Systematic Review: Anticancer Potential of Active Compounds from Galangal (*Alpinia galanga*)

Anugerah Suciati(✉) and Maryati

Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Jl. A. Yani Tromol Pos I, Pabelan, Kartasura, Sukoharjo 57162, Indonesia
anugerahsuci95@gmail.com

Abstract. Galangal (*Alpinia galanga*) is a plant that is widely spread in Southeast Asia and is widely used for cooking spices. Research related to the effect of *A. galanga* on cancer cells has been carried out. The purpose of this systematic review is to examine the potential of *A. galanga* as an anticancer agent and co-chemotherapy. The literature search was carried out through the Pubmed, Science Direct, Springer Link, DOAJ, and Garuda Portal databases. The keywords used were "Alpinia Galanga and Anticancer", "Alpinia Galanga and Cytotoxicity", "Lengkuas dan Sitotoksik", "Lengkuas dan Kanker", and "Alpinia Galanga and Cancer". Of the 965 articles found at the beginning of the search, 31 articles were obtained which had been filtered and discussed further. The results showed that the ethanolic extract of *A. galanga* had a cytotoxic effect because it contained antioxidant polyphenols that inhibited cell proliferation by stopping the cell cycle. The most abundant compounds in *A. galanga* as anticancer agents are 1'-Acetoxychavicol Acetate (ACA) and Galangin. ACA works to inhibit cancer cells by inducing apoptosis through mitochondrial depolarization and DNA fragmentation in the cell cycle phase. Meanwhile, Galangin works as a chemopreventive agent that reduces oxidative stress and inflammation by suppressing the MAPKs pathway.

Keywords: Alpinia galanga · galangal · anticancer · 1'-Acetoxychavicol Acetate · Galangin

1 Introduction

Cancer has become a health problem that is difficult to avoid. Various parts of the continent such as Africa, Asia, and America found more than 60% of new cases and about 70% of cancer deaths. Annual cancer cases are expected to increase from 14 million in 2012 to 22 million in 2032 [1]. This increase has been seen in the global cancer incidence in 2018 of 28.5% with a risk of 18.1 million new cases and 9.6 million deaths [2].

A. Sri Wahyuni et al. (Eds.): ICB-Pharma 2022, AHCPS 3, pp. 269–282, 2023.
https://doi.org/10.2991/978-94-6463-050-3_23

Lung, female breast, and colorectal cancers are the top three types of cancer in terms of incidence and are in the top five in terms of mortality. This ranking is also followed by cervical cancer. These types of cancer are responsible for one-third of the cancer incidence and burden of death worldwide. Cancer is the most common disease in 154 of the 185 countries included in Globocan 2018. Breast cancer is also the leading cause of cancer death in women (15.0%), followed by lung cancer (13.8%), colorectal cancer (9.5%), and cancer with incidence (6.6%), and mortality (7.5%) [2, 3].

The increasing incidence of cancer is caused by several factors, including population growth, aging, and changes in the prevalence of cancer-related causes of social and economic development. This incident mainly afflicts industrialized countries with the characteristics of an unhealthy lifestyle that tends to cause cancer [2]. Data from Basic Health Research (Riskesdas) 2018, shows the prevalence of cancer sufferers in the population of all ages in Indonesia is 1.8%, with the highest prevalence in the Province of the Special Region of Yogyakarta, which is 4.9%.

Treatments commonly used to cure cancer are chemotherapy, surgery or surgery, radiation, and biological therapy. Side effects that often occur during chemotherapy include feeling tired, nauseated, vomiting, depressed bone marrow, anemia, hair loss, easy infection, diarrhea, constipation, dyspnea, insomnia, and decreased appetite. Several types of chemotherapy can affect the function of the heart, lungs, kidneys, and nervous system [4, 5]. Chemotherapy errors, especially the oral route, occur in approximately one to four cases per 1000 treatments, accounting for 1–3% of adult and pediatric oncology patients, and occur at all stages of the drug use process [6].

Cancer chemoprevention has been suggested as a potential strategy to reduce cancer incidence and mortality since 1970 [7]. Natural ingredients play an important role in cancer therapy, especially as chemopreventive agents [8]. Research for the discovery of new compounds that have the potential as anticancer is still being carried out [9]. The discovery of new compounds is mostly done through the extraction and isolation of plants. Some crude extracts proved to be more effective than isolated results because the active ingredients that act on the receptor target are more so that the therapeutic effect is increased [10]. Many herbal treatments are used, one of which is using plants from the Zingiberaceae family such as *Alpinia galanga.*

Alpinia galanga and *Alpinia officinarum* which are cousins of ginger have been superior herbs for medicine for more than a thousand years [11]. The rhizome of *A. galanga* or galangal is empirically used as a medicine for facilitating menstruation, aches and pains, colds, fever, diarrhea, heartburn or stomach pain, eliminating bad breath and body odor, severe thrush, sore throat, cough, eliminating phlegm in bronchitis, and inflammation. Lungs [12]. The rhizome of *A. galanga* is used in food and as traditional medicine in South and Southeast Asia [13].

Various studies have stated that the compounds contained in *A. galanga* can affect cancer cells in cell proliferation and apoptosis [14, 15]. A. galanga reduces the growth and multiplication of tumor cells and suppresses the growth of tumor cells [11]. The compound that has a major effect on the cytotoxic activity of *A. galanga* is 1'-Acetoxychavicol Acetate (ACA). In addition to anticancer, ACA also has antiobesity, antiallergic, antimicrobial, antidiabetic, gastroprotective, anti-inflammatory, and antidementia activities [16]. Based on these data, it is interesting to study the evaluation of

the cytotoxic effects and anti-proliferative mechanisms of galangal (*Alpinia galanga)* on various types of cancer cells by collecting various related articles in a review article.

2 Research Method: Data Search Strategy

2.1 Sources of Data in Research

The databases used include Pubmed, Science Direct, Springer Link, DOAJ, and Garuda Portal with a search for articles published until June 2021. The search limits are journaled articles in English and Indonesian. The search flow is presented in Fig. 1.

The keywords for each database are different. The search keywords used in Pubmed, Science Direct, Springer Link, and DOAJ are "ALPINIA GALANGA AND ANTICANCER" and "ALPINIA GALANGA AND CYTOTOXICITY". The keywords used in the DOAJ are "ALPINIA GALANGA AND ANTICANCER", "ALPINIA GALANGA AND CYTOTOXICITY", and "LENGKUAS DAN SITOTOKSIK". The keywords used in the Garuda Portal are "LENGKUAS DAN SITOTOKSIK", "LENGKUAS DAN KANKER", and "ALPINIA GALANGA AND CANCER". Search results based on predefined keywords are then calculated.

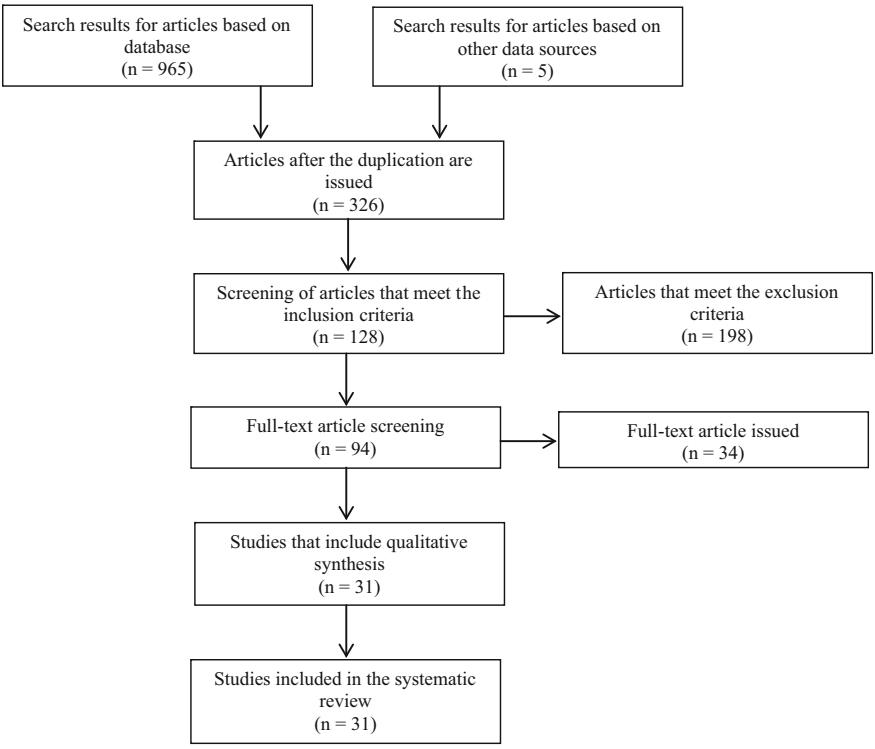

Fig. 1. Data Search and Extraction Based on PRISMA Diagram 2009

2.2 Inclusion and Exclusion Criteria

This study evaluated the anticancer effect of galangal (*Alpinia galanga*). After the initial screening of articles, the abstracts were manually checked for research relevance. The articles used are English and Indonesian articles published until June 2021, both in vivo and in vitro tests. Articles that do not mention the anticancer activity of the active compound in galangal (*Alpinia galanga*) in the abstract fall into the exclusion criteria. Articles that cannot be accessed in full text by researchers are also excluded.

2.3 Quality Evaluation

The next stage is the evaluation of the articles based on the filtered abstracts. Full-text articles are taken in (.pdf) format, compiled, and then independently validated by considering the inclusion and exclusion criteria that have been determined. The inclusion criteria were articles that discussed the anticancer effects of the active compounds in galangal (*Alpinia galanga*), while the exclusion criteria were articles that did not discuss the anticancer effects of the active compounds in galangal (*Alpinia galanga*). A bibliography or bibliography of selected articles is also searched to identify original articles that may not have been retrieved in the previous search stage.

2.4 Data Extraction

Data extraction from the selected articles was done manually. The study characteristics highlighted were cytotoxic activity based on IC_{50} values, antiproliferative mechanisms whether induced by apoptosis or not, cancer cell types, sample concentrations, methods, and tables created to display these data. Information regarding the author and year of publication is also included.

After going through the search process, the total article results obtained from the entire database were 965 articles. All article citations were submitted to Mendeley for reprocessing. Articles related to Alpinia galanga are released through the search tools in the Mendeley application. The articles were separated, then the articles were re-selected articles related to Cancer through search tools and separated again to produce 337 articles. Duplicated articles are removed by sorting on the Mendeley application, resulting in 326 articles.

The next stage is the screening of articles based on abstracts. Articles covering the study of *Alpinia galanga*'s cytotoxic activity against cancer cells were included in the inclusion criteria. Articles other than journals (books and short communications) are issued. There were 128 articles that met the inclusion criteria based on the abstract. Then the articles are screened again based on full-text. There are 10 articles with inaccessible full-text. Full-text articles containing research information related to cytotoxic activity totaled 94 articles. The articles that continued to be discussed in the literature review were 31 articles.

3 Results and Discussion

Various studies related to the anticancer effects of *Alpinia galanga* have been carried out. The results of a systematic review show that research related to the anticancer effects

of *A. galanga* appeared from 1988 to 2021. Most of the research was carried out on the Asian continent, especially East, Southeast, and South Asia. Countries that have conducted a lot of research on the cancerous effects of *A. galanga* include China, India, Indonesia, England, Iran, Japan, Germany, Taiwan, and Thailand.

The solvent that is often used in various studies to produce *A. galanga* extract is ethanol. In addition, methanol, water, acetone, dichloromethane, petroleum ether, and chloroform were also used (Table 1). Each solvent is used for different purposes [17]. Polar solvents will attract polar compounds such as saponins and polyphenols, while nonpolar solvents will attract nonpolar compounds such as monoterpenes and alkaloids. Each compound has been identified to have a different function. Saponins and monoterpenes are active against biomembranes, polyphenols interact with proteins, and alkaloids interact with proteins or DNA [18]. This could be one of the mechanisms of the anticancer properties of *A. galanga.*

In addition to interacting with proteins, polyphenols also have other activities, namely as antioxidants that function to ward off free radicals. Polyphenol compounds may be produced by the ethanol extract of *A. galanga* [19]. The ethanolic extract of *A. galanga* had a very high IC50 value against NIH-3T3 fibroblast cells. The IC50 values for these cells reached 620.5 ug/ml for 24 h and 666.6 ug/ml for 48 h. A high value indicates that the content in the ethanolic extract of *A. galanga* tends to be safe for normal human cells [20].

The anticancer potential of the ethanolic extract of *A. galanga* against HeLa cervical cancer cells showed good effectiveness. The IC_{50} values varied between 7.26 ug/ml, 13.26 ug/ml, and 36.32 ug/ml [21, 22]. The difference in value may be caused by differences in the place of origin of the plant. According to Da'i et al. (2019) and Suhendi et al. (2017), the cytotoxic effect may be due to the presence of the compound 1'-Acetoxychavicol Acetate (ACA) in *A. galanga* (Fig. 2).

The ethanolic extract of *A. galanga* was also tested against several breast cancer cells: 4T1, MCF-7, and T47D. IC50 values in 4T1 cells were 135 ug/mL, MCF-7 cells were 400 ug/ml after 48 h and 170 ug/ml after 72 h, in T47D cells were 3.14 ug/ml. The ethanolic extract of *A. galanga* contains compounds that inhibit cell proliferation which involves apoptosis. A possible mechanism is the stimulation of cell cycle arrest, which is associated with the induction of aging due to an increase in Reactive Oxygen Species (ROS) in cancer cells in response to increased doxorubicin [14, 21, 23].

In other cells such as HepG2 liver cancer cells, the ethanolic extract of *A. galanga* has a hypolipidemic effect by increasing the expression of LDLR, ApoA1, and SR-B1

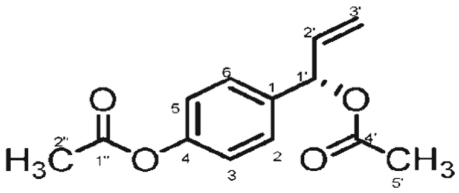

Fig. 2. *1'-Acetoxychavicol Acetate* (ACA)

genes, but the synergistic effect has not been elucidated. The resulting IC_{50} value is quite good, namely 0.33 ug/ml [24].

Besides ethanol, other solvents used are methanol, water, acetone, and ethyl acetate. Methanol as a solvent attracts flavonoids as anticancer substances. The flavonoids contained were able to provide a cytotoxic effect on murine leukemia P388 cells with an IC50 value of 16.76 ug/ml [25]. In the aqueous extract tested against lung cancer cells A549 and breast cancer cells MCF-12A, the IC_{50} value was in the range of 100 ug/ml. The possible mechanism of action is extensive DNA damage [26]. Acetone extract of *A. galanga* was tested against B16 melanoma cells yielding an IC50 value of 7.3 ug/ml. The mechanism of inhibition of melanogenesis occurs in tyrosinase inhibition [27]. The ethyl acetate extract of *A. galanga* also produced ACA. ACA in the ethyl acetate extract of *A. galanga* increased the activity of caspase 3 as a balancing protein for cell proliferation. The highest value of caspase 3 against breast, liver, kidney, and gastric cancer tissue from experimental animals was at a dose of 225 mg [28].

Research by Suja & Chinnaswamy [11] combines four kinds of solvents; petroleum ether, chloroform, aqueous, and ethanol. The experiment was carried out on PC-3 prostate cancer cells and resulted in an IC50 value of 37.6 ug/ml. The mechanism identified from the combined solvent extract was that *A. galanga* reduced the growth and multiplication of tumor cells and suppressed the growth of tumor cells.

The compound 1'-Acetoxychavicol Acetate (ACA) is the main compound identified as an anti-cancer agent in *A. galanga* (Table 2). The content of ACA inhibits the growth of cancer cells [17]. ACA induces apoptosis without harming the cell cycle [29]. The mechanism of ACA apoptosis with mitochondrial depolarization and DNA fragmentation in the G0/G1 phase cell cycle [30].

In HL-60 leukemia cancer cells, ACA inhibits myeloma cell growth through inactivation of the NF-kB pathway. The resulting IC_{50} value was 2 g/ml [31]. ACA can also be an alternative inhibitor for uPA and FGF2 because it can bind to them through a hydrogen formation pattern [32].

In the study of Xu et al. (2008), ACA and its enantiomer, R-ACA, were tested against EATC mammalian tumor cells. The results show the different mechanisms of the two compounds, but the resulting IC_{50} values are not significantly different. ACA causes tumor cell accumulation in the G1 phase, accompanied by a decrease in phosphorylated Rb protein, an increase in Rb, and a decrease in p27 phosphorylation. Meanwhile, R-ACA caused the accumulation of tumor cells in the G2 phase, increased Rb hyperphosphorylation, and increased phosphorylation of p27. The resulting IC50 values were 30.9 ug/ml for ACA and 22.2 ug/ml for R-ACA.

The next compound that is also dominant in Zingiberaceae is galangin. The chemopreventive effect of galangin was tested on cisplatin-induced BALB/c mice. Galangin relieves cisplatin-induced acute kidney injury via the ERK and NF-kB signaling pathways. Galangin reduces cisplatin-induced oxidative stress and inflammatory response. Galangin suppresses cisplatin-induced cell death, apoptosis, and necroptosis. The optimal dose given to experimental animals is 75mg/kg [33]. In albino Wistar rats induced by cisplatin, galangin was able to reduce the cytotoxic effect of cisplatin on the kidneys at an optimal dose of 100 mg/kg. Galangin reduces oxidative stress and inflammation by suppressing the MAPKs pathway [34].

Table 1. Mechanism of Action of *Alpinia galanga* Extract against Various Types of Cancer Cells

No	Sample	Cancer Cells	IC_{50} value	Mechanism of Action	Reference
1	Ethanol extract 70%	Fibroblast cells (NIH-3T3)	620.5 ug/ml for 24 h and 666.6 ug/ml for 48 h	A very high IC_{50} indicates that the extract is safe for fibroblast cells	[20]
2	Ethanol extract 95%	Breast cancer cells (T47D), cervical (HeLa), colorectal (WiDr), and normal Vero cells	3.14 g/ml T47D cells; 7.26 g/ml HeLa cells; 12.49 ug/ml WiDr. Cells	Compound 1'-Acetoxychavicol Acetate (ACA) was identified as selective against cancer cells	[21]
3	Ethanol extract 95% with 1:4. Ratio	Neuroblastoma cells	2.53 ± 0.1 ug/ml (leaf) and 0.34 ± 0.02 ug/ml (rhizome)	The content of polyphenols and antioxidant compounds helps ward off free radicals	[19]
4	Ethanol extract 96%	Breast cancer cells (4T1)	135 ug/mL	Stimulates cell cycle arrest, which is associated with induction of aging due to increased ROS in cancer cells in response to increased doxorubicin	[23]
5	Partitioned ethanol extract 96%with ethyl acetate	Cervical cancer cells (HeLa)	13.26 ug/ml (Surakarta) and 36.32 ug/ml (Yogyakarta)	Cytotoxic properties are influenced by the content of ACA in the extract	[22]
6	Ethanol extract	MCF-7 breast cancer cells and MRC-5 lung fibroblast cells	400 ug/ml after 48 h and 170 ug/ml after 72 h	*A. galanga* contains compounds that inhibit cell proliferation which involves apoptosis, but the mechanism is unknown	[14]
7	Ethanol extract combination of *A. galanga* and *P. emblica* (7:3)	Liver cancer cells (HepG2)	0,33 ug/ml	Has a hypolipidemic effect by increasing the expression of LDLR, ApoA1, and SR-B1 genes, but the synergistic effect has not been elucidated. Gallic acid increases LDLR gene expression	[24]
8	Methanol extract	Murine cell leukemia (P388)	16,76 ug/ml	In methanol extract, there are flavonoids as anti-cancer	[25]

(*continued*)

Table 1. (*continued*)

No	Sample	Cancer Cells	IC_{50} value	Mechanism of Action	Reference
9	Aqueous extract	Lung cancer cells (A549), fibroblasts (CRL2522), breast (MCF-12A), normal cells (CRL2321 & CRL2335)	100 ug/ml	The toxicity of *A. galanga* is probably due to extensive DNA damage	[26]
10	Acetone Extract	skin cancer cells B16	7,3 ug/ml	Melanogenesis inhibition mechanism on tyrosinase	[27]
11	Ethyl acetate extract	Breast, liver, kidney, and stomach cancer tissue from experimental animals	the highest caspase 3 value at a dose of 225 mg	ACA in *A. galanga* increases the activity of caspase 3 as a balancing protein for cell proliferation	[28]
12	Dichloromethane, methanol, and aqueous extract	HeLa cervical cancer cells	2357.3 ug/ml (aqueous), 55.7 ug/ml (dichloromethane), 111.7 ug/ml (methanol)	saponins and monoterpenes are active against biomembranes, polyphenols interact with proteins, alkaloids interact with proteins or DNA	[18]
13	Petroleum ether extract, chloroform, water, and ethanol	Prostate cancer cells (PC-3)	37,6 ug/ml	Reduce the growth and multiplication of tumor cells and suppress the growth of tumor cells	[11]

In breast cancer cells, galangin has a cytotoxic effect at doses of 20–34.11 g/ml [35, 36]. Mechanism of inhibition of cancer cells by galangin via the TRAIL/Capase-3/AMPK signaling pathway [35]. Meanwhile, the mechanism of apoptosis by galangin is seen in DNA fragmentation. Galangin can be absorbed by the intestine and has shown efficacy on tumor cells [36].

Other compounds are found in *A. galanga* and have anticancer effects on certain cells. The compounds found included: 4-hydroxycinamaldehyde (4'-HCA); pinocembrin; 5,7-dihydroxyflavone (chrysin); 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (BHPHTO); bisdemethoxycurcumin (BDMC); skeletal diterpenes; galanal A; galanal B; diterpene labdane; cardamonins; 9-phenyl propanoid; and 2,2,3-triemtyldecan (Table 2).

Overall, these compounds work to inhibit cell proliferation and induce apoptosis with mitochondrial targets. Inhibition of cell proliferation was seen in cell viability assays [37]. The increase in cell accumulation occurred in the S phase then inhibition occurred in the G1/S phase [38]. Induction of apoptosis occurs by targeting mitochondria. Compounds in *A. galanga* induce ROS production and translocation of bax protein to

Table 2. Mechanism of Action of *Alpinia galanga* Isolate against Various Types of Cancer Cells

No	Sample	Cancer cell	IC_{50} value	Mechanism of Action	Reference
1	1'-Acetoxychavicol Acetate (ACA)	Colorectal cancer cells (SW480) and human epithelial cells (HMEC)	Proliferation at IC_{50} 80 ug/ml in 48 h	The mechanism of ACA apoptosis with mitochondrial depolarization and DNA fragmentation in the cell cycle in the G0/G1	[30]
2	ACA standard and its enantiomers	EATC cells (unspecified mammalian tumor cells)	IC_{50} ACA 30,9 ug/ml and R-ACA 22,2 ug/ml	ACA causes tumor cell accumulation in the G1 phase, accompanied by a decrease in phosphorylated Rb protein, an increase in Rb, and a decrease in p27 phosphorylation. R-ACA causes tumor cell accumulation in the G2 phase, increased Rb hyperphosphorylation, and increased p27 phosphorylation.	[39]
3	ACA isolates from Zingiberaceae	Leukemic cells (HL-60)	2 ug/ml	Inhibits myeloma cell growth through inactivation of the NF-KB pathway	[31]
4	ACA	MCF7, MCF7/LCC2, MCF7/LCC9, and MCF7/HER2 cells and in vivo with zebrafish	MCF7 IC50 value 19.54 ug/ml at 24 h 11.78 ug/ml at 48 h and 5.01 ug/ml at 72 h	ACA can be an alternative inhibitor for uPA and FGF2 because it can bind to them through a hydrogen formation pattern	[32]
5	ACA	Lung cancer cells (COR L23) and breast cancer (MCF-7)	L23 lung cancer cells 7.8 g/ml and MCF-7 23.9 g/ml	The content of ACA inhibits the growth of cancer cells	[17]
6	5 compounds including ACA	Cervical cancer cells (HeLa), lung cancer (A549), liver cancer (HepG2 and SMMC-7721)	60–90 ug/ml for 4 of the 5 compounds isolated	Isolate induces apoptosis without harming the cell cycle	[29]
7	Galangin standard	Pathogen-free mice aged 6 weeks weighing 22–25 g induced by cisplatin	dose 75 mg/kg in rats	Galangin relieves cisplatin-induced acute kidney injury via ERK and NF-B signaling pathways, reduces cisplatin-induced oxidative stress and inflammatory response; suppresses cisplatin-induced cell death, apoptosis and necroptosis.	[33]

(*continued*)

Table 2. (*continued*)

No	Sample	Cancer cell	IC_{50} value	Mechanism of Action	Reference
8	Galangin standard	Breast cancer cells (MCF-7) and EAC cells	34.11 ug/ml and 22.29 ug/ml	The mechanism of apoptosis by Galangin is seen in DNA fragmentation, Galangin can be absorbed by the intestine and shows efficacy in tumor cells	[35]
9	Galangin standard	MCF-7 and T47D breast cancer cells	20 ug/ml	Mechanism of inhibition of cancer cells by Galangin via the TRAIL/Capase-3/AMPK signaling pathway	[36]
10	Galangin standard	Cisplatin induced Wistar albino mice	Galangin is able to reduce the cytotoxic effect of cisplatin on the kidneys at a dose of 100 mg/kg	Reduces oxidative stress and inflammation by suppressing the MAPKs pathway.	[34]
11	4-hydroxycinamaldehyde (4'-HCA) isolate	Leukemic cancer cells (HL-60 and U937)	Cell apoptosis 10–50 g/ml for 4 and 24 h	Induces ROS production in cancer cells by targeting mitochondria	[13]
12	pinocembrin isolate from petroleum ether extract of A. galanga	Breast cancer cells (MCF-7), cervical cancer (HeLa, SiHa), colon cancer (SW480)	IC_{50} above 50 ug/ml	Induces Bax translocation to mitochondria. Excess Bax induces apoptosis (as evidenced by MTT). The lack of Bax in position makes it resistant to apoptosis.	[40]
13	5,7-dihydroxyflavone (chrysin) isolate from petroleum ether and ethyl acetate extract	Lymphoma cells (DLA) and lung cancer cells (A549)	Apoptosis at 25, 50 and 75 ug/ml	Increases cell accumulation in S phase leading to inhibition in G1/S phase	[38]
14	Isolate 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (BHPHTO) and bisdemethoxycurcumin (BDMC)	Human (A2058) and mouse (B16-F10) skin cancer cells	25 ug/ml	inhibits the proliferation of melanoma cells in cell viability tests, and inhibits the activity of cellular tyrosinase and melanin	[37]
15	Skeletal diterpene isolates, galanal A, galanal B, and labdane diterpenes	Human epithelial cells (KB)	ED_{50} value for galanal A 3.25 ug/ml and B 15 ug/ml	Galanal has cytotoxic activity and protects epithelial cells	[42]
16	Cardamonin	Skin cancer cells (A375) and normal fibroblast cells	For 48 h 3.89 ug/ml and 96 h 2.43 ug/ml	Affect cancer cell proliferation	[15]
17	9 phenylpropanoids from extract DCM (1): MeOH (1) *Alpinia galanga*	Cancer cells lung (A594 & NCI H460), colon (Colo-205 & HT-29), skin (A431), prostate (PC-3)	Between 1.8–13.4 and 5.6–19,9 ug/ml	The cytotoxic mechanism may be due to the hydroxyl groups in the compounds	[41]

(*continued*)

Table 2. (*continued*)

No	Sample	Cancer cell	IC_{50} value	Mechanism of Action	Reference
18	essential oil with the most dominant content of 2,2,3-trimethylbutane	B16 melanoma cells and LNCaP prostate cancer cells in 48 male mice	B16 cells 88.11 ug/ml and LNCaP cells 101.39 ug/ml	decreased anti-inflammatory activity by decreasing COX-2, TNF-a, IL-6 and IL-1 in mice	[43]

mitochondria [13]. Excess bax protein induces apoptosis as evidenced by MTT assay. Lack of bax protein in its position makes cells resistant to apoptosis [40]. Compounds having a hydroxyl group also play a role in the cytotoxic effect but the mechanism is still not elucidated [41].

4 Conclusion

The ethanolic extract of *A. galanga* has a cytotoxic effect because it contains antioxidant polyphenols that inhibit cell proliferation by stopping the cell cycle. The most abundant compounds in *A. galanga* as anticancer agents are ACA and galangin. ACA works to inhibit cancer cells by inducing apoptosis through mitochondrial depolarization and DNA fragmentation in the cell cycle phase. Meanwhile, galangin works as a chemopreventive agent that reduces oxidative stress and inflammation by suppressing the MAPKs pathway.

References

1. Kemenkes, Infodatin: Pusat Data dan Informasi, Kementrian Kesehatan RI, Jakarta, 2015
2. IARC, Latest Global Cancer Data, WHO, Geneva, 2018
3. J. T. DiPiro, R. L. Talbert, G. C. Yee, G. R. Matzke, B. G. Wells, L. M. Posey, Pharmacotherapy a Pathophysiologic Approach, Mc Graw Hill Medical, New York, 2008.
4. W. N.Ambarwati, E. K. Wardani, Response and Coping on Physically to Side Effect Chemotherapy in Women Suffered Cervical Cancer, Jurnal Ners, 2015, 48–60.
5. D. A. Juwita, Almahdy, R. Afdhila. Pengaruh Kemoterapi Terhadap Health Related Quality Of Life (HRQOL) Pasien Kanker Payudara di RSUP Dr. M. Djamil Padang, Universitas Andalas, Padang, 2018.
6. S. N. Weingart, L. Zhang, M. Sweeney, M. Hassett, Chemotherapy Medication Errors, Lancet Oncol, 2018, e191–99.
7. S. Umezawa, T. Higurashi, Y. Komiya, J. Arimoto, N. Horita, T. Kaneko, Chemoprevention of Colorectal Cancer: Past, Present, and Future, Cancer Science, 2019, 3018–3026.
8. C.-Z. Wang, Z. Zhang, S. Anderson, C.-S. Yuan, Natural Products and Chemotherapeutic Agents on Cancer: Prevention vs. Treatment, The American Journal of Chinese Medicine, 2014, 1555–1558.
9. N. J. Jacobo-Herrera, F. E. Jacobo-Herrera, A. Zentella-Dehesa, A. Andrade-Cetto, M. Heinrich, C. Pérez-Plasencia, Medicinal Plants Used in Mexican Traditional Medicine for The Treatment of Colorectal Cancer, Journal of Ethnopharmacology, 2016, 391–402.

10. P. Rasoanaivo, C.W. Wright, M.L., Willcox, B. Gilbert, Whole Plant Extracts Versus Single Compounds for The Treatment of Malaria: Synergy and Positive Interactions, Malaria Journal, 2011.
11. S.Suja, P. Chinnaswamy, Inhibition of in vitro cytotoxic effect evoked by *Alpinia galanga* and *Alpinia officinarum* on PC-3 cell line. Ancient Science of Life, 2008, 27(4), 33–40, http://www.ncbi.nlm.nih.gov/pubmed/22557284
12. R. Evizal, Rusdi. Tanaman Rempah dan Fitofarmaka, Lembaga Penelitian Universitas Lampung, 2013.
13. R. Banjerdpongchai, P. Punyati, A. Nakrob, W. Pompimon, P. Kongtawelert, 4'-hydroxycinnamaldehyde from *Alpinia galanga* (Linn.) induces human leukemic cell apoptosis via mitochondrial and endoplasmic reticulum stress pathways, Asian Pacific Journal of Cancer Prevention, 201, 12(3), 593–598.
14. S. Samarghandian, M. A. R. Hadjzadeh, J. T. Afshari, M. Hosseini, Antiproliferative activity and induction of apoptotic by ethanolic extract of Alpinia galanga rhizome in human breast carcinoma cell line, BMC Complementary and Alternative Medicine, 2014, 14. https://doi.org/10.1186/1472-6882-14-192
15. L. Berning, L. Scharf, E. Aplak, D. Stucki, Von C. Montfort, A. S. Reichert, … P. Brenneisen, In vitro selective cytotoxicity of the dietary chalcone cardamonin (CD) on melanoma compared to healthy cells is mediated by apoptosis., PLoS ONE, 2019 14(9), https://doi.org/10.1371/journal.pone.0222267
16. A. Kojima-Yuasa, I. Matsui-Yuasa, Pharmacological Effects of 1'-Acetoxychavicol Acetate, a Major Constituent in the Rhizomes of *Alpinia galanga* and *Alpinia conchigera*, Journal of Medicinal Food, 2020, Vol. 23, pp. 465–475. https://doi.org/10.1089/jmf.2019.4490
17. C. C. Lee, P. Houghton, Cytotoxicity of plants from Malaysia and Thailand used traditionally to treat cancer, Journal of Ethnopharmacology, 2005, 100(3), 237–243. https://doi.org/10.1016/j.jep.2005.01.064
18. F. Herrmann, M. R. Romero, A. G. Blazquez, D. Kaufmann, M. L. Ashour, S. Kahl,… M. Wink, Diversity of pharmacological properties in Chinese and European medicinal plants: Cytotoxicity, antiviral and antitrypanosomal screening of 82 herbal drugs, Diversity, 2011, 3(4), 547–580. https://doi.org/10.3390/d3040547
19. F. J. Hashim, S. Vichitphan, P. Boonsiri, K. Vichitphan, Neuroprotective assessment of moringa oleifera leaves extract against oxidative-stress-induced cytotoxicity in shsy5y neuroblastoma cells, Plants, 2021, 10(5), 889. https://doi.org/10.3390/plants10050889
20. F. Sandra, J. Sudiono, P. Trisfilha, D. Pratiwi, Cytotoxicity of *Alpinia galanga* rhizome crude extract on NIH-3T3 cells, Indonesian Biomedical Journal, 2017 9(1), 23–28. https://doi.org/10.18585/inabj.v9i1.212
21. M. Da'i, K. A. Meilinasary, A. Suhendi, Haryanti S., Selectivity Index of *Alpinia galanga* Extract and 1'-Acetoxychavicol Acetate on Cancer Cell Lines. Indonesian Journal of Cancer Chemoprevention, 2019, 10(2), 95. https://doi.org/10.14499/indonesianjcanchemoprev10iss2pp95-100
22. A. Suhendi, E. R. Wikantyasning, G. Setyadi, A. S. Wahyuni, M. Da'i, Acetoxy Chavicol Acetate (ACA) Concentration and Cytotoxic Activity of Alpinia galanga Extract on HeLa, MCF7 and T47D Cancer Cell Lines, Indonesian Journal of Cancer Chemoprevention, 2017, 8(2), 81. https://doi.org/10.14499/indonesianjcanchemoprev8iss2pp81-84
23. F. N. Ahlina, N. Nugraheni, Salsabila, I. A. S. Haryanti, M. Da'i, E. Meiyanto, Revealing the reversal effect of galangal (*Alpinia galanga* L.) extract against oxidative stress in metastatic breast cancer cells and normal fibroblast cells intended as a Co-chemotherapeutic and anti-aging agent. Asian Pacific Journal of Cancer Prevention, 2020, 21(1), 107–117. https://doi.org/10.31557/APJCP.2020.21.1.107

24. N. Tirawanchai, P. Homongkol, C. Chansriniyom, A. Somkasetrin, J. Jantaravinid, K. Kengkoom, S. Ampawong, Lipid-lowering effect of *Phyllanthus embilica* and *Alpinia galanga* extracts on HepG2 cell line, PharmaNutrition, 2019, 9. https://doi.org/10.1016/j.phanu.2019.100153
25. I. A. K. Pramushinta, P. S. Ajiningrum, Uji Aktivitas Sel Kanker dengan menggunakan senyawa Flavonoid dari Lengkuas (*Alpinia Galanga*). STIGMA: Jurnal Matematika Dan Ilmu Pengetahuan Alam Unipa, 2017, 10(02). https://doi.org/10.36456/stigma.vol10.no2.a1036
26. P. Muangnoi, M. Lu, J. Lee, A. Thepouyporn, R. Mirzayans, X. C. Le, … S. Changbumrung, Cytotoxicity, apoptosis and DNA damage induced by *Alpinia galanga* rhizome extract, Planta Medica, 2007, 73(8), 748–754. https://doi.org/10.1055/s-2007-981542
27. Y. Manse, K. Ninomiya, R. Nishi, I. Kamei, Y. Katsuyama, T. Imagawa, … T. Morikawa, (). Melanogenesis inhibitory activity of a 7-O-9'-linked neolignan from *Alpinia galanga* fruit. Bioorganic and Medicinal Chemistry, 2016, 24(23), 6215–6224. https://doi.org/10.1016/j.bmc.2016.10.001
28. V. Karlowee, N. Wijayahadi, Pengaruh Ekstrak Lengkuas Merah (*Alpinia Galanga*) Dosis Bertingkat Terhadap Ekspresi Caspase 3 dan Grading Kanker Payudara Mencit C3H, Media Medika Indonesiana, 2010, Vol. 44. https://ejournal.undip.ac.id/index.php/mmi/article/view/21901
29. Q. H. Zeng, C. L. Lu, X. W. Zhang, J. G. Jiang, Isolation and identification of ingredients inducing cancer cell death from the seeds of *Alpinia galanga*, a Chinese spice, Food and Function, 2015, 6(2), 431–443. https://doi.org/10.1039/c4fo00709c
30. R. G. Baradwaj, M. V. Rao, T. Senthil Kumar, (). Novel purification of 1'S-1'-Acetoxychavicol acetate from *Alpinia galanga* and its cytotoxic plus antiproliferative activity in colorectal adenocarcinoma cell line SW480. Biomedicine and Pharmacotherapy, 2017, 91, 485–493. https://doi.org/10.1016/j.biopha.2017.04.114
31. T. Misawa, K. Dodo, M. Ishikawa, Y. Hashimoto, M. Sagawa, M. Kizaki, H. Aoyama, Structure-activity relationships of benzhydrol derivatives based on 1′-acetoxychavicol acetate (ACA) and their inhibitory activities on multiple myeloma cell growth via inactivation of the NF-κB pathway, Bioorganic and Medicinal Chemistry, 2015, 23(9), 2241–2246. https://doi.org/10.1016/j.bmc.2015.02.039
32. N. Pradubyat, A. Giannoudis, T. Elmetwali, P. Mahalapbutr, C. Palmieri, C. Mitrpant, W. Ketchart, 1'-Acetoxychavicol Acetate from *Alpinia galanga* Represses Proliferation and Invasion, and Induces Apoptosis via HER2-signaling in Endocrine-Resistant Breast Cancer Cells. Planta Medica, 2021. https://doi.org/10.1055/a-1307-3997
33. Z. Huang, Q. Huang, L. Ji, Y. Wang, X. Qi, L. Liu, … L. Lu, Epigenetic regulation of active Chinese herbal components for cancer prevention and treatment: A follow-up review, Pharmacological Research, 2016, Vol. 114, pp. 1–12. https://doi.org/10.1016/j.phrs.2016.09.023
34. A. Tomar, S. Vasisth, S. I. Khan, S. Malik, T. C. Nag, D. S. Arya, J. Bhatia, Galangin ameliorates cisplatin-induced nephrotoxicity in vivo by modulation of oxidative stress, apoptosis and inflammation through interplay of MAPK signaling cascade, Phytomedicine, 2017, 34, 154–161. https://doi.org/10.1016/j.phymed.2017.05.007
35. J. V. Jaiswal, P. A. Wadegaonkar, S. W. Hajare, The bioflavonoid galangin suppresses the growth of ehrlich ascites carcinoma in Swiss Albino Mice: A molecular insight, Applied Biochemistry, and Biotechnology, 2012, 167(5), 1325–1339. https://doi.org/10.1007/s12010-012-9646-3
36. W. Song, C. yang Yan, Q. Qian Zhou, L. lin. Zhen, Galangin potentiates human breast cancer to apoptosis induced by TRAIL through activating AMPK, Biomedicine, and Pharmacotherapy, 2017, 89, 845–856. https://doi.org/10.1016/j.biopha.2017.01.062

37. C. Y. Lo, P. L. Liu, L. C. Lin, Y. T. Chen, Y. C. Hseu, Z. H. Wen, H. M. Wang, Antimelanoma and antityrosinase from *Alpinia galangal* constituents. The Scientific World Journal, 2013. https://doi.org/10.1155/2013/186505
38. S. Lakshmi, S. Suresh, B. S. Rahul, R. Saikant, V. Maya, M. Gopi, … P. Remani, In vitro and in vivo studies of 5,7-dihydroxy flavones isolated from *Alpinia galanga* (L.) against human lung cancer and ascetic lymphoma, Medicinal Chemistry Research, 2019, 28(1), 39–51. https://doi.org/10.1007/s00044-018-2260-3
39. S. Xu, A. Kojima-Yuasa, H. Azuma, X. Huang, T. Norikura, D. O. Kennedy, I. Matsui-Yuasa, (1′S)-Acetoxychavicol acetate and its enantiomer inhibit tumor cells proliferation via different mechanisms, Chemico-Biological Interactions, 2008, 172(3), 216–223. https://doi.org/10.1016/j.cbi.2008.01.002
40. M. A. S.Kumar, M. Nair, P. S. Hema, J. Mohan, T. R. Santhoshkumar, Pinocembrin triggers Bax-dependent mitochondrial apoptosis in colon cancer cells, Molecular Carcinogenesis, 2007, 46(3), 231–241. https://doi.org/10.1002/mc.20272
41. S. S. Chourasiya, E. Sreedhar, K. S. Babu, N. Shankaraiah, V. L. Nayak, S. Ramakrishna, … M. V. B. Rao, Isolation, synthesis and biological evaluation of phenylpropanoids from the rhizomes of *Alpinia galanga*, Natural Product Communications, 2013, 8(12), 1741–1746. https://doi.org/10.1177/1934578x1300801222
42. H. Morita, H. Itokawa, Cytotoxic and antifungal diterpenes from the seeds of *Alpinia galanga.* Planta Medica, 1988, 54(2), 117–120. https://doi.org/10.1055/s-2006-962365
43. L. Zhang, X., Liang, Z. Ou, M. Ye, Y. Shi, Y. Chen, … H. Xiang, Screening of chemical composition, anti-arthritis, antitumor and antioxidant capacities of essential oils from four Zingiberaceae herbs. Industrial Crops and Products, 2020, 149. https://doi.org/10.1016/j.indcrop.2020.112342