of all cancer deaths. In Indonesia, breast cancer is the most common cause with 66,271 cases, ranking first [1]. Chemotherapy, radiotherapy, hormonal therapy, transplantation, immunotherapy, and surgery are methods of cancer treatment [2] . Because of the limited cancer treatments available, medicinal plants are an alternative because they have anticancer properties [3], [4]. The indigenous Indonesian medicinal plant *Typhonium flagelliforme* has been widely used in various studies for its potential as an anticancer [5-11]

The active compounds contained in *Typhonium flagelliforme* as anticancer agents are isovitexin, vitexin, kaempferol, p-coumarin, quinic acid, ferulic acid, and pheophorbide [12]. The use of *T. flagelliforme* as an additional and alternative therapy for breast cancer treatment by boiling the leaves or tubers of *Typhonium flagelliforme*, drinking the decoction, or using powdered simplisia inserted into capsules, which are more sensitive to moisture and temperature, which can affect drug stability [13] so to make it easier to use, it was made into tablet form.

A tablet is a solid dosage form containing one or more active substances with or without various excipients (which improve the quality of the tablet dosage form, free-flowing properties, cohesiveness, disintegration speed, and anti-adhesion properties) and is made by compressing a powder mixture in a tablet machine [14] . Long term cancer medicine treatment has quite severe side effects, cytotoxic drugs are potentially very dangerous to the body unless they are very specific to cancer cells and new medicines that will be more selective for cancer cells Therefore, this study was conducted to make *Typhonium flagelliforme* extract an alternative to breast cancer drugs in tablet form so that it is easy to consume and has good physical quality.

MATERIALS AND METHODS

Materials

The materials used were tuber simplicia from *T.flegelliforme*, MCF-7 cells, n-hexane, ethyl acetate, ethanol, methanol, DMSO, DMEM, calf bovine serum (Gibco), PBS, 10% FBS, EDTA trypsin, fungizone, streptomycin, 10 mg tamoxifen, tryphan blue, Dragendroff reagent, Lieberman Burchard reagent, Mayer reagent, Wagner reagent, Avicel pH 101, methyl paraben, propyl paraben, Explotab, Aerosil, lactose mesh 200, Methocel, Mg stearate, and talcum.

Methods

Simplicia preparation

The carefully selected *Typhonium flagelliforme* tubers are separated by removing foreign objects and dirt attached to the tubers. The tubers are washed under running water until clean, then tied together to facilitate the drying and grinding process. Next, *Typhonium flagelliforme* tubers are dried by airing them at room temperature [15].

Extract preparation

To prepare the extract, n-hexane, ethyl acetate, and ethanol solvents were used in a maceration or stepwise cold extraction method. 500 grams of *Typhonium flagelliforme* simplicia powder was macerated with 4 liters of n-hexane for ± 24 hours and stirred once daily. The filtered filtrate is evaporated with a rotary vacuum evaporator at a speed of 80 rpm and a temperature of 40 °C. Then the residue is macerated with 4 liters of ethyl acetate solvent 6 times for ± 24 hours, and stirred once every day. The filtered results were evaporated using a rotary vacuum evaporator at a speed of 80 rpm and a temperature of 40 °C. Next, the residue was macerated with 4 liters of ethanol solvent 6 times for ± 24 hours, and stirred once every day. The filtered extract was evaporated using a rotary vacuum evaporator at a speed of 80 rpm and a temperature of 40 °C. This resulted three extracts: n-hexane, ethyl acetate, and ethanol [15].

Extract yield test

The extract obtained was then weighed and the extract yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Extraxt weight}}{\text{Simplicia weight}} \text{ x } 100\% \quad \text{.....(1)}$$

Organoleptic test of extracts

Typhonium flagelliforme tuber extract's shape, color, smell, and taste are all determined by organoleptical observations, which are made utilizing the five senses.

Cytotoxicity test of extracts and comparators on MCF-7 cells

Cytotoxicity testing of n-hexane, ethyl acetate, and ethanol extracts against MCF-7 cancer cells was conducted at BRIN (National Research and Innovation Agency) with varying concentrations, namely 5; 10; 20; 40; and 80 µg/mL. The control

(tamoxifen 10 mg) had concentrations of 2.5, 10, 20, and 40 µg/mL. Each sample containing DMEM medium, calf bovine serum 10%, fungizone, and antibiotics was incubated using a 5% CO_2 incubator for 72 hours. The cells were counted using a microscope with 4000x magnification. [11]. From the three extracts, the most active extract was selected so that the subsequent research process focused on the most active extract.

Moisture content test of extracts

About 20 anhydrous methanol should be added. Karl Fischer reagent should be used to titrate until the end point is achieved. Fill the titration flask with weighed samples that have an estimated water content of 10–50 mg, and mix for one minute. Titrate using the Karl Fischer reagent, which has a known water equivalent.

The equation is used to determine the water content in milligrams:

$$\% \text{ test water content} = \frac{V \times F}{m} \quad \text{.....(2)}$$

Noted V: Volume of Karl Fischer reagent at titration
F : Water equivalence factor
M: sample weight (mg)

Ash content test of extracts

An ignition cup is prepared, 1 g of extract is added, and it is then burned in a furnace at 600°C until it turns to ash and the weight is left behind. It is then cooled in a desiccator and weighed. The calculation that follows is used to determine the amount of ash present:

$$\% \text{ ash content} = \frac{W1}{W0} \times 100\% \quad \text{.....(3)}$$

Noted W1 : initial weight after planting
W0 : initial weight before planting

Residual solvent test of extracts

Approximately 2 g of the sample was weighed into a 100 mL flask. Dissolved and mixed with water. Pipette 10 mL into a 100 mL flask, then add water to the limit. Pipet 1.0 mL into a 50 mL flask, dissolve, then fill with water to the mark. The ethanol concentration in the extract was determined using the Gas Chromatography (GC) technique and a Flame Atomization Detector (FAD). The analysis used the following parameters: column G43, velocity 6.8 cm/sec, pressure 19 kPA, column temperature 35 °C for 10 minutes, then 10 °C/minute increase to 200 °C for 4 minutes, injector temperature 210°C, detector temperature 280 °C, injection volume 0.2 µL-0.4 µL. The system appropriateness test for this analysis was performed with the following provisions: alcohol tailing factor < 2.0 and RSD of area 6x comparator injection < 4.0%. The ethanol content is determined by comparing the sample peak area to the calibration curve of ethanol standards with a specific concentration range. The findings of this examination are utilized to guarantee that the extract's residual ethanol content remains below the safe limits.

Phytochemical screening test of extracts

Alkaloids

0.1 g sample was obtained and placed in two test tubes; 3 mL of ethanol was added, boiled over a water bath, and filtered. The filtrate was treated with 5 drops of Mayer's and Dragendorff's reagents. A white precipitate indicates the presence of alkaloids; a red-orange precipitate indicates the presence of alkaloids when Mayer's reagent is used.

Flavonoids

1 g sample was placed in a test tube, followed by 2 mL of 2 N HCl, then 1 mg of mg powder, and agitated until homogenous. If a yellow-orange or red tint appears in the sample, it is considered positive for flavonoids.

Tannins

1 g sample was placed in a test tube, filled with distilled water, and then dripped with 1% $FeCl_3$. A blackish blue color form indicates that the sample is positive.

Saponins

1 g sample was placed in a test tube, followed by 10 drops of hot distilled water, a vigorous shaking for ten seconds, and three drops of 2 N HCl. The sample is judged positive when it develops and remains stable for ten minutes.

Steroids and triterpenoids.

A total of 0.5 g of sample is mixed with 2 mL of ethanol. The sample is then heated and filtered. The resulting filtrate is evaporated to a thick consistency and added with ether and three drops of anhydrous acid and 1 drop of concentrated sulfuric acid. A positive sample contains triterpenoids if a red or purple color is formed. A positive sample contains steroids if a green color is formed.

Tablet Formulation

Table 1 explains the tablet formulation using ingredients in accordance with the recommendations of the handbook of pharmaceutical excipients. This study used ethanol extract concentrations of 0.05 g in formula 1, formula 2 at 0.075 g, and formula 3 at 0.1 g. This is based on the results of the cytotoxicity test of ethanol extract, which is the most active extract compared to n-hexane extract and ethyl acetate extract

because it has the smallest IC_{50} value of 16.04 µg/mL. The results of the comparison (tamoxifen 0.01 g) had an IC_{50} value of 4.71 µg/mL. Tamoxifen 0.01 g had 4 times the cytotoxic activity compared to ethanol extract, which is why a concentration ≥ 0.04 g was used in the tablet formulation. The procedure for making the tablets is as follows: Methocel, methylparaben, and propylparaben are dissolved in ethanol to obtain a clear binding solution. The active ethanol extract of rat taro tubers is dissolved in ethanol. Avicel and lactose are mixed until homogeneous, then the binding solution is added little by little until a wet mass suitable for granulation is formed. The wet mass is filtered using a 20 mesh sieve to form wet granules, then dried in an oven at 40–45 °C until the moisture content is 3–5%. The dry granules are filtered again to remove lumps. Next, talc, outer phase aerosil, and explotab are added, then mixed homogeneously using a dry mixer. Magnesium stearate is added last and mixed for 1 minute. The granules are tested for physical properties including flow rate, angle of repose, and compressibility, then compressed into round tablets weighing 0.530 g, 0.555 g, and 0.580 g, respectively.

Flow Rate Test of Granule

The granules are placed in a funnel to a height of 2/3 of the funnel height, then poured through the funnel tip and the flow time is measured. Requirement: no more than 10 seconds for 100 g of granules [16].

Table 1. Tablet Formulations

Materials	Concentration (g)		
	Formula 1	Formula 2	Formula 3
Active extract (ethanol) of *Typhonium flagelliforme* tuber	0.05	0.075	0.1
Avicel pH 101	0.2	0.2	0.2
Laktose mesh 200	0.16	0.16	0.16
Methocel	0.022	0.022	0.022
Methyl paraben	0.00102	0.00102	0.00102
Prophyl paraben	0.00026	0.00026	0.00026
Talcum	0.020	0.020`	0.020`
Mg stearate	0.004	0.004	0.004
Internal phase aerosil	0.01	0.01	0.01
External phase aerosil	0.020	0.020	0.020
Explotab	0.04272	0.04272	0.04272
Tablet weight	0.530	0.555	0.580

Angle of Repose Test of Granule

The angle of repose is determined using a funnel with an upper diameter of 12 cm, a lower diameter of 1 cm, and a height of 10 cm. Granules are placed in the funnel, then poured through the funnel tip and the angle of repose is determined. Requirements: the test is considered satisfactory if the angle of repose is < 25^0 [16].

$$\alpha = [\tan]\hat{}(-1)\,{}^{2h}/_{d} \quad \text{.....(4)}$$

Noted: h = height of the cone (cm)
d = diameter of the cone (cm)
α = angle of repose

Compressibility Test of Granule

Weigh 100 g of tablet granules, place them in a measuring cup and record the volume, then compress the granules 500 times with a testing device, record the test volume before compression (Vo) and the volume after 500 compressions (V). Requirement: no more than 20% [16].

Weight Uniformity Test of Tablets

Weigh 20 tablets from each formula and calculate the average weight. There should be no deviation in the weight of two tablets greater than 5% and no deviation in the weight of one tablet greater than 10% from the average weight [16].

Size Uniformity Test of Tablets

Twenty tablets were selected from each formula, and the thickness and diameter of each tablet were measured using a measuring device. The requirement was met if the diameter of the tablet was not more than three times and not less than one-third times the thickness of the tablet [16].

Hardness Test of Tablets

The tool used is a hardness tester. The way it works is that a tablet is placed perpendicular between the anvil and punch, and the tablet is clamped by turning the adjustment screw until the stop light comes on. Then the knob is pressed until the tablet breaks. The number shown on the scale pointer is read.

This test is performed 5 times. The tablet hardness requirement is 4-8 kgf [16].

Friability Test of Tablets

The equipment used is a friability tester. The method is to weigh 20 tablets, record their weight (A grams), then place them in the device and run the device for 4 minutes (100 rotations). After the specified time limit, the tablets are removed and cleaned of fine powder, then weighed again (B grams). Requirement: weight loss ≤ 1% [16].

Disintegration Test of Tablets

The equipment used was a Disintegration Tester, using 6 tablets, water as the medium, and a temperature control of ± 37 °C. Place each tablet in the basket of the device, then immerse the basket in water and start the timer. The tablet is considered disintegrated if there are no parts remaining on the mesh [16].

Water Content Test of Tablets

Weigh the tablet sample (crushed, ± 2 g). Place in a tared LOD container. Heat at 105 °C until the weight remains constant (difference between consecutive weighing ≤0.25 mg). Calculate the water content (% w/w) from the drying loss [16].

Data Analysis

Data collection was carried out by observing and measuring the cytotoxic activity of *Typhonium flagelliforme* tuber extract on MCF-7 cells. Observations and measurements of the physical properties of the granules included: flow rate, angle of repose, and compressibility of the granules. The physical properties of the tablets included: weight uniformity, size uniformity, hardness, friability, disintegration time, and moisture content of the *Typhonium flagelliforme* tuber extract tablets

RESULTS AND DISCUSSION

Determination, Organoleptic Properties, and Cytotoxic Effects of MCF-7 Cells

The results of the identification of *Typhonium flagelliforme (G.Lodd)* Blume tubers conducted at the Bogoriense Herbarium, Directorate of Scientific Collection Management, BRIN Cibinong, show that the samples used are correct.

The results of the research showed that the yield of n-hexane extract was 3.38%, ethyl acetate extract was 3.97%, and ethanol extract was 5.31%. The calculation of sample yield is very important to determine how much extract is produced during the extraction process [17]. A good extract yield value is more than 10%, but the quality of the extract is more determined by the concentration and quality of the active compounds [18,19]. Specific parameters determined using the five senses are organoleptic tests, which aim to provide initial recognition and identify extracts that exhibit distinctive characteristics in terms of shape, color, and smell. The results of organoleptic tests show that *T. flagelliforme* tuber extracts are thick, yellowish-green in color, and have a strong smell. The results of cytotoxicity tests on MCF-7 cells from n-hexane extracts of *T. flagelliforme* tubers showed IC_{50} values of 22.73 µg/mL, ethyl acetate extracts 18.21 µg/mL, and ethanol extracts 16.04 µg/mL respectively as shown in **Table** 2. All three extracts have anticancer potential because they have IC_{50} values < 30 µg/mL. According to the National Cancer Institute (NCI) cited by Paputungan *et al*., extracts have strong activity if they have cytotoxic activity with IC_{50} values < 30 µg/mL [20]. Of the three extracts, ethanol extract is the most active extract, so further research focused on ethanol extract.

Moisture content, ash content, solvent residue, and phytochemical extracts

The ethanol extract moisture content was 4.96%, which meets the requirements of the Indonesian Herbal Pharmacopoeia, namely <10% [18] . Extracts with high water content are easily contaminated by bacteria, and active chemical compounds are easily hydrolyzed, thereby affecting the quality of the extract [21].

The ethanol extract ash content obtained was 5.54%, which meets the requirements of the Indonesian Herbal Pharmacopoeia, namely <10.2% [18]. Ash content testing to determine the internal and external mineral content from the processing stage to the formation of the extract. This parameter can indicate the purity and contamination of the extract [22].

The remaining ethanol extract solvent was 269.536 µg/mL, which meets the requirements of the Food and Drug Administration, namely <10,000 µg/mL as shown in **Table** 3 [23].

The results of phytochemical screening of ethanol extracts showed positive alkaloids, flavonoids, tannins, and triterpenoids, which are bioactive compounds that have anticancer mechanisms [24-27].

Table 2. Results Of Yield, Organoleptic, And Cytotoxic Tests On MCF-7 Cells

Parameters	*n*-hexane extract	Ethyl acetate extract	Ethanol extract	Tamoxifen
% Yield (%)	3.38	3.98	5.31	-
Form	Thick	Thick	Thick	-
Color	Yellowish green	Yellowish green	Yellowish green	-
Smell	Strong	Strong smell	Strong	-
IC_{50} (µg/mL)	22.73	18.21	16.04	4.71

Table. 3 Results of Moisture Content, Ash Content, Solvent Residue, And Phytochemical Extract Tests

Parameters	Ethanol extract	Requirements
Water content (%)	4.96	<10
Ash content (%)	5.54	< 10.2
Solvent residue (µg/mL)	269.536	<10,000
Phytochemicals		
Alkaloids	Positive	-
Flavonoids	Positive	-
Tannins	Positive	-
Saponins	Negative	-
Triterpenoids	Positive	-
Steroids	Negative	-

Physical parameters of granules

The granules fall into the category of fairly good flow properties with a flow time of 4-10 g/sec, and have good flow properties with a flow time of 1.6-4 g/sec. The results of the granule angle of repose test fall into the very good category with an angle of repose of <250. The results of the granule compressibility test fall into the exceptional category with compressibility of 5–15% as shown in **Table 4** [16].

Physical parameters of tablets

The results of the physical parameter tests of the tablets are shown in **Table 5**. The weight uniformity test results are satisfactory, with no weight deviation of more than 5% for two tablets of ethanol extract of *Typhonium flagelliforme* tubers and no weight deviation of more than 10% from the average weight for one tablet [16] . The uniformity of active ingredient content is related to weight diversity; if the weight of each tablet differs, the active ingredient dosage may also differ, especially in cases where the percentage of active ingredient in the formulation is very small [28].

The results of the tablet size uniformity test are satisfactory; the diameter of the tablets is no more than three and less than one-third the tablet thickness [16] . According to Joshi *et al.*, tablet size affects tablet quality, including dose consistency, disintegration time, and tablet stability [29].

The tablet hardness test results are satisfactory, with a strength of 4 - 8 kg [16]. Studies show that the type of tablet binder used and the temperature during the tableting process affect hardness, which can result in harder tablets, leading to longer disintegration times and slower dissolution [30]. Since the methocel binder is used at a constant amount (0.022 g) in all formulas, changes in the active ingredient dosage affect the relative proportion of the binder to the tablet weight. As the total weight increases (formulas 2 and 3), the proportion of binder decreases relatively, resulting in lower hardness [31].

The friability test results met the requirements for Formulas 1, 2, and 3, which were 0.7, 0.72, and 0.94%, respectively, in accordance with the requirement that tablets should not exceed 1.0% [16]. Magnesium stearate and talc function as lubricants/anti-adherents. The amount is fixed, but in larger tablet weights, lubrication is relatively reduced so that friction during compression is higher, which can affect tablet brittleness [32].

The Disintegration test results for Formula 1 and 2 met the requirements, which were 10.24 and 12.67 minutes. Meanwhile, Formula 3 did not meet the requirements, which were 15.20 minutes, because it was stipulated that it could not exceed 15 minutes [16] . Explotab as a superdisintegrant is used as is (0.04272 g). However, because the tablet weight is greater, the relative percentage of disintegrant decreases in Formula 3, resulting in longer disintegration.

The water capacity test results for Formula 1 tablets were 2.87%, Formula 2 tablets were 2.94%, and Formula 3 tablets were 2.92%, which met the requirements as they were no more than 10% [33].

Table. 4. Results Of Physical Parameter Testing Of Granules

Parameters	Formula 1	Formula 2	Formula 3	Requirements
Flow rate (g/second)	3.48	4.12	4.33	Fair = 4–10 Good = 1.6–4
Angle of repose (°)	20.69	20.56	23.19	<25°
Compressibility	7.84	8.16	6.25	Excellent = <10 Good = 11–15

Table 5. Results of Tablet Physical Parameter Testing

Parameters	Formula 1		Formula 2		Formula 3	
Average weight uniformity (g)	0.533	Requirements met	0.556	Requirements met	0.582	Requirements met
Size uniformity	-	-	-	-	-	-
Average diameter (cm)	1.307	Requirements met	1.318	Requirements met	1.317	Requirements met
Average thickness	0.461	Requirements met	0.462	Requirements met	0.473	Requirements met
Average hardness (Kgf)	6.87	Requirements met	6.42	Requirements met	6.19	Requirements met
Friability (%)	0.70	Requirements met	0.72	Requirements met	0.94	Requirements met
Disintegration (minutes)	10.24	Requirements met	12.67	Requirements met	15.20	**Not requirements met**
Water capacity (%)	2.87	Requirements met	2.94	Requirements met	2.92	Requirements met

CONCLUSION

Ethanol extract of *Typhonium flagelliforme* tubers can be formulated into tablets that have potential as a breast cancer treatment. Ethanol extract is the most active extract with an IC_{50} value of 16.04 µg/mL. The physical parameters of the *Typhonium flagelliforme* tuber extract granules from Formulas 1 to 3 meet the requirements. The physical parameters of tablets in Formulas 1 and 2 meet the requirements, while the disintegration time of tablets in Formula 3 does not meet the requirement. Furthermore, in future research, attention should be given to the disintegrant formula and in vivo tablet testing should be conducted.

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