

Potential of Indonesian Herbal as an Anti-Cancer Therapy: A Systemic Review of in vitro Studies

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Introduction: In the world, the second most common cause of mortality is cancer, and its prevalence is increasing in both developing and developed states. Cancer therapy has severe side effects for people with cancer. The selection of natural ingredients in the form of herbal plants is expected to provide therapeutic effectiveness with low side effects. A total of 6000 plant species are utilized as herbal medicines in Indonesia by the local population for various ailments.

Objective: To describe the potential of Indonesian herbal plant products as a cancer therapy in vitro.

Methods: This systematic review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-SR) guidelines. The selection of articles published in the last 5 years (2018–2023) from Pubmed, Ebsco, Garuda portal, ScienceDirect, Cochrane, and Webscience was carried out in January 2023 with the keyword “Indonesian herbal” AND/OR “Anti-cancer” AND/OR “In Vitro”. Risk of bias assessment using OHAT tools.

Results: A total of 1,816,511 articles then through inclusion, exclusion criteria screening, and the risk of bias were obtained 23 (twenty-three) low risk of bias articles. Some herbal plant products such as Soursop (*Annona muricata L.*), Nyamplung (*Calophyllum spp.*), Benalu Cengkeh/Clove Benalu (*Dendrophthoe pentandra*), Rumput Mutiara/Pearl Grass (*Hedyotis corymbosa L.*), Rasamala (*Altingia excelsa*), Sarang Semut/Anthill plant (*Myrmecodia pendans*), Basil (*Ocimum sanctum Linn.*), and Tepus (*Zingiber griffithii*) showed different potentials for activity as an in vitro anti-cancer therapy. The three Indonesian herbal plants that are most studied in vitro as anti-cancer are Soursop, Rasamala, and Benalu Cengkeh/Clove Benalu.

Conclusion: The most widely studied Indonesian herbal plant in vitro as an anti-cancer is Soursop, while the anti-cancer activity that is widely reported is by inhibiting cell proliferation through intrinsic pathways.

Keywords: Indonesian herbal, anti-cancer, in vitro

Introduction

In the world, the second most common cause of mortality is cancer, and its prevalence is increasing in both developing and developed states. One of the non-communicable diseases affecting the world’s population, including Indonesia, is cancer. In 2020, 10.3 million cancer-related deaths and 19.3 million new cases are anticipated globally.¹ Basic Health Research confirms that cancer has risen to the sixth most common cause of death in Indonesia, has a prevalence of 478 cases per 100,000 individuals.² Based on data from GLOBOCAN (Global Burden of Cancer) / IARC (International Agency of Research on Cancer) in 2020, the ten highest cancer cases in Indonesia were breast, lung, colorectal, uterine cervix, liver, nasopharynx, prostate, non-Hodgkin’s lymphoma, leukemia, and ovaries.³

Despite advancements in disease diagnosis techniques, therapy, and preventive measures, one of the leading causes of death and a severe form of metabolic syndrome is cancer. It is unclear what variables contribute to the development of cancer. A list of internal and external parameters has identified factors related to cancer. External factors including pollution, radiation, tobacco, smoking, drug effects, certain metals, and infectious agents. The World Health Organization (WHO) lists smoking, alcohol consumption (both light and hard), obesity, and physical inactivity among the primary

triggers. The internal factors of cancer, which are unchangeable and endogenous in origin, are mostly associated with spontaneous mutations during deoxyribose nucleic acid (DNA), aging, hormonal changes, and inflammation.^{4,5}

Cancer treatment consists of four major modules that integrate surgery, radiation, chemotherapy, and immunotherapy.⁵ Conventional strategies of cancer cell management still rely on surgery, radiotherapy, chemotherapy, and targeted therapies.⁶ Frequent failures in cancer treatment efforts, especially with chemotherapy, are due to the low selectivity of anti-cancer drugs and the selectivity of the cancer cells themselves to chemotherapy agents.⁷ Cancer conventional therapy has severe side effects for people with cancer, therefore due to side effects and expensive treatments, now research on cancer therapy is more inclined to natural sources such as herbal plants.⁸ This is consistent with what Mohammed et al stated, who claimed that plant-based natural products have been utilized to treat cancer and that more than 3000 plant species have been identified as having anticancer activity.⁴ Mohammed et al further claimed that plant-based products have provided workable replacements and adjuvants to current anti-cancer chemotherapies as a part of alternative and complementary therapy.⁹ Herbal plants have less side effects than conventional cancer therapies.⁸ A total of 6000 plant species are utilized as herbal medicines in Indonesia by the local population for various ailments.^{10,11}

The aim of this systematic review was to describe the potential of Indonesian herbal plant products as a cancer therapy *in vitro*.

Method

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-SR) guidelines. The method of this systematic review used the Population, Intervention, Comparison, and Outcome (PICO) method according to the purpose of writing. The population in this systematic review is the cancer cell line; intervention with herbal plant products; comparison with control groups; the result is an Indonesian herbal plant product that has the potential to prevent the growth of cancer cells *in vitro*.

The search for articles to be studied in this systematic review was carried out on 6 (six) electronic databases, namely Pubmed, Ebsco, Garuda portal, Scencedirect, Cochrane, and Webscience using the keyword “Indonesian herbal” AND/OR “Anti-cancer” AND/OR “In Vitro”.

These systematic review article search inclusion criteria are limited to articles published in the last 5 years (2018 to 2023), indexed and accredited articles, in English and Indonesian, full text and accessible, *in vitro* research, and human cancer cell line. The articles exclusion criteria are clinical trial research, a combination of Indonesian herbal plants, and articles that are literature review and systematic review. The next step is to evaluate each article’s risk of bias in order to measure its quality. The evaluation of research quality and bias risk according to the eligibility criteria is carried out in accordance with the Office of Health Assessment and Translation (OHAT) tool. OHAT tool requires at least 2 (two) people to assess, consisting of 6 (six) domains, and 8 (eight) questions. The response options for each question consist of “definitely low risk of bias”, “probably low risk of bias”, “probably high risk of bias”, or “definitely high risk of bias”. After answering all the questions, the value of each question is accumulated and divided by the number of questions. Then the results are divided into 3 tier consisting of low (1), moderate (2), and high risk of bias (3) results.¹²

Discussion

A total of 1,816,511 (one hundred and sixteen thousand five hundred and eleven) articles were obtained from the search. The next stage is applied articles from the last 5 (five) years from 2018 to 2023 so that the total articles issued are 1,225,947 (one million two hundred and twenty-five thousand nine hundred and forty-seven) articles so that the data is screened as many as 590,564 (five hundred and twenty thousand five hundred and sixty-four) articles. Then the predetermined inclusion and exclusion are applied as well as manual searches so that the final results of 23 (twenty-three) appropriate articles are obtained. Following the assessment of the risk of bias, 23 (twenty-three) articles with low risk of bias and none with high risk of bias are discovered. The process of article search and article selection can be seen in (Figure 1), while the risk of bias assessment is shown in (Table 1).

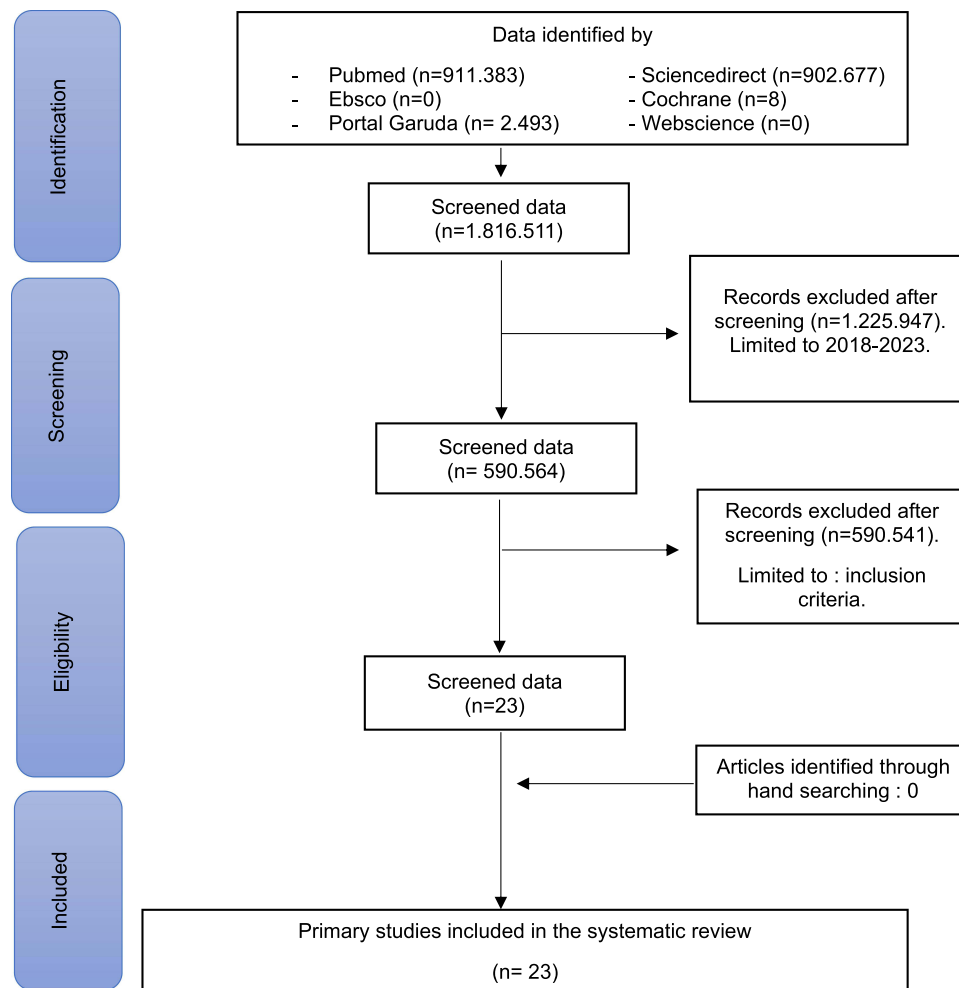


Figure 1 Flowchart of the Article Search Process based on the PRISMA-SR Guidelines.

The following stage is a synopsis of each article that includes data on the author, year, journal quality, herbal plants, where they came from, model systems, different forms of cancer, test procedures, mechanisms of action, outcomes, and conclusions (Table 2).

Based on (Table 2), it is shown that the year that the most in vitro studies were carried out in cancer was in 2019. A total of 6 articles are head and neck cancer and 17 articles are not head and neck cancer. Among the cancers that are not the most head and neck cancer, namely breast cancer, as many as 6 articles. The most frequently used human cancer cell lines in the reviewed articles are *SP-C1*, *MCF-7*, and *HeLa*.

The most widely researched Indonesian herbal plant in vitro as an anti-cancer is Soursop (*Annona muricata L.*), as many as 12 (twelve) articles. The most widely taken part of Soursop is in the form of leaves as many as 10 (ten) articles, then 1 (one) article in the form of fruit, and 1 (one) article in the form of roots. Among the three forms, the fruit does not provide cytotoxic activity against cancer cells. In general, cytotoxic research uses soursop leaves more often than fruits, This is as a result of their higher phytochemical content. When compared to its presence in soursop leaves, the phytochemical content of soursop fruit, which includes alkaloids, annonaceous acetogenin compounds (AGEs), and phenols, demonstrates that each phytochemical category has a smaller variance in the fruit.¹⁷

Soursop has the potential to be anti-cancer^{14,15,17-19,31} because it contains various compounds such as flavonoids, AGEs, and alkaloids that have anticancer capabilities. AGEs have the ability to inhibit mitochondrial complex I which can inhibit the formation of adenosine triphosphate (ATP), resulting in a decrease in ATP in cancer cells so that it can inhibit proliferation and induce apoptosis of cancer cells.^{13,21,32} Preliminary research using molecular docking

Table 1 Risk of Bias Assessment Results and Quality of Articles Reviewed Using OHAT Tools

		Risk of Bias Question								Overall Risk of Bias		
		Randomization	Allocation Concealment	Blinded Study	Missing Outcome Data	Exposure Characterization	Outcome Assessment	Outcome Reported	Other Bias	Score	Tier	Conclusion
Review	Fatmawati, dkk. ¹³	+2	+2	+2	+1	+2	+2	+2	+1	+1,75	I	Low Risk of Bias
	Fertilita, dkk. ¹⁴	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Suhendar U. ¹⁵	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Ibrahim A.A., dkk. ¹⁶	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Widyanto R.M., dkk. ¹⁷	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Abdullah M, dkk. ¹⁸	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Bhanuwati AV and Pakpahan A. ¹⁹	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Ramandhita AP, dkk. ²⁰	+2	+2	+2	+1	+2	+2	+2	+1	+1,75	I	Low Risk of Bias
	Tulloh NRA and Andriane Y. ²¹	+2	+2	+2	+1	+2	+2	+2	+1	+1,75	I	Low Risk of Bias
	Astuti Y, et al ²²	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Fathani IJ and Miladiyah I. ²³	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Mutiah R. ²⁴	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Susilowati, dkk. ²⁵	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Novitasari D, dkk. ²⁶	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Anwar R, et al ²	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Anwar R, et al ⁶	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Anwar R, et al ⁷	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Anwar R, et al ²⁷	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Lestari W, et al ²⁸	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
	Wihadmadyatami H, et al ²⁹	+2	+2	+2	+2	+2	+2	+2	+1	+1,875	I	Low Risk of Bias
Lutfia A, et al ³⁰	-1	+2	+2	+2	+2	+2	+2	+1	+1,5	I	Low Risk of Bias	
Hasan AEZ, et al ³¹	-1	+2	+2	+2	+2	+2	+2	+1	+1,5	I	Low Risk of Bias	
Nugraha AS, et al ¹¹	+2	+2	+2	+2	-1	+2	+2	+1	+1,5	I	Low Risk of Bias	

Notes: Definitely Low Risk of Bias +2: Probably Low Risk of Bias +1: Probably High Risk of Bias -1

Table 2 Characteristic and Comparison Result of Researched Article

No.	Author	Year	Quality of Journal	Herbal Plant	Origin of Herbal Plant	Model System	Type of Cancer	Method Assay	Mechanism of Action	Result	Conclusion
1.	Fatmawati, dkk. ¹³	2018	National Accredited	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	Semarang	MCF-7 cell	Breast cancer	MTT Assay	Soursop leaf extract causes some cancer cells to damage the defense mechanism against ROS so that they cannot use additional anti-oxidants for the repair process causing a buildup of free radicals in cancer cells which has the effect of triggering apoptosis in cancer cells	The IC50 value obtained in MCF-7 cells was 44.94 µg/mL	Soursop extract is selective cytotoxic against MCF-7 breast cancer cells
2.	Fertilita, dkk. ¹⁴	2020	S2	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	East Java	T47D cell	Breast cancer	MTT Assay	Decreases BCL2 protein regulation, increases Bax, inhibits mitochondrial I complexes, and inhibits NADH ubiquinone-oxidase on the plasma membrane of cancer cells causing apoptosis	The IC50 value of <i>Annona muricata</i> leaf ethanol extract against T47D cancer cells was 109.91 ±3.04 µg/mL	Soursop (<i>Annona muricata</i>) leaf ethanol extract has the potential to inhibit the proliferation of T47D cancer cells
3.	Suhendar U. ¹⁵	2018	S3	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	Sukasirna (Cianjur I), Sukasarana (Cianjur II), Ciharang (Cianjur III), Coral Pakpak (Sukabumi I), Coral Pakpak (Sukabumi II), and Sukasari (Sukabumi III)	MCF-7 cell	Breast cancer	MTT Assay	Inhibits the proliferation of cancer cells	Cianjur I's IC50 value was 24.72; Cianjur 2 of 17.26; Sukabumi 1 of 22.39; Sukabumi 2 of 12.05; Sukabumi 3 by 19.49	All extracts exhibit cytotoxic activity against MCF-7 cancer cells. Cianjur III soursop leaf extract has the highest IC50 value, which is 9.12 µg/mL
4.	Ibrahim A.A., dkk. ¹⁶	2020	S3	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	Kota Batu (East Java)	MCF-7 cell	Breast cancer	MTT Assay	Stop the cell cycle in phase G1 and decrease the number of cells in phase S by decreasing the expression of cyclin D1, an important regulatory protein in the cell cycle	IC50 value of soursop leaf ethanol extract (<i>Annona muricata</i>) against MCF-7 cancer cells is 117.87 µg/mL	<i>Annona muricata</i> leaf ethanol extract is effective in inhibiting the growth of MCF-7 breast cancer cells

(Continued)

Table 2 (Continued).

No.	Author	Year	Quality of Journal	Herbal Plant	Origin of Herbal Plant	Model System	Type of Cancer	Method Assay	Mechanism of Action	Result	Conclusion
5.	Widyanto R.M., dkk. ¹⁷	2019	S2	<i>Annona muricata</i> (Soursop) Note: Soursop fruit extract	Materia Medika (East Java)	HeLa cell	Cervix cancer	MTT Assay	–	IC50 value of soursop juice in HeLa cells is 2522.33 µg/mL	Soursop juice has very low anti-oxidant activity and has no potential as an anti-cancer against HeLa cells in vitro.
6.	Abdullah M, dkk. ¹⁸	2019	S2	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	West Java	HT-29 cell	Colorectal cancer	MTT Assay	Inhibits the activity of cyclin protein D1	CC50 soursop leaf ethanol extract is 278 µg/mL	Soursop leaf ethanol extract may decrease the viability of HT-29 colon cancer cells
7.	Bhanuwati AV and Pakpahan A. ¹⁹	2022	S1	<i>Annona muricata</i> (Soursop) Note: Ethanol extract; Fractions of ethanol, ethyl acetate, and n-hexane	Bandung (West Java)	HSC-3 cell	Oral Squamous Cell Carcinoma	CCK-8 assay	Reduces cancer cell growth by interfering with the G1/S and G2/M phases of the cell cycle	The IC50 value of <i>A. muricata</i> ethyl acetate fraction extract against HSC-3 cancer cell is 76.66 µg/mL; IC50 value of n-hexane fraction extract is 84.14 µg/mL; and IC50 value of ethanol fraction extract is 101,32 µg/mL	The ethanol, ethyl acetate, and hexane fractions of <i>Annona muricata</i> leaf extract have moderate cytotoxic activity
8.	Ramandhita AP, Yuniarti L, Hanum L ²⁰	2022	National Accredited	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	Lembang (West Bandung)	HepG2 cell	Liver cancer	MTT Assay	Nanoparticles trigger easier cellular internalization through the pores of the endothelium to reach the cancer cells and more quickly or efficiently due to the charge on the surface of the nanoparticles which causes electrostatic bonds with cancer cells to be stronger	IC50 value of soursop leaf extract alginate nanoparticles against HepG2 liver cancer cell is 14.5 µg/mL	Alginate nanoparticles of soursop leaf extract have a high cytotoxic activity against HepG2 cancer cell
9.	Tulloh NRA and Andriane Y ²¹	2022	National Accredited	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	–	HTB183 cell	Lung cancer	MTT Assay	Nanoparticles trigger easier cellular internalization through the pores of the endothelium to reach the cancer cells and more quickly or efficiently due to the charge on the surface of the nanoparticles which causes electrostatic bonds with cancer cells to be stronger	IC50 value of soursop leaf extract alginate nanoparticles against HTB183 lung cancer cell is 31,261 278 µg/mL	Soursop leaf extract alginate nanoparticles have a moderate cytotoxic activity against HTB183 cancer cell

10.	Astuti Y, et al ²²	2022	S3	<i>Annona muricata</i> (Soursop) Note: Ethanol extract	Tawangmangu	Widr cell	Colorectal cancer	MTT Assay	Induces cell viability loss, morphological changes, membrane mitochondrial potential loss, and cell termination in the G0/G1 phase	The IC50 value of soursop leaf ethanol extract against Widr cells ranges from 0.03124–0.5 µg/mL at a dosage range of 33.125–450 µg/mL	Soursop leaf ethanol extract against Widr cancer cells has a high cytotoxic activity
11.	Hasan AEZ, et al ³¹	2022	Q1	<i>Annona muricata</i> (Soursop) Note: Ethyl acetate extract endophytic mushroom of Soursop leaf	Sukabumi, Cianjur, Garut	HeLa cell	Cervix cancer	MTT Assay	Inhibits cell proliferation	All three endophytic mushroom extracts (Sir-CA1, Sir-G2, and Sir-SM2) showed IC values of <30 lg mL	All three endophytic mushroom extracts (Sir-CA1, Sir-G2, and Sir-SM2) have cytotoxic effects against HeLa cancer cell
12.	Nugraha AS, et al ¹¹	2019	Q3	<i>Annona muricata</i> (Soursop) Note: Methanol extract; alkaloid fraction; bioactive compound of coclaurine, reticuline, argentinine, atherosperminine, xylopinine	Malang	HL-60, A549, HepG2 cell	Leukemia, lung, and liver cancer	MTT Assay	Inhibits cell proliferation	The IC50 value of xylopinine bioactive compound of <i>Annona muricata</i> root extract against cancer cells HL-60, A549, and HepG2 is between 20–80 µg/mL	Xylopinine bioactive compound of <i>Annona muricata</i> root extract has the highest cytotoxic effect among other compounds against HL-60, A549, and HepG2 cancer cell
13.	Fathani IJ and Miladiyah I ²³	2021	S2	<i>Calophyllum</i> spp. (Nyamplung) Note: Ethanol extract	–	Widr cell	Colorectal cancer	MTT Assay	Nyamplung fruit extract inhibits cancer cells through apoptosis and non apoptosis mechanisms (reducing NO production, cytoskeleton disintegration, and stimulation of cell death by autophagy).	The IC50 value of Nyamplung fruit shell ethanol extract in WiDr cell is 42.47 µg / mL, while the IC50 value of Nyamplung seed ethanol extract is 1030.41 µg / mL	Nyamplung seed ethanol extract is not cytotoxic to WiDr colorectal cancer cells, while Nyamplung fruit shell ethanol extract is moderately cytotoxic
14.	Mutiah R. ²⁴	2019	S5	<i>Dendrophthoe pentandra</i> (Benalu Cengkeh) Note: Ethanol extract	Kediri, Pekalongan, Sumatra and Kalimantan	T47D cell	Breast cancer	MTT Assay	<i>Dendrophthoe pentandra</i> ethanol extract inhibits proliferation of T47D cancer cell	<i>Dendrophthoe pentandra</i> ethanol extract from Kalimantan has IC50 value of 287.39 µg/mL, from Kediri of 304.79 µg/mL, from Pekalongan of 4646.34 µg/mL, and from Sumatra of 540.91 µg/mL	Extract from Kediri and Kalimantan have anti cancer effect against T47D cancer cell. Extract from Kalimantan has better cytotoxic effect than from Kediri against T47D cancer cell

(Continued)

Table 2 (Continued).

No.	Author	Year	Quality of Journal	Herbal Plant	Origin of Herbal Plant	Model System	Type of Cancer	Method Assay	Mechanism of Action	Result	Conclusion
15.	Susilowati, dkk. ²⁵	2022	S4	<i>Dendrophthoe pentandra</i> (Benalu Cengkeh) Note: Ethanol extract	Tawangmangu	HeLa cell	Cervix cancer	MTT Assay	Cytotoxic activity of ethanol extract parasite clove leaf against HeLa cell suspected to be able to go through cell cycle pathways as well as apoptosis	Ethanol extract of parasite clove leaf against HeLa cells showed an IC50 value of 43.90 µg/mL	Ethanol extract of parasite clove leaf with flavonoid compound has active moderate cytotoxic activity against HeLa cervical cancer cell
16.	Novitasari D, dkk. ²⁶	2018	S2	<i>Hedyotis corymbosa</i> L. (Rumput Mutiara) Note: Ethanol extract	–	4T1 cell	Breast cancer	MTT Assay	Ethanol extract <i>Hedyotis corymbosa</i> L. inhibits cell proliferation and modulating signaling pathway such as FoxM1 expression, STAT3, Jun N-terminal kinase, dan NF-κB in anti-cancer activity; inhibits cancer invasion by inhibiting activity of MMP-9; and inhibits cancer cell migration	Ethanol extract <i>Hedyotis corymbosa</i> L. has IC50 value of 400 µg/mL	Ethanol extract <i>Hedyotis corymbosa</i> L. has anti-cancer effect against 4T1 cancer cell
17.	Anwar R, et al. ²	2018	S2	<i>Altingia excelsa</i> (Rasamala) Note: Methanol extract; ethyl acetate fraction; bioactive compound of Kaempferol and Quercetin	Wayang Windu (Pengalengan, West Java)	SP-C1 cell	Tongue cancer	MTT Assay	Inhibits cell proliferation of SP-C1 cancer cell	Kaempferol compound IC50 value of Rasamala leaf extract is 2.50 µM; while quercetin IC50 value of Rasamala leaf extract is 2.31 µM	Quercetin has higher cytotoxic effect than kaempferol of Rasamala leaf extract, however all of them have high cytotoxic activity
18.	Anwar R, et al. ⁶	2018	S3	<i>Altingia excelsa</i> (Rasamala) Note: Ethyl acetate extract; A-E fraction; bioactive compound of kaempferol and quercetin	Wayang Windu (Pengalengan, West Java)	SP-C1 cell	Tongue cancer	MTT Assay	Inhibits cell proliferation of SP-C1 cancer cell by reducing proto onkogen c-myc expression	IC50 value of ethyl acetate extract against SP-C1 cell is 12.85 µg/mL, has a highest cytotoxic effect than others. IC50 value of quercetin bioactive is 0.70 µg/mL, has a higher cytotoxic activity than kaempferol compound	Ethyl acetate extract, water extract, quercetin and kaempferol compounds of Rasamala leaf (<i>Altingia excelsa</i>) has high cytotoxic activity against SP-C1 cancer cell

19.	Anwar R, et al ⁷	2019	S4	<i>Altingia excelsa</i> (Rasamala) Note: Ethyl acetate extract; A-E fraction; bioactive compound of 3,4-dihydroxy benzoic acid, gallic acid, apigenin	Wayang Windu (Pengalengan, West Java)	SP-C1 cell	Tongue cancer	MTT Assay	Inhibits cell proliferation of SP-C1 cancer cell	The compound 3,4-dihydroxy benzoic acid, gallic acid, and apigenin from ethyl acetate extract of <i>Altingia excelsa</i> (Rasamala) against SP-C1 cancer cells had IC50 values of 75.41 µg/mL, 17.92 µg/mL, and 12.96 µg/mL	These three compounds are secondary metabolites of Rasamala leaves that can inhibit the proliferation of human tongue cancer cells in vitro.
20.	Anwar R, et al ²⁷	2021	S3	<i>Altingia excelsa</i> (Rasamala) Note: Methanol extract; ethyl acetate, n-hexane, and water fraction; bioactive compound of kaempferol and quercetin	Wayang Windu (Pengalengan, West Java)	SP-C1 cell	Tongue cancer	MTT Assay	Kaempferol dan quercetin induces apoptosis can relate with MAPK cascade in inhibiting p90RSK activity, which p90RSK is inhibiting pro-apoptotic BAD. Increased apoptosis leads to increased activity of caspase-8 and -9.	The IC50 values of kaempferol and quercetin from acetylacetate extract Rasamala leaf are 0.72 µg/mL and 0.70 µg/mL. The bioactive compounds of kaempferol and quercetin induce increased caspase-8 and -9 activity	The kaempferol and quercetin compounds of acetylacetic extract Rasamala leaf can inhibit the proliferation of human SP-C1 tongue cancer cells in vitro
21.	Lestari W, et al ²⁸	2019	S1	<i>Myrmecodia pendans</i> (sarang semut) Note: Aqua extract	Bintuni (West Papua)	HSC-3 cell	Oral Squamous Cell Carcinoma	Flow cytometric analysis and qRT-PCR	Inhibits cell proliferation of SP-C1 cancer cell	The IC50 value of kaempferol from Rasamala leaf extract is 2.50 µM; while the IC50 quercetin value of Rasamala leaf extract is 2.31 µM	Quercetin has a higher cytotoxic effect than kaempferol in Rasamala leaf extract, but both have a high cytotoxic effect
22.	Wihadmadyatami H, et al ²⁹	2019	Q1	<i>Ocimum sanctum</i> Linn. (Basil) Note: Ethanol extract	Tawangmangu	Sel A549	Lung adenocarcinoma	MTT assay, Caspase-Glo 3/7 assay	Decrease cell viability and proliferation, increase intracellular ROS, affect SOD and GPx activity, so that increase apoptosis in A549 cell	Adhesion and viability examination showed that EEOS improved cell attachment and decreased cell viability at EEOS concentration of 100 µg/mL, EEOS induced apoptosis in A549 cells, EEOS showed a significant increase in ROS, EEOS showed an increase in expression levels of caspase-3, while this substance decreased the activity of the anti-apoptotic Bcl-2 protein	Ethanol extract <i>Ocimum sanctum</i> gives anti-cancer activity

(Continued)

Table 2 (Continued).

No.	Author	Year	Quality of Journal	Herbal Plant	Origin of Herbal Plant	Model System	Type of Cancer	Method Assay	Mechanism of Action	Result	Conclusion
23.	Lutfia A, et al ³⁰	2021	Q1	<i>Zingiber griffithii</i> (Tepus) Note: Ethyl acetate extract	Tahura Tongkoh Bukit Barisan (North Sumatra)	Viz. Panc-1, NBT-T2, HCT116 cell	Pancreas, gallbladder, and colon cancer	MTT Assay	Increased apoptosis	The IC50 values of compound 1 (Terpenoid-Alkaloids) against Panc-1, NBT-T2, and HCT116 cells are 0.05, 0.75, and 0.05 ppm; IC50 values for compound 2 (Sesterterpenoids) against Panc-1, NBT-T2, and HCT116 cells are 0.71, 0.30, and 0.67 ppm	Extract from the endophytic mushroom <i>Hypomontagnella monticulosa</i> Zg155U and its host <i>Zingiber griffithii</i> Baker provides a high anticancer effect

simulations proved that acetogenin derived from soursop has a strong bond with the B Cell Lymphoma-extra Large (BCL-xL) protein and has the potential to induce apoptosis from intrinsic pathways.³² In addition, AGEs are able to inhibit lactate dehydrogenase which is an enzyme that functions as an antioxidant so as to induce oxidative stress and trigger apoptosis and cell autophagy.²¹ Another active substance found in soursop leaves is quercetin. Quercetin is an anti-oxidant, however on the other hand it is able to induce apoptosis in cancer cells. The selectivity of soursop leaf extract to breast cancer cells is thought to be related to the quercetin content in soursop leaves which can trigger apoptosis in cancer cells but not in normal cells. Lamson and Brignall mentioned that some cancer cells have mechanism damage defenses against reactive oxygen species (ROS) so that these cells cannot utilize additional anti-oxidants for the repair process. This causes a buildup of free radicals in cancer cells which has an impact on the death of these cancer cells.¹³ In addition to AGE, flavonoids are also bioactive components that have a role in anticancer activity through apoptosis with mechanisms that are not much different from AGE. Flavonoids work as pro-oxidants in cancer cells. One of the mechanisms is to inhibit epidermal growth factor receptor/mitogen activated protein kinase (EGFR/MAPK) so that cell growth is inhibited.²⁰

The anticancer activity of soursop not only induces apoptosis and antiproliferation, but may decrease migration, motility and invasion of cancer cells.²⁰ Antiproliferative effects were also shown on *HL-60 cells* by inducing loss of cell viability, morphological changes, loss of mitochondrial potential of membranes, and capture of G0/G1 phase cells. This confirms the potential of soursop as an agent of chemotherapeutic and cytostatic activity in *HL-60 cells*.²² Previous research has shown that after pancreatic cancer cells *FG/COLO357* are given soursop leaf extract, the motility of these cancer cells decreases. Soursop leaf extract has also shown to inhibit migration and invasion of colorectal cancer cells *HT-29* and *HCT-119* significantly. The cytotoxic effect of alginate nanoparticles is greater than that of soursop leaf ethanol extract against *HepG2 cells*. Research of Liu et al. It showed that soursop leaf ethanol extract had an Inhibitory Concentration 50 (IC50) value of about 150 µg / mL against *HepG2 liver cancer cells*, while in this study alginate nanoparticles of soursop leaf extract had an IC50 of 14.5 µg/mL.²⁰ Tests using the Terminal deoxynucleotidyl transferase dUTP nick and labeling (TUNEL) method showed that soursop leaf ethanol extract is able to induce apoptosis in cancer cells.²¹

A total of 2 of the 12 articles with the herbal plant soursop are alginate nanoparticles of soursop leaf ethanol extract. Extract preparations are currently being developed in the form of nanoparticles. Nanoparticles have characteristics with a small size (1–300 nm). The size makes it easier for nanoparticles to extravasate through the endothelial pores of blood vessels to cancer cells, cellular internalization becomes faster due to the charge on the surface of the nanoparticles causing a stronger electrostatic bond with cancer cells thus increasing bioavailability which causes the nanoparticles to have a higher cytotoxic effect. The nanoparticle material being developed into anticancer therapy is a polymer, which can be classified into synthetic or natural polymers. One of the nanoparticle biopolymers is alginate. Alginate has good biodegradability, low toxicity and high absorption.²⁰

Other Indonesian herbal plants in this systematic review are *Calophyllum spp.* (Nyamplung), *Dendrophthoe pentandra* (clove benalu/ benalu cengkeh), *Hedyotis corymbosa* L. (pearl grass/ rumput mutiara), *Altingia excelsa* (Rasamala), *Myrmecodia pendans* (anthill plant/ sarang semut), *Ocimum sanctum* Linn. (Basil), and *Zingiber griffithii* (Tepus).

Nyamplung fruit consists of seeds and shells. Polar hazardous potential substances such triterpenoids, calophyllolides, coumarins, flavonoids, saponins, and resins are known to be present in the shells and seeds of nyamplung.²³ One of the anticancer substances that can be found in nature are saponin chemicals. Numerous investigations have been conducted on the cytotoxic mechanism of saponin compounds. The investigations came to the conclusion that saponins are responsible for the effects of apoptosis or non-apoptosis in cells. The intrinsic pathway of apoptosis is the apoptosis mechanism that has received the most media attention. Reduced NO generation, cytoskeleton breakdown, and autophagy-stimulated cell death are some of the non-apoptotic pathways. Triterpenoids are known to have anti-cancer activities through activating nuclear-kappa B factor and inducing apoptosis as preventive strategies.²³ In (Table 2), It is discovered that whereas the ethanol extract of Nyamplung fruit shell is only moderately cytotoxic to *WiDr* colorectal cancer cells, the ethanol extract of Nyamplung seeds is not.

According to the polarity of the molecule to be extracted, extraction can generally be carried out using either polar solvents (water, ethanol, methanol, etc.) or non-polar solvents (petroleum ether, chloroform, etc.). This method is known

as the principle of like dissolves like.¹⁷ Hexane fraction extracts contain steroid and triterpenoid compounds, which can produce almost the same cytotoxic activity as the ethyl acetate fraction. In ethanol fraction extracts, there are saponin compounds that are known to be involved in DNA replication, preventing cancer cell proliferation pathways and inhibiting cancer cell proliferation by stopping the cell cycle in the G1/S and G2/M phases.¹⁹ The most solvents from (Table 2) are ethanol as many as 14 (fourteen articles), then ethyl acetate solvents as many as 4 (four) articles, and methanol as many as 3 (three) articles.

Based on (Table 2), it was found that the most frequently used cytotoxic testing method is with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as many as 21 (twenty-one) articles, with 1 (one) article using the Cell Counting Kit-8 (CKK-8) assay method and 1 (one) article using flow cytometry analysis and quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) assay. The development of the cell cycle was determined using cytometric flow analysis after staining with propidium iodide (PI). Similar to the MTT test, various extract concentrations are applied to the cells. The fraction of cells in phases G0/G1, S, and G2/M represents the cell cycle distribution. The two stages of quantitative RT-PCR analysis are as follows: ribonucleic acid (RNA) samples are reverse transcribed into complementary deoxyribonucleic acid (cDNA), and then the qRT-PCR assay is used to analyze the results.²⁸

Apoptosis is a highly regulated process of cell death. It takes place both during typical cell development and morphogenesis as well as as part of the cell's response to stress and injury. Pathological cells go through necrosis, which is the death process as a result of ischemia as well as chemical, physical, and mechanical causes. A balanced process of cell division and death produces controlled cellular homeostasis and prevents aberrant proliferation. Apoptosis is preferable to necrosis because, unlike necrosis, it does not result in the surrounding cells becoming inflamed. Apoptosis, or cell death, is a closely controlled process that is initiated by either of the following two pathways: the death receptor (extrinsic) or the mitochondrial (intrinsic) pathway.²⁸ The anti-cancer activity widely reported in this systematic review is by inhibiting cell proliferation through intrinsic pathways.

Some genes have varied patterns of expression. All biological processes, including cell death, are governed by a fundamental dogma that starts with genes. Important cell functions like apoptosis depend on the regular activation of a subset of apoptosis-related genes. BCL-2 and Bcl-2 Associated X (BAX) are two previously mentioned apoptosis-related genes. BAX is a proapoptotic effector, whereas BCL-2 is an anti-apoptosis gene (prosurvival effector). The integrity of the mitochondria's outer membrane is regulated by genes from the BCL-2 family to govern apoptosis through the mitochondrial pathway. Complex connections that have a negative impact on the release of pro-apoptosis proteins are regulated by the interaction of the BCL-2 gene with other BCL-2 family members. Instead, BAX protein causes mitochondrial permeability by creating pores or joining with the outer mitochondrial membrane. Proteins that cause cell death are hence.²⁸

Apoptosis also contributes to morphological changes in some images inside the cell. Chromatin condensation, nuclear fragmentation, increased cell density, and the development of cytoplasmic blebs make up the morphological picture of apoptosis. The nucleus develops an atypical shape, the nucleolar size rises, and the granules of the nucleolar enlarge and spread. DNA degradation and cell damage into fragments surrounded by a dense membrane (apoptosis body) characterize the final stage of apoptosis. Some objects of apoptosis contain fragments of the nucleus, while others contain only cytoplasm. Therefore, nuclear condensation can be used to determine the apoptosis of healthy or necrotic cells.²⁹

IC50 or half the maximum inhibitory concentration is a measure of the effectiveness of a substance in inhibiting certain biological or biochemical functions, also defined as the concentration or amount of the drug needed to kill 50% of the cell population.¹⁵ Based on the US National Cancer Institute (NCI) crude extracts are considered to have cytotoxicity activity *in vitro* if they have an IC50 value of less than 20 µg/mL and less than 4 µg/mL for pure compounds.¹⁷ IC50 values of crude extracts less than 20 µg/mL have high cytotoxic activity, 21–200 µg/mL are moderate, 201–500 µg/mL are low, and more than 500 µg/mL have no cytotoxic activity.^{20,23}

Secondary metabolite compounds in plants have many benefits for humans including as medicine. The extraction and isolation process are necessary to separate and take secondary metabolite compounds so that benefits can be obtained. The method of separation and purification of secondary metabolite compounds from plants has the purpose of looking for bioactive compounds from extracts. The goal of looking for bioactive compounds is to find the right method that can

filter the source material for bioactivity such as cytotoxicity. In vitro methods are more desirable because animal experiments are expensive, require more time, and are prone to ethical controversy.³³

The concentration of herbal plants is inversely proportional to the results of cell viability indicating cytotoxic cells. The average of the articles in Table 2, the higher the concentration, the lower the cell viability which indicates high cell death, indicating that it has a higher cytotoxic effect.

Limitations in this systematic review are the possibility of Indonesian herbal plants that have not been found, no information has been obtained related to the difference in the content of bioactive components from parts of Indonesian herbal plants that cause differences in the results of anti-cancer cytotoxic activity, and has not been proven the mechanism of cytotoxic activity involved from each herbal plant molecularly through in vitro examination.

Conclusion

The most widely studied Indonesian herbal plant in vitro as an anti-cancer is *Annona muricata* (Soursop), while the anti-cancer activity that is widely reported is by inhibiting cell proliferation through intrinsic pathways.

Acknowledgment

The authors thank Padjadjaran University for funding this review article.

Disclosure

The authors report no conflicts of interest in this work.

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