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Cytotoxic Tests On Rimpang Plants In Indonesia Used As An Anticancer: A Review

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ABSTRACT: Rhizome is a plant part of the toga plant which is commonly used by Indonesian people for traditional medicine and cooking spices. The content of chemical compounds from rhizome curcuminoids, essential oils and several different chemical ingredients in each rhizome such as falvonoids, tannins, flavones, falvonone, polyphenols, oleoresin, geranial and several other chemical ingredients. To test the cytotoxic activity using the BSLT (Brine Shrimp Lethality Test) and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylthiazol bromide) methods. Based on the 13 rhizome plants in Indonesia that have been described, including showing a fairly strong cytotoxic ability, 8 of them showed very strong cytotoxic activity, namely, Curcuma heyneana showed an IC_{50} value of 0.1 µg/ml by the MTT method, Kaempferia galanga which showed an IC_{50} value of 0.52 µg/ml with the BSLT method, Curcuma mango showed an IC_{50} value of 1.5 ± 0.2 µg/mL with the MTT method, Curcuma ochrorhiza showed an IC_{50} value of 1.6 µg/ml with the MTT method, Zingiber officinale showed an IC_{50} value of 2.18 µg/ml with the MTT method, Curcuma xanthorrhiza Roxb. showed an IC_{50} value of 2.88 µg/ml with the MTT method, Zingiber officinale Roscoe var. rubrum showed an IC_{50} value of 20.350 µg/ml with the MTT method and Curcuma zedoria showed an LC_{50} value of 22.86 ppm with the BSLT method.

Keywords: Rhizoma, Cytotoxic, Anticancer.

I. INTRODUCTION

Cancer is an abnormal growth of cells from body tissue cells that turn malignant. These cells can grow further and spread to other parts of the body so that it can cause death, the mutated body cells will grow and divide faster and out of control like normal cells. Cancer is also commonly called a malignant tumour or neoplasm. Until now, cancer is still a disease that is a world problem. Cancer causes a large number of deaths, in 2008 there were 12.7 million cases of cancer and caused 7.6 million deaths or about 13% of all deaths in the world population due to cancer. In Indonesia, cancer is the 6th cause of death after infectious, cardiovascular, traffic accidents, malnutrition and congenital diseases. There are several approaches used to treat cancer, namely surgery, radiation and chemotherapy. The use of this method depends on the type of tumour and its stage of development. [1]

Due to the increasing incidence of cancer each year, efforts to find new anticancer agents have also increased. Several studies have been conducted to find anticancer agents from natural products to prevent and cure cancer. There are so many natural ingredients that exist in parts of the world that can be utilized by humans, one of which is in Indonesia, which is a tropical country that has biodiversity so that it has great potential in obtaining alternative medicines as anticancer from plants.

Some plants that are known to function as anti-cancer agents are rhizome plants such as kunyit putih(Curcuma mango Vall),[2] and several other rhizomes such as Temu giring (Curcuma heyneana), Temu Kunci (Boesenbergia rotunda), Lempuyang (Zingiber zerumbet), Ginger (Zingiber officinale), Kencur (Kaempferia galanga), Temu ireng (Curcuma aeruginosa), Temulawak (Curcuma zanthorrhiza), Galangal (Alpinia galanga), Temu putih (Curcuma zedoaria/Curcuma ochrorhiza), turmeric (Curcuma domestika val.), Kecombrang (Nicolaia speciosa Horan.) And Bangle Rhizome (Zingiber ottensi L.) which are cytotoxic. Cytotoxic is a compound or substance that can kill or stop the growth of cancer cells. Cytotoxic tests of plants that have the potential to be anticancer have been carried out, therefore this review was made to compare rhizome plants that have anticancer potential. It is hoped that the explanation from this review can increase knowledge and can contribute

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to the development of anticancer drugs from natural ingredients.

II. DATA COLLECTION

In preparing the review of this article, the technique used is to use literature to find a source of pharmaceutical scientific literature or in the form of national and international journals in the last 10 years (2010-2020). Also in the making of this review article search data using online media with keywords is a cytotoxic test on Rizhoma Plant. The main reference searches used in the review of this article are through trusted websites such as ScienceDirect, Researchgate, Google Scholar, Pubmed, Sci-hub and other reliable journal publications.

III. RESULTS AND DISCUSSION

Table 1. Cytotoxic activity test on rhizome plants using the BSLT method

Plant Name	Sample	Nilai LC_{50}	References
Curcuma zedoria	Ethanol	22.86 ppm	[3]
Curcuma xanthorrhiza Roxb.	Ethanol 70%	65.09 µg/ml	[7]
Curcuma xanthorrhiza Roxb.	Ethanol	210.3 µg/ml	[8]
Curcuma aeruginosa	Ethanol	593.2 µg/ml	
Alpinia purpurata	n-hexsane	109 ppm	[16]
	n-hexane nanoparticles	86.783 ppm	
Kaempferia galanga	acetone	4.78 µg/ml	[18]
	Methanol	9.77 µg/ml	
	Petroleum ether	6.76 µg/ml	
	Chloroform	7.24 µg/ml	

The cytotoxic activity test of the ethanol extract of Temu putih (Curcuma zedoaria) has a high potential for cytotoxic activity using the BSLT method at concentrations of 25, 50, 75, and 100 ppm, the LC_{50} value in the ethanol extract Curcuma zedoaria is 22.86 ppm. Temu putih (Curcuma zedoaria) contains active compounds of the flavonoids, tannins and saponins, besides that it also contains curcuminoid chemical compounds, RIP (Ribosome Inacting Protein), isocurcumenol, demothxycurcumin, bisdemothxycurcumin, epicurzerenone, curdione, and ethylpycin. Disable the function of cancer cell growth and inhibit the growth of cancer cells.[3]

The cytotoxic activity of the ethanol extract of Temulawak (Curcuma xanthorrhiza Roxb.) Using the BSLT method shows an IC_{50} value of 65.09 µg/mL at a concentration of 10- 500 mg L^{-1}. The results of this study indicate that the ethanol extract of Temulawak (Curcuma xanthorrhiza Roxb.) Has cytotoxic activity and also shows the best bioactivity product.[7]

The cytotoxic activity of the ethanol extract of the medicinal plant Temulawak (Curcuma xanthorrhiza Roxb.) and Curcuma aeruginosa using the BSLT method showed LC_{50} values of 210.3 µg/ml and 233.6 µg/ml at concentrations of 10, 100, 500, and 1000 µg/ml. In this test, Temulawak (Curcuma xanthorrhiza Roxb.) Has a lower LC_{50} value than Curcuma aeruginosa. The ethanol extract of both plants showed the presence of antioxidants and phenolic compounds so that they have the potential to be anticancer.

The cytotoxic activity of n-hexane extract and nanoparticle extract of n-hexane of red galangal (Alpinia purpurata) using the BSLT method showed LC_{50} values of 109.668 µg/mL and 86.783 µg/mL. The results obtained on the n-hexane extract nanoparticles had a smaller LC_{50} value than the n-hexane extract so that the red galangal n-hexane extract nanoparticles had stronger cytotoxic activity. The secondary metabolites in red galangal are flavonoids, alkaloids, tannins, triterpenoids/steroids, and saponins.[16]

The cytotoxic activity of the acetonic, methanol, petroleum ether and chloroform extracts of kencur rhizome (Kaempferia galanga) using the BSLT method showed LC_{50} values of 4.78 µg/ml,

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77 µg/ml, 6.76 µg/ml, and 7.24 µg/ml while The LC_{50} of vincristine sulphate is 0.52 µg/ml. All extracts showed moderate cytotoxic activity when compared with the standard drug vincristine sulphate. The results of this study indicate that the plant extract has a cytotoxic activity.[18]

Table 2. Cytotoxic activity test on rhizome plants using the MTT method

Plant Name	Sample	cancer cells	Nilai IC_{50}	References
Curcuma mangga val	essential oil	HeLa	122.462 µg/ml	[4]
Curcuma xanthorrhiza Roxb.	essential oil	YMB-1	3.20 µg/ml	[5]
	Xanthorrhizole	YMB-1	2.88 µg/ml	
Curcuma xanthorrhiza Roxb.	Methanol	T47D	19.15 µg/ml	[6]
	Ethyl acetate	T47D	17.07 µg/ml	
Boesenbergia pandurata	Ethanol 70%	HeLa	87 µg/ml	[9]
		WiDr	76 µg/ml	
Boesenbergia pandurata	Ethanol 90%	HeLa	56 µg/ml	[10]
Zingiberofficinale Roscoe var. Rubrum	n-hexsane	HeLa	20.35 µg/ml	[11]
	Ethyl acetate	HeLa	27 µg/ml	
	Ethanol	HeLa	35.35 µg/ml	
Zingiber officinale	essential oil	HO-8910	5.47 µg/ml	[12]
		Bel-7402	2.18 µg/ml	
Curcuma longa L.	essential oil	HeLa	36.6 µg/ml	[13]
Zingiber officinale R	essential oil	HeLa	129.9 µg/ml	
Zingiber ottensii L	Ethanol	MCF-7	60 µg/ml	[14]
Zingiber zerumbet L	Ethanol	MCF-7	50 µg/ml	
Nicolaia speciosa Horan	Ethanol	MCF-7	625 µg/ml	
Curcuma domestica val	essential oil	HeLa	91.833 µg/ml	[15]
Curcuma aeruginosa	essential oil	MCF-7	161 µg/ml	[17]
Curcuma zanthorrhiza	essential oil	MCF-7	139.8 µg/ml	
Curcuma ochrorhiza	Hexane	T(CEM-SS)	6 µg/ml	[19]
	dichloromethane	T(CEM-SS)	>30 µg/ml	
	Methanol	T(CEM-SS)	>30 µg/ml	
	Zerumbone	T(CEM-SS)	0.6 µg/ml	
	Zederone	T(CEM-SS)	1.6 µg/ml	
Curcuma heyneana	Petroleum ether	T(CEM-SS)	>30 µg/ml	
	Chloroform	T(CEM-SS)	>30 µg/ml	
	Acetone	T(CEM-SS)	>30 µg/ml	
	Oxycurcumenol epoxide	T(CEM-SS)	13.3 µg/ml	
	Curcumenol	T(CEM-SS)	11.9 µg/ml	
	Isocurcumenol	T(CEM-SS)	12.6 µg/ml	
	Standard doxorubicin	T(CEM-SS)	0.1 µg/ml	
Curcuma mangga	Ethanol	MCF-7	27.9	[20]

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			±0.3µg/mL
		KB	24.6 ± 0.7µg/mL
		A549	30.7 ± 2.0 µg/mL
		Ca Ski	1.5 ± 0.2 µg/mL
		HCT 116	36.8 ± 3.8µg/mL
		HT-29	22.0 ± 1.1µg/mL
		MRC-5	>100µg/mL
	n-hexsane	MCF-7	8.1 ± 0.2µg/mL
		KB	15.4 ± 1.7µg/mL
		A549	17.4 ± 0.6 µg/mL
		Ca Ski	11.4 ± 1.0µg/mL
		HCT 116	31.5 ± 0.1µg/mL
		HT-29	17.9 ± 0.3µg/mL
		MRC-5	>100µg/mL
	Ethyl acetate	MCF-7	47.1 ± 0.5µg/mL
		KB	23.6 ± 0.8 µg/mL
		A549	21.2 ± 0.7µg/mL
		Ca Ski	>100µg/mL
		HCT 116	29.4 ± 0.2µg/mL
		HT-29	18.5 ± 0.1 µg/mL
		MRC-5	>100µg/mL

The cytotoxic activity of the L-asparaginase enzyme from kunyit putih (Curcuma mango Val.) extract using the MTT method against HeLa cancer cells showed an LC_{50} value of 122.462 µg/mL. It can be concluded that the L-asparaginase enzyme from white turmeric extract can inhibit the growth of Hela cells, but it is less potential as an anticancer agent based on NCI (National Cancer Institute) standards.[4]

The cytotoxic activity of essential oils and xanthorrhizol from the rhizome of Curcuma xanthorrhiza Roxb. using the MTT method against cancer cells YMB-1 showed IC_{50} values of 3.20 µg/mL and 2.88 µg/mL. Temulawak (Curcuma xanthorrhiza Roxb.) is a plant known to have cytotoxic activity against cancer cells or function as an anticancer. One of the active compounds of Temulawak that has been studied to have activity against some cancer cells is xanthorrhizol. Based on the LC_{50} value, it can be seen that the cytotoxic activity of essential oils is not much different when compared to the cytotoxic activity of xanthorrhizol.[5]

The cytotoxic activity of methanol extract, ethyl acetate fraction and isolate on the rhizome of Temulawak (Curcuma xanthorrhiza Roxb.) using the MTT method against cancer cells T47D showed IC_{50} values of 19.15 µg/mL, 17.07 µg/mL, and 19.22 µg/mL. By using ethyl acetate fraction, and ethanol extract of Curcuma xanthorrhiza Roxb.

rhizome has anti-proliferative activity against T47D breast cancer cells.[6]

Cytotoxic activity of interstellar ethanolic extracts using the MTT method against cervical cancer HeLa and colon cancer cells WiDr showed IC_{50} values of 87 µg/mL and 76 µg/mL. The low IC_{50} value (<100 µg / mL) indicates that the ethanol extract of Temu Kunci has the potential to be developed as a chemoprevention agent in cervical cancer and colon cancer. The rhizome plant of Temu Kunci has the main cytotoxic content of Panduratin A. This is proven by research that pandurate a contained in Temu Kunci can inhibit the growth of MCF7 breast cancer cells and HT-29 colon adenocarcinoma cells in humans through COX- inhibition. Two which is an important factor in the development of inflammation and tumour cells. The exploration of Temu kuci extract as a chemopreventive agent is expected to be an alternative cancer therapy.[9]

The cytotoxic activity of the ethanol extract of Temu Kunci rhizome (Boesenbergia pandurata Roxb.) using the MTT method against HeLa and Vero cells showed IC_{50} values of 56 µg/mL and 125 µg/mL. Rizoma Boesenbergia pandurata (Roxb.) contains active compounds with anticancer properties. The results showed that the ethanol extract of Boesenbergia pandurata (Roxb.) was more cytotoxic to HeLa cells than Vero cells. The extract had higher anti-proliferative and apoptotic activity in HeLa than Vero cells.[10]

The cytotoxic activity of the ethanol extract, n-hexane fraction and ethyl acetate of Red Ginger (Zingiber officinale Roscoe var. Rubrum) using the MTT method on HeLa cells showed IC_{50} values of 35.350 µg/mL, 20.350 µg/mL and 27 µg/mL. The three samples, the n-hexane fraction of red ginger was the fraction that had the highest cytotoxic effect compared to the ethyl acetate fraction and the ethanol extract of red ginger. The n-hexane fraction contains one class of the same compounds, namely terpenoids, flavonoids and alkaloids. The ginger plant has a cytotoxic activity that has anti-cancer properties.[11]

The cytotoxic activity of ginger (Zingiber officinale) essential oil using the MTT method against HO-89810 and Bel-7402 cancer cells showed IC_{50} values of 52.47 µg/ml and 2.18 µg/ml, from these results Bel-7402 cancer cells had an effect. highest cytotoxic compared to cancer cells HO-89810. Different cytotoxic activity against the two cancer cell lines in humans was generally investigated, a dose-dependent decrease in the viability of the two tumour cell lines was observed at a concentration of 0.000625% (v/v), the viability of cells treated with ginger essential oil for HO - 89810 and Bel-7402 were 97.37% ± 3.49, and 74.51% ± 6.46, respectively, at a concentration of 0.01% (v/v), ginger essential oil showed strong cytotoxicity against the two lines. cell viability for HO-89810 and Bel-7402 was 39.17% ± 6.63, and 28.46% ± 8.42, respectively, the concentrations gave 50% inhibition (IC_{50}) value of ginger essential oil against HO- 8910 and Bel-7402 were 0.00547 µg/ml, and 0.00218 µg/ml, respectively. Bel-7402 is a more sensitive cell line compared to HO-8910.[12]

The cytotoxic activity of the essential oils of white turmeric (Curcuma longa L.) and ginger (Zingiber officinale R.) plants using the MTT method against HeLa cancer cells showed IC_{50} values of 36.6 µg/mL, and 129.9 µg/mL, respectively. The results of the IC_{50} value of Curcuma longa L. rhizome shows the highest cytotoxic activity so that it has the potential as an anticancer agent for cervical cancer cells compared to ginger (Zingiber officinale R.).[13]

The cytotoxic activity of ethanol extracts in three species of plants from the Zingiberaceae tribe that are widely grown in Indonesia, namely bangle ghost (Zingiber ottensii L.), lempuyang Gajah (Zingiber zerumbet L.), and Kecombrang (Nicolaia speciosa Horan) by using the MTT method against MCF cells. -7 indicates the IC_{50} values are 60 µg/ml, 50 µg/ml, and 625 µg/mL. The results showed that two of the three rhizome extracts tested showed strong cytotoxic power, from the results of this study it can be concluded that the ethanol extracts of the rhizome of bangle ghost and lempuyang Gajah have great potential to be further researched and developed as a source of raw materials for new anti-cancer drugs. Therefore it is advisable to continue the research by conducting cytotoxicity tests on polar, semi-polar and non-polar fractions of the extract so that later the cytotoxic active substances can be isolated and identified. In addition, it is also recommended to carry out further research to determine the mechanism of action of the anticancer of the active substance in the rhizome.[14]

The cytotoxic activity of the L-asparaginase enzyme in the extract of turmeric (Curcuma domestica Val) using the MTT method against HeLa cells showed an LC_{50} value of 91.833 µg/mL. The extract cytotoxicity test was made with a concentration series of 1000 µg/mL, 500 µg/mL, 250 µg/mL, 125 µg/mL, 62.5 µg/mL, 31.25 µg/mL, 15.625 µg/mL, 7.812 µg/mL, 3.906 µg/mL, and

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1.95 µg/mL in RPMI medium. The L-asparaginase enzyme isolate from turmeric is able to inhibit the growth of HeLa cells, but has less potential as an anticancer agent based on NCI standards.[15]

The cytotoxic activity of the rhizome essential oil of Curcuma aeruginosa and Curcuma zanthorrhiza using the MTT method against cancer cells MCF-7 showed IC_{50} values of 161.0 µg/mL and 139.8 µg/mL. The essential oil was obtained from the rhizomes of Curcuma aeruginosa and Curcuma zanthorrhiza by the hydrodistillation method. The composition of the volatile essential oils was analyzed using gas chromatography and mass spectrophotometry (GC/MS). The cytotoxic activity contained in the essential oils of Curcuma aeruginosa and Curcuma zanthorrhiza showed lower activity. The main compounds of Curcuma aeruginosa are tropolone (18.1%), eucalyptol (17.9%), and curcumol (5.7%), while Curcuma zanthorrhiza is xanthorrhizol (26.8%), curcumene (17.0%), ar-curcumene (15.0%), and germacrone (5.4%). [17]

The cytotoxic activity of the extracts of Hexane, methanol, dichloromethane zerumbone and zederone from Curcuma ochrorhiza using the MTT method against T cells (CEM-SS) showed IC_{50} values of 6 mg/mL, > 30 mg/mL, > 30 mg/mL, 0.6 mg/mL, and 1.6 mg/mL. Meanwhile, cytotoxic activity against petroleum ether extract, chloroform, acetone, oxycurcumenol epoxide, curcumenol, isocurcumenol and doxorubicin standard from Curcuma heyneana using the MTT method against T cells (CEM-SS) showed IC_{50} values > 30 mg/mL, > 30 mg/mL, > 30 mg/mL, 13.3 mg/mL, 11.9 mg/mL, 12.6 mg/mL, and 0.1 mg/mL. The result of the IC_{50} value of all extracts in both plants had very strong cytotoxic activity. Curcuma ochrorhiza and Curcuma heyneana are two zingiberaceous species commonly used in traditional medicine in Indonesia. The search for phytochemicals in these rhizomes has resulted in the isolation of six sesquiterpenes, namely zerumbone, furanodienone, zederone, oxycurcumenol epoxide, curcumenol and isocurcumenol, along with the phytosterols stigmasterol and sitosterol. Zerumbone and furanodienone were obtained for the first time for Curcuma ochrorhiza while oxycurcumenol epoxide was only introduced to Curcuma heyneana. [19]

Cytotoxic activity of extracts and fractions (methanol, hexane and ethyl acetate) of Curcuma Mangga using the MTT method against seven human cancer cells, namely hormone-dependent breast cell line (MCF-7), nasopharyngeal epidermoid cell line (KB), lung cell line (A549), cervical cell line (Ca Ski), colon cell line (HCT 116 and HT-29), and one non-cancerous human fibroblast cell line (MRC-5) showed the IC_{50} value of ethanol extract on MCF-7 cancer cells, KB, A549, Ca Ski, HCT 116, HT-29, and MRC-5 are 27.9 ± 0.3 µg/mL, 24.6 ± 0.7 µg/mL, 30.7 ± 2.0 µg/mL, 31.5 ± 0.2 µg/mL, 36.8 ± 3.8 µg/mL, 22.0 ± 1.1 µg/mL, and > 100 µg/mL, for IC_{50} the n-hexane fraction in cancer cells MCF-7, KB, A549, Ca Ski, HCT 116, HT-29, and MRC-5 are 8.1 ± 0.2 µg/mL, 15.4 ± 1.7 µg/mL, 17.4 ± 0.6 µg/mL, 11.4 ± 1.0 µg/mL, 31.5 ± 0.1 µg/mL, 17.9 ± 0.3 µg/mL, and > 100 µg/mL. The IC_{50} value of ethyl acetate fraction in cancer cells MCF-7, KB, A549, Ca Ski, HCT 116, HT-29, and MRC-5 was 47.1 ± 0.5 µg/mL, 23.6 ± 0.8 µg/mL, 21.2 ± 0.7 µg/mL, > 100 µg/mL, 29.4 ± 0.2 µg/mL, 18.5 ± 0.1 µg/mL, and > 100 µg/mL. From these results, the methanol extract and fractionation (hexane and ethyl acetate) on Curcuma magga showed a good cytotoxic effect against seven cancer cells because it had an IC_{50} value <100 µg/mL and had high cytotoxic activity so that it was effective as an anticancer agent. [20]

IV. CONCLUSION

Based on the 13 rhizome plants in Indonesia that have been described, including showing strong cytotoxic abilities, 8 of which showed very strong cytotoxic activity, namely, Curcuma heyneana showed an IC_{50} value of 0.1 µg/ml by the MTT method (3-(4,5-dimethylthiazol)-2-yl)-2,5-diphenylthiazol bromide), Kaempferia galanga which shows an IC_{50} value of 0.52 µg/ml with the BSLT (Brine Shrimp Lethality Test) method, Curcuma mango shows an IC_{50} value of 1.5 ± 0.2 µg/mL using the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylthiazol bromide), Curcuma ochrorhiza showed an IC_{50} value of 1.6 µg/ml by the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylthiazol bromide), Zingiber officinale which showed an IC_{50} value of 2.18 µg/ml with the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylthiazol bromide), Curcuma xanthorrhiza Roxb showed an IC_{50} value of 2.88 µg/ml with the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylthiazol bromide), Zingiber officinale Roscoe var. rubrum showed an IC_{50} value of 20.350 µg/ml with the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylthiazol bromide), and Curcuma zedoria showed an LC_{50} value of 22.86 ppm with the BSLT (Brine Shrimp Lethality method) Test)

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