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Potential of Ethanol Extract of Ketapang Kencana Tree Mistletoe (Lorantus sp.) as an Alternative Therapy for Breast Cancer (MCF-7) in Vitro

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ABSTRACK

Cancer is a non-communicable disease where there is a very rapid growth and development, uncontrolled from cells and tissues, and is the most common type of cancer suffered by women throughout the world. Existing chemotherapeutic drugs have side effects by damaging the patient's healthy cells. The search for plant-derived drugs is expected to find effective anticancer with minimal side effects. Benalu Tree Ketapang Kencana (Lorantus sp.) tribe Lorathanceae, is a plant used by the people of Indonesia as a protective plant. The purpose of this study was to determine the potential of Benalu Tree extract as an alternative therapy against MCF-7 cell line. The research method used is the MTT assay analysis method by looking at the inhibition of MCF-7 cell line proliferation in vitro. The results showed that the IC50 value of ethanol extract of Benalu Tree Leaves was 267.8 µg/mL. The resulting cytotoxic activity is included in the weak category, because on the extract scale it can be categorized as potentially cytotoxic if IC50 < 100 µg / mL, but Benalu Tree Leaves still have potential as an alternative therapy for breast cancer, because it contains secondary metabolites of Alkaloid and Flavonoid types as anti-cancer that can be used as treatment

Keywords: ***Alternative Therapy , Lorantus sp., MCF-7, MTT assay***

INTRODUCTION

Cancer is a non-communicable disease in which there is very rapid growth and development, uncontrolled from cells and tissues. This growth can interfere with the body's metabolic processes and spread between cells and body tissues (Susmini & Supriyadi, 2021). Cancer is one of the non-communicable diseases that is a burden on health throughout the world. Cancer is a disease characterized by the presence of abnormal cells that can develop and are not affected and have the ability to invade and move between cells and tissues in the body (Kartini, Lubis & Moriza., 2019).

Based on GLOBOCAN data (*Global Cancer Observatory , International Agency for Research on Cancer (IARC*) In 2020 there were 19.2 million cases of cancer in the world with a death rate of 9.96 million, which is estimated to increase in 2024 by 16.2 million cases of cancer deaths. Of the many types of cancer, there are 5 cancers that have the highest prevalence in the world in 2020, namely breast cancer (11.7%), lung cancer (11.4%), colon cancer (10%), prostate cancer (7.3%) and stomach cancer (5.6%) judging from the prevalence of these data, breast cancer ranks first in the highest cancer cases in the world (GLOBOCAN, 2020).

Plants that have anticancer potential are plants that contain secondary metabolites such as alkaloids, falvonoids, steroids, triterpenoids and high antioxidants (Nola dkk, 2021). One plant that has been empirically proven to be used by the community as an anticancer drug and has these criteria is the Ketapang Kencana Tree Benalu plant (*Lorantus sp.*) that grows on a protective tree or commonly called the ketang kencana tree (*Terminalia mantaly*) found in the Bugis tribe, precisely in Soppeng Regency, South Sulawesi. How to use it is to take a few leaves and then boil and drink.

According to Mutia's research dkk., (2017) that ethanolic extract from star fruit leaves (*Eleutherine palmifolia*) was able to selectively inhibit the growth of HeLa cervical cancer cells (uterine cancer) with values at IC50: 40.36 µg/ml, In addition, based on empirical data that the combination of sabrang onion (*Eleutherine palmifolia*) and star fruit (*Macrosolen cochinensis*) can help cure cancer patients and it has been proven that many are helped by this herb. Soeranggi (2019), In his research also found that ethanol extract of Moringa Benalu Leaves has a cytotoxic effect on T47D breast cancer cell line with an IC50 value of 33.89 µg / mL. Phytochemical screening shows the presence of compounds from the alkaloid group in the methanol extract of Moringa leaves, so that compounds from that group have anticancer activity.

METHOD

Design, place and time

The research was conducted at Hasanuddin University Laboratory , *medical research center.* In December 2023 to January 2024.

Tools and Materials

Tool : 96-well *plate, cell counter,* ELISA *reader*, *grinder*, hemasitometer, CO2 carbon dioxide incubator, *Laminar Air Flow* (LAF), 200, 1000 µL micropipette, inverted *microscope*, oven, water bath, sterile *pasteur* pipette, small tube rack, *rotary evaporator*, *centrifuge*, tube *conical*, small test tube, *tissue culture flask*, *yellow tip* and *blue tip*.

Ingredients: Ketapang Kencana Tree Benalu Leaf Extract (*Lorantus sp*.), ethanol 96%, aluminum foil, dimethyl sulfoxide (DMSO), Trypsin-EDTA solution 0.25%, Dulbecco's Modified Eagle's Medium (DMEM) media, complete media or MK (*Fetal Bovine Serum* (FBS) 10% + Penstrep 2% + Amphoterizine B 0.5% + 87.5% RPMI 1640 media or DMEM media), RPMI culture media, Roswell *Park Memorial Institute* (RPMI) 1640 media, MTT 5mg/mL PBS (50 mg MTT and 10 mL PBS), *Phosphat Buffer Saline (PBS), SDS 10%* in 0.1 NH4Cl, WiDr Cells and feeding tissues.

Research Steps

Sample Preparation

Benalu Tree leaves are obtained from the Ketapang Kencana Tree (*Lorantus sp.*) that grew around the residential area of the Bugis people, precisely in Soppeng Regency, South Sulawesi. The Benalu obtained is washed first and then dried then mashed and extracted.

Extraction

The extraction process is carried out by maceration method using ethanol solvent. At the maceration stage, 500 grams of Benalu Tree which has been mashed and put into an Erlenmeyer glass is weighed. Added 96% ethanol as much as 1 L and stirred for 30 minutes until completely mixed. This mixture is left for one night until it settles. Furthermore, filtering is carried out from the top layer of the mixture of ethanol (solvent) and active ingredients that have been mixed using filter paper. The soaking process is carried out 3 times. Furthermore, the evaporation stage is carried out on the filtration results.

Evaporasi

At the evaporation stage, the filtered mixture is put into the evaporation flask. The evaporating flask is mounted on the evaporator and the waterbath is connected to electricity and the temperature is set to 78.40C (corresponding to the boiling point of ethanol). Separation of ethanol solvent with active ingredient is done until ethanol solution stops dripping on a 900 ml container flask (1.5 to 2 hours for one flask). Benalu Tree ethanol extract contained in the container flask is then transferred to a glass bottle and stored in the refrigerator.

Phytochemical Analysis

Uji Flavonoid

To determine the presence of flavonoid compounds, thick extracts are first dissolved in ethanol which is then added with aquadest to taste. The extract solution is then added with 1 ml of concentrated HCl and magnesium powder (1 ml of extract + 1 ml of concentrated HCl + magnesium powder). A change in color to yellow, orange, red, or purple indicates that the extract contains flavonoid compounds (Pahlani et al., 2022).

Uji Alkaloid

To determine the presence of alkaloid compounds, the extract is first dissolved using 1 ml of chloroform and then added wagner reagent drop by drop until an orange or brown precipitate is formed which indicates that the extract contains alkaloid compounds.

Ekstrak + 1 ml kloroform + preaksi wagner

Water Saponin

For the identification of saponin compounds, a viscous extract is first dissolved in ethanol which is then added with aquadest to taste. The extract solution is then added with 10 ml of warm water, then shaken vigorously. Positive results by showing steady foam for no less than 10 minutes, as high as 1 cm to 10 cm then at the addition of 1 tets of 1% HCl, foam or foam does not disappear (Jayadi, 2022).

Uji Steroid

For the identification of steroid compounds, a viscous extract is first dissolved in ethanol which is then added with aquadest to taste. The extract solution is then added with concentrated H2SO4 as much as 1ml from the tube wall. Positive results are shown by the formation of a black ring between the extract solution and concentrated H2SO4 (Safruddin &; Nurfitasari, 2018). 1 ml of extract + 1 ml of concentrated H2SO4.

Uji Tanin

For the identification of saponin compounds, a viscous extract is first dissolved in ethanol which is then added with aquadest to taste. The extract solution is then added 3 drops of 10% FeCl3 solution. Pay attention to the color that occurs, blue, green, black or bluish-black indicates the presence of tannins (Yanty et al., 2019). 1 ml of extract + 3 drops of FeCl3

Uji Triterpenoid

A total of 0.5 grams of extract added 2 mL chloroform, then added 3 mL sulfuric acid (H2SO4) to form a layer. The presence of a brownish-red color between the layers indicates the presence of terpenoids.

Anticancer Testing

Making Stock Solution of Benalu Leaves of Ketapang Kencana Tree (*Lorantus sp.*)

Benalu Tree Leaf Extract was weighed in *microtubes,* then the extract was sterilized under UV light in BSC (*Blohazard Safety Cabinet*) for 20 minutes, then dissolved with DMSO, divortex until homogeneous and made a test solution with 6 concentration series, namely 200 µg / ml, 100 µg / ml, 50 µg / ml, 25 µg / ml, 12.5 µg / ml, 6.25 µg / ml. Concentrations were made three times each for treatment on MCF-7 cells.

Thawing and Cell Culture of MCF-7

The cells inside the *cryovial* are melted in a *waterbath* at 37°C. The cell is inserted into a conical tube containing 6 ml DMEM + FBS 10%, centrifuge 1000 rpm for 5 minutes, the supernatant is discarded then the pellets are suspended with MI DMEM 1640 + FBS, the cell suspension is inserted into *the flask culture,* and Incubated in an incubator temperature of 37o C, CO2 5% until the cell reaches a density of 70-80% covering the surface of the *flask culture*. Cells are subcultured when the density has reached 70-80% covering the surface of *the culture flask*.

MCF-7 Cell Subcultuvation

Thawing cells are observed in a microscope and dispose of media using micropipettes. Washing cells is repeated 2 times with PBS (PBS volume is ± 1/2 volume of initial media), trypsin-EDTA (0.25% trypsin) is added evenly and incubated in the incubator for 3 minutes. Then it is observed in a microscope. After that, add 5 mL ± media to inactivate trypsin, and transfer the released cells one by one into a new sterile conical, added with DMEM medium plus 10% FBS as much as 5 mL. Centrifuged at a speed of 1500 rpm for 5 minutes, after which the supernatant is removed (try not to waste pellets), and the pellets formed are suspended into 2 ml of DMEM medium plus 10% FBS, then homogenize until they become a cell suspension in the medium.

Cell Calculation

Taken 10 micro liters of cell suspension + tripan blue 10 micro liters, homogenized and then dripped on a *haemocytometer.* Then, count the cells under a microscope (*inverted* or light microscope) with a *counter.* After counting the cells to be planted (for treatment) transfer the required number of cells into another *conical* and add MK (Culture Media) according to the desired concentration.

Cytotoxicity Testing

Transfer cells into sumurs, 100 µl each, and leave 3 empty wells (do not fill cells). Then, observe the state of the cells in an inverted microscope to see the distribution of cells and document them. Incubate cells in the incubator for at least 1x24 hours so that the cells *attach* again after harvesting). Take a *plate* from the CO2 incubator to take it to LAF, then remove the cell media (turn the *plate* 180°) over the drain with a distance of 10 cm, then press the *plate* slowly on a feeding tissue to slice the remaining liquid, then insert 100 µl of PBS into all wells filled with cells, then dispose of PBS by turning the *plate* and drain the remaining liquid with a paper towel. Put 100 µl series of sample concentration into the well (triplo). Incubation inside the CO2 incubator. The duration of incubation depends on the effect of the treatment on the cells. If within 24 hours no cytotoxic effects have been seen, re-incubate for 24 hours (total incubation time: 24-48 hours). Then incubate again for 2-4 hours in a CO2 incubator. Then, the condition of the cell is examined with a microscope, looking at the formazan formed, if the formazan has been clearly formed, a *100 µl* stopper solution is added using an MTT *stopper.* Then, the plate is wrapped in aluminum foil and incubated in a dark place at room temperature overnight. Results were then observed using an ELISA *reader* at wavelengths of 550-600 nm.

DATA ANALYSIS

Linear regression *equations* using Microsoft *Excel and* ELISA *reader programs.*

To determine the percentage of cell death can be analyzed from the absorbance results using the formula:

$$\% \text{ live cells x } 100\% = \frac{absorbansi\ perlakuan - absorbansi\ kontrol\ media}{absorbansi\ kontrol\ sel - absorbansi\ kontrol\ media}$$

A small IC50 value indicates that there is a high cytotoxic effect on the test compound, while a large IC50 value indicates that the cytotoxic effect is low. IC50 values > 501 µg/ml are said to have no cytotoxic effect, 201-500 µg/ml means having weak cytotoxicity, 21-200 µg/ml means having moderate cytotoxicity, and values less than 20 µg/ml means having high cytotoxic properties (Sajjadi *et al.*, 2015).

RESULT

Based on calculations, ethanol extract yield of Benalu Leaves of Ketapang Kencana Tree *(Lorantus sp.)* is 15.238%, as per the following table:

Table 1. Yield of Ketapang Kencana Tree Benalu Leaf Extract *(Lorantus sp.)*

Character	*Lorantus sp. powder*	Extract Ethanol *Lorantus sp.*
Weight	500g	76.19 g
Color	Dark green	Dark green
Rendeming	-	15,238 %

Source : Primary Data

Based on the results of phytochemical screening, ethanol extract of Benalu Tree Leaf Leaves contains Flavonoids, Alkaloids, Saponins, Steroids, Tannins, Triterpenoids, Terpenoids produced which are positive (+).

Table 2. Phytochemical Screening Results of Ketapang Kencana Tree Benalu Leaf Extract *(Lorantus sp.)*

Metabolite Seconds	Pereaksi	Observations	Ket
Flavonoid	1 ml HCl pekat + Mg	Color change to yellow	+
Alkaloid	Wagner Reagents (Potassium Iodide and Iodine Resublymed)	Brown deposits are formed	+
Saponins	10 ml of warm water, shake vigorously. Stable foam, +1 ml HCl 1%	Forms a stable froth	+
Steroids	1 ml H2SO4 Pekat	The formation of a black ring	+
Tannins	FeCl3	Discoloration to black	+
Triterpenoid	Uji Salkowski	Discoloration to golden yellow	+
Terpenoid	2 ml kloroform + 3 ml H2SO4	Brownish-red discoloration	+

Based on the calculation of the IC50 value of Ketapang Kencana Tree Benalu Leaf Extract *(Lorantus sp.)* resulting in 267.8 µg/mL.

Tabel 3. Antiproliferative Test Results of Ketapang Kencana Tree Benalu *(Lorantus sp.)* against Cancer cells (MCF-7).

Concentration (µg/mL)	Absorbansi			Installment Absorbansi	% Average living cell	IC_{50}
200	0.3397	0.3154	0.3151	0.323	106.280	267,8 µg/mL
100	0.34	0.3189	0.2664	0.308	99.857	
50	0.3588	0.4019	0.2704	0.344	114.993	
25	0.3892	0.4322	0.3658	0.396	137.325	
12,5	0.5408	0.563	0.5138	0.539	198.898	
6,25	0.7573	0.7555	0.8691	0.794	308.240	

DISCUSSION

The purpose of this study was to determine the potential of Benalu Tree Ketapang Kencana (*Lorantus sp.*) extract as an alternative therapy for breast cancer (MCF-7). Cytotoxic test is an *in vitro* toxicity test using cell culture used in the safety evaluation of drugs, cosmetics, food additives, pesticides and used to detect the presence of antineoplastic activity of a compound. The test method chosen is the MTT *assay method*. The reason for using MTT *assay* is that this method is fast, sensitive and most commonly used in *in vitro testing*(Sitorus,2013).

In this study, plant determination was also carried out which aimed to find out the truth of the plants to be studied and avoid errors in the collection of material and avoid the possibility of mixing plants to be studied with other plants, in addition to determining the correctness of the samples used in the study (Akbar,2021). The results obtained from the determination of this plant carried out at the UPT Herbal Laboratory Medica Batu Malang, stated that the samples studied were true Benalu Leaves of the Ketapang Kencana Tree *(Lorantus sp.)* which belongs to the family *Lorantahaceae*.

Based on the research that has been done, the yield of Ketapang Kencana Tree Benalu Leaf extract *(Lorantus sp.)* by 15.238%. The higher the yield percentage, the more extracts produced. The

calculation of the percentage of yield aims to find out how much simplisia is needed for extraction in order to obtain the desired amount of extract. The yield results can be used as a reference to determine the amount of simplisia needed for the manufacture of a certain amount of viscous extract. This yield value meets the requirement of a good extral viscous yield of >10% (Egra,2019).

The results of the resulting phytochemical screening stated that the Benalu Leaf of the Ketapang Kencana Tree *(Lorantus sp.)* positively contains flavonoid compounds, alkaloids, saponins, steroids, tannins, triterpenoids and terpenoids. These results are in line with research conducted by Gusungi 2020 which states that Benalu Tree contains phytochemical compounds such as flavonoids, alkaloids, triterpenoids, and saponins that can act as antioxidants and anticancer. Antioxidants are compounds that can inhibit free radical reactions in the body. Falvonoids and alkaloids work as antioxidants by donating hydrogen atoms, so that radicals can be reduced. Flavonoids, alkaloids and triterpenoid compounds are said to be anticancer, namely by inhibiting the mechanism of division and activation of the apoptosis pathway of cancer cells.

Cytotoxicity testing can be done by observing cells that survive after giving test samples that are suspected of having cytotoxic activity. The MTT *assay* method is a method used in cytotoxicity testing in this study. Observation of cells that survive after sampling can be done by looking at the absorbance value obtained using *an elisa reader*. Living cells after sampling can be detected from discoloration due to MTT *reagent*. The number of crystals formed has a positive correlation with the number and activity of these cells, and measuring the absorbance value describes the number of living cells and the activity of those cells (Renggana,2022).

Results of MCF-7 cell microscopy after the addition of 6 concentrations of ethanol extract of Benalu Leaves of the Ketapang Kencana Tree *(Lorantus sp.)* In Appendix 15, it shows that the higher the concentration, the more concentrated the color in the media. This is caused by the reaction of forming formazan crystals that are purple. Color changes that occur in *the* 96 *well* plate can be observed through its absorbance using *an elisa reader with a* wavelength of 550-600 nm. Color change is used to see cell proliferation. Cells that experience proliferation in mitochondria will absorb MTT so that these cells will be purple due to the formation of tetrazolium crystals *(formazan)*. The intensity of purple is formed proportionally with the number of living cells, so that if the intensity of purple is greater, the fewer the number of living cells. From the results of color changes in the extract of Benalu Leaves of the Ketapang Kencana Tree *(Lorantus sp.)* Then observed the growth of cells under a microscope in each extract sample. The results showed that a concentration of 200 µg/mL had a higher number of dead cells compared to the number of dead cells at a lower concentration.

Based on the results of cytotoxicity testing of ethanol extract of Benalu Leaf Ketapang Kencana Tree *(Lorantus sp.)* against breast cancer cells (MCF-7), the resulting IC50 value is 267.8 µg/mL. IC50 values > 501 µg/ml are said to have no cytotoxic effect, 201-500 µg/ml means having weak cytotoxicity, 21-200 µg/ml means having moderate cytotoxicity, and values less than 20 µg/ml means having high cytotoxic properties (Sajjadi *et al*., 2015). Benalu Leaf Ketapang Kencana Tree *(Lorantus sp.)* is included in the weak category, but still has potential as an alternative therapy for breast cancer because it has secondary metabolite compounds, namely types of flavonoids and alkaloids that can be used as anticancer in treatment because it can inhibit the mechanism of cell division and activation of the apoptosis pathway (cell death) of cancer cells.

This study is an initial study to determine the cytotoxic activity as anticancer of Benalu Tree Leaves (*Lorantus sp*). Therefore, to determine the mechanism of action as an anticancer in Benalu Tree (*Lorantus sp.*) and knowing the active substances that are anticancer need further research, considering the diverse characteristics of cancer cells and the various mechanisms of action of these anticancer compounds.

CONCLUSION

Based on the results of research on the potential of Ketapang Kencana Tree Benalu Leaf extract (*Lorantus sp.*) as an alternative therapy for breast cancer (MCF-7) in *vitro* produced an IC50 value of 267.8 µg / mL. IC50 values below 100 µg/mL are categorized as having strong cytotoxic activity. In this study the IC50 value obtained was categorized as weak, but still potential as an alternative therapy for breast cancer, because it has secondary metabolite compounds of alkaloid types and flavonoids as anti-cancer that can be used as treatment.

SUGGESTION

It is necessary to conduct research on the extract of Benalu Tree Leaves (*Lorantus sp.*) with polar, semi-polar and non-polar fractions so that in the future cytotoxic active substances as anticancer can be isolated and identified. In addition, to determine the mechanism of action of anticancer compounds contained in Benalu Tree Leaves (*Lorantus sp.*) Need to conduct more in-depth research and cytotoxicity testing on other types of cells.

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