Phytochemical and Pharmacology Effect of Calotropis Gigantea as Anti-Cancer Therapy: Systematic Review

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Abstract

The high prevalence of cancer in the world makes many researchers look for alternative therapies that can be used to treat cancer. One of them is by using traditional plants, namely *Calotropis gigantea* R.Br. This is due to the presence of alkaloids, glycosides and tannins in plants that function as anticancer. The purpose of this study was to dig deeper into information related to the phytochemistry and pharmacology effect of *Calotropis gigantea* as an anticancer therapy, and can be used as a reference for the development of traditional medicines. The method used is PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-analyses*), with inclusion and exclusion criteria, 11 articles were selected for review. The results showed that *Calotropis Gigantea* contains *Calotropin, Calotroposide A, oxypregnane oligoglycoside compounds* which have activity in inhibiting cancer cell growth through the mechanism of apoptosis induction and ROS inhibition. From this systematic review, it can be recommended that the plant *Calotropis gigantea* can be further developed into standardized herbal medicine and phytopharmaceuticals.

***Keywords**: Calotropis gigantea, anticancer, pharmacotherapy and phytochemicals*

Introduction

Cancer is a disease caused by uncontrolled cell growth and can be cured if diagnosed early (Mathur, 2015). Cancer in Indonesia itself has a high mortality rate. Based on data from the *International Agency for Research on Cancer (IARC)* shows that in 2020 there are 234,511 cancer deaths, with a total of women experiencing cancer more than men (IARC, 2020). The high prevalence of cancer in the world makes researchers interested in using traditional plants because side effects are smaller than chemotherapy treatment (Rahman, 2015).

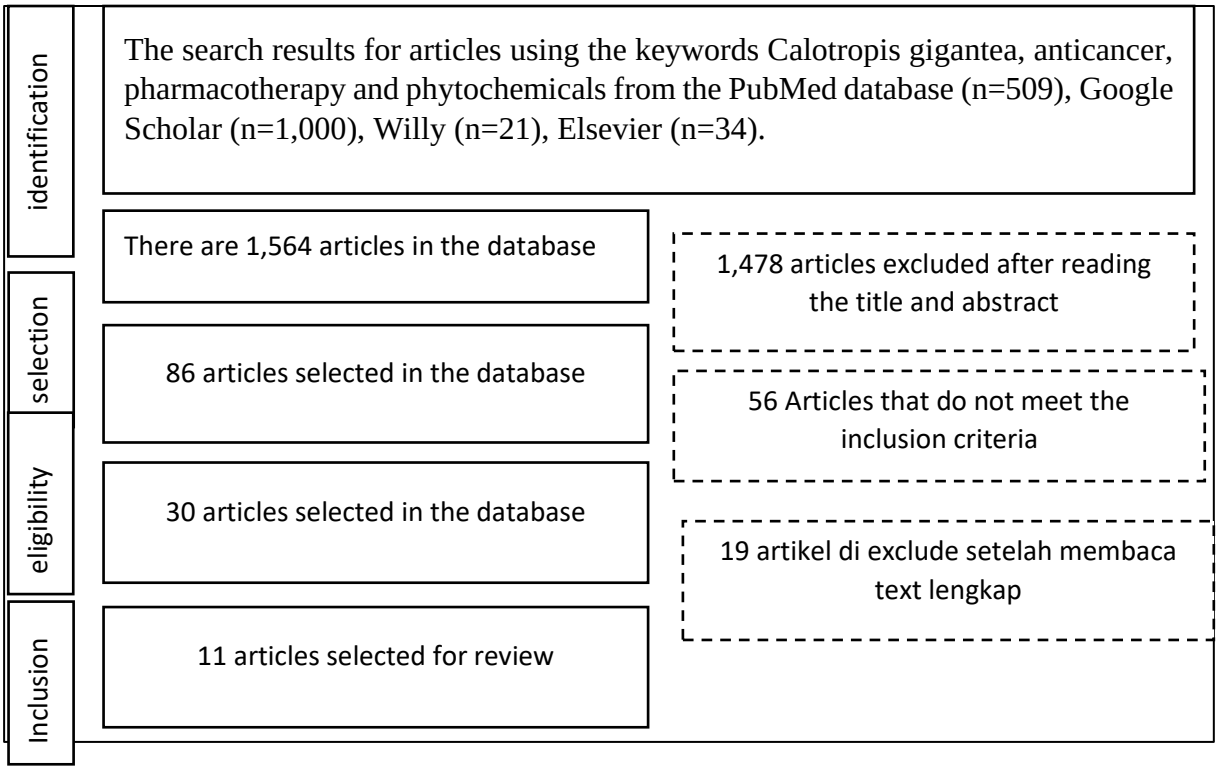
One of the plants that can be an alternative cancer treatment is *Calotropis gigantea* R.Br. *Calotropis gigantea* R.Br. is a wild plant found in several areas of India, Indonesia, Malaysia, Thailand, and Sri Lanka, China. This plant belongs to the Apocynaceae family and is a latex-producing plant. *Calotropis gigantea is* known for its various traditional medicinal properties to cure various diseases. This plant is reported to have analgesic activity, antimicrobial activity, antioxidant activity, antipyretic activity, insecticidal activity, cytotoxicity activity,

hepatoprotective activity, laxative activity, procoagulant activity and wound healing activity (Sarkar et al., 2015).

Supported by the results of Padhi's research, (2019) it was found that on phytochemical screening and anticancer activity ofleaf extract *Calotropis gigantea* (L.) Dryand. revealed that the presence of alkaloids, glycosides and tannins in plant leaves that function as anticancer (Avinash, 2019). The purpose of this literature review is to dig deeper into information related to the phytochemistry and pharmacology of *Calotropis gigantea* as an anticancer therapy, and can be used as a reference for the development of traditional medicines.

Method

The research method used is PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-analyses*). This study uses articles from the Google Scholar, Pubmed and Elsivier databases published from 2016-2021. The keywords used were *Calotropis gigantea*, anticancer, pharmacotherapy and phytochemicals. The inclusion criteria used in this study were Indonesian or English articles, articles published in 2016-2021, *original articles*. As for the exclusion criteria, namely publications outside the years 2016-2021, *Systematic review*.



Results

Taxonomic

Classification Taxonomic classification *Calotropis gigantea* L according to Singh (1996):

Kingdom: *Plantae*
subkingdom: *Tracheobionta*
Super Division: *Spermatophyta*
Division: *Magnoliophyta*
Class: *Dicotyledons*

Sub-class: *Asteridae*
Series: *Bicarpellatae*
Order: *gentianales*
Family: *Apocynaceae*
subfamily: *Asclepidiaceae*
Genus: *Calotropis*
Species: *Calotropis gigantea* L.

Plant morphology

Leaf
Calotropis gigantea has a single leaf, which are arranged opposite, oval or elliptical, short-stemmed, grows face. pale green in color and has a fairly large size of about 30x25 cm (Sarkar et al., 2015).

Flowers
Compound, bisexual, pale rose in color, purple or greenish yellow and have a faint odor. The flower buds are ovate, green petals, and long flower stalks (Sarkar et al., 2015).

Bark & Branches
The bark is thick, leathery and yellow to brown in color, the twigs are green and fleshy and may have a tomentum covering (white fur like hair) (Sarkar et al., 2015).

Inflorescences
The inflorescences emerge from the base of the leaf in the *pedunculate* (7cm) (Sarkar et al., 2015).

Fruits
The fruits are green ovate (follicle), up to 15 cm long by 10 cm wide. when split to release feathers, light brown thin seeds with white filamentous pappus up to 6cm long on one side. The flowering period is from March to October (Sarkar et al., 2015).

(A) (B) (C) (D)
Figure 1. (A) Flowers (B) Leaves, (C) Bark and stems, and (D) Fruit

Distribution of geography

Calotropic gingantea is distributed in tropical and sub-tropical areas of Asia and Africa. In India it is represented by two species namely, *C. procera* and *C. gigantea*. *C. procera is* more common in southwest and central India and western Himalayas whereas *C. gigantea is* abundant throughout India directly from the Himalayas to southern India (Ahmed, 2016).

The search results for articles using the keywords *Calotropis gigantea*, anticancer, pharmacotherapy and phytochemicals from the Google Scholar database, Pubmed, Elsivier (n = 1564). Screening of articles by title and abstract (n=86). The excluded articles did not meet the inclusion criteria (n = 56). Screening of articles based on full text and eligibility criteria (n = 19). So that 11 selected articles were obtained for review.

Table 1. In vitro preclinical test for *Calotropis gigantea*

No.	Author name	Research method (on cancer)	Plant part (compounds)	Research results
1.	Avinash et al (2019)	MTT test, to see cytotoxic activity using MCF7 breast cancer cells.	leaf extract (alkaloids, glycosides and tannins)	Ethyl acetate extract has anticancer activity with IC50 of 84.45 g/ml.
2.	Mutiah, et al (2018)	MTT test to see the activity of WiDr colon cancer cells	Roots (Calotroposide A)	Calotroposide A was able to inhibit the growth of WiDr colon cancer cells at IC_{50} 17.23µg/ml. Induction of cell apoptosis was indicated by increased cell apoptosis, cell accumulation in S and G2/M phases and caspase-8 expression.
3.	Zhou et al (2019)	MTT and BrdU trials. The anti-tumor activity of CTP was observed in a mouse tumor model.tests were *In vitro* and *in vivoperformed*. Invivo test using mice as experimental animals.	Calotropin (CTP)	Calotropin (CTP) significantly suppressed cell proliferation in colorectal cancer cells, indicated by reduced colony formation. Thus, these results suggest that CTP inhibits the proliferation of colorectal cancer cells in vitro. In *vivo* showed a significant reduction in tumor growth compared to the control group.
4.	Pederson et al (2020)	Intracellular Ca2+ Imaging, Western Blotting and qRT-PCR Methods. Using breast cancer cells, namely BT-549 cells and TNBC cells	Extract	The results showed that the extract from Calotropis gigantea caused selective cytotoxicity in BT-549 cells compared to the other four TNBC cell lines. The IC50 values in BT-549 cells ranged from 14.6 m for uscharin and 3.9 m for uzarigenin.
5.	Lee (2019)	Cell cycle analysis, *realtime polymerase chain reaction* (RT-PCR), western blotting, JC-1 staining, and ROS detection assay. Lung cancer cell line A549 and NCI-H1299	Ethanol extracts from whole plants.	extract *Calotropis gigantea* causes apoptosis through extrinsic and intrinsic activation pathways, cell cycle inhibition, and ROS generation in A549 and NCI-H1299 lung cancer cells.
6.	Mahar., et al (2016)	MTT method NMR-LC analysis and spectroscopy on MDAMB23cells	root bark (Calotroposides)	Oxypregnane oligoglycosides (Calotroposides) in the ethyl acetate fraction actively inhibit cancer cell growth
7.	Amutha., et al (2020)	MTT test on MDAMB231 cells,	Flower Extract	Cytotoxic potential against breast cancer cells

				(MDAMB231) with IC values of$_{50}$ hexane and methanol extract obtained 84.05 g/mL and 72.27 g/mL respectively
8.	Thanwarat., et al (2021)	HPLC and MTTTest	Bark	Results show that DCM extract has anticancer activity through apoptotic induction mechanism
9.	Mutiah, et al (2016)	MTT test on WiDr cells	Root Extract (Calotropin Compound)	Root *Calotropis gigantea* can inhibit cancer cell growth with IC_{50} value of 44.2 g/ml.
10.	Immaculate., et al (2020)	MTT test on MCF7cells	stem(methanol extract)	Produced an anticancer effect value of (10µL, 5 mg/mL).
11.	Mutiah, et al (2016)	MTT test on breast cancer cells T47D	Roots, Leaves and Flowers (Ethanol)	Extractroot extract *Calotropis gigantea* had a higher cytotoxic effect (IC50 89.76 g/mL) than leaf extract (IC50 459.51 g/mL) and flower extract (IC50>1000) on T47D breast cancer cells.

Discussion

Common cancer treatments such as surgery (surgery), chemotherapy (including immunotherapy and hormone administration) and radiotherapy have not given satisfactory results and have several weaknesses, so an alternative for anticancer treatment is sought (Setiawan, 2015). One of them by utilizing traditional plants.

Anticancer activity of compounds in the leaves

Previous studies have reported that the leaves are known to contain compounds belonging to the group of alkaloids, glycosides and tannins. The compounds are known to inhibit the growth of cancer cells through induction of apoptosis pathway activation of the extrinsic and intrinsic, inhibition of cell cycle, and the generation of ROS (Padhi, et al, 2021; Lee, 2019).

Activities anticancer compounds in the Flower

Activities anticancer in this part of the flower *Calotropis gigantea* are compounds extract methanol and chloroform fraction. The results showed that the cytotoxic potential against breast cancer cells (MDAMB231) with IC50 values of hexane and methanol extract obtained 84.05 g/mL and 72.27 g/mL, respectively (Amutha, et al, 2020).

Anticancer activity of compounds in The bark

ethyl acetate fraction in the bark of theplant *Calotropis gigantea* contains Calotroposides (oxypregnane oligoglycosides). It was also reported that the ethyl acetate fraction had higher anticancer activity than ethanol extract *(*Mahar., et al, 2016). Other studies reported thatextract *dichloromethane* had anticancer activity with mechanism to increase the induction of apoptosis (Thanwarat et al, 2021).

Anticancer activity of compounds in roots and stems

The roots of *Calotropis gigantea* have been reported to contain Calotroposide A compounds that are able to inhibit the growth of colon cancer cells (WiDr *cell line*) at IC_{50} 17.23µg/

ml (Mutiah, et al, 2018). Roots have also been reported to have high potency in T47D breast cancer cells. This effect was evidenced by the inhibition value of the ethanolic root extract (IC_{50} 89.76 g/mL) which was higher than that of the leaf extract (IC50 459.51 g/mL) and flower extract (IC50>1000). This shows that the root extract has a high potential for inhibiting the growth of breast cancer (Mutiah et al. 2016). It was also reported Extract Methanol stems have anticancer potential with a value of inhibition of 5mg / mL (Immaculate et al., 2020).

Conclusion

The results of this study showed that the plant *Calotropis gigantea* containing compounds *Calotropin, Calotroposide A, oxypregnane oligoglikosida* that had activity in inhibiting the growth of cancer cells through the mechanism of apoptosis induction and ROS inhibition. From this systematic review, it can be recommended that theplant *Calotropis gigantea* can be further developed into standardized herbal medicines and phytopharmaceuticals.

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