Indonesian Journal of Cancer Chemoprevention, June 2025
ISSN: 2088–0197
e-ISSN: 2355-8989

Anti-Cancer Activity of Rhizome of Emprit Ginger (*Zingiber officinale* Rosc.) and Tiwai Onion (*Eleutherine palmifolia*) through Apoptosis Induction and Cell Cycle Arrest: A Review

Aisyah Nur Salsabilan, Annisa Khumaira, Ika Afifah Nugraheni

Biotechnology, Faculty of Science and Technology, Universitas 'Aisyiyah Yogyakarta,
Jl. Ringroad Barat No. 63 Nogotirto, Gamping, Sleman, DI Yogyakarta, 55592

Abstract

Cancer is a disease caused by the abnormal growth of cells and tissues. One of the main therapeutic approaches for cancer is chemotherapy. The use of plants as an alternative treatment is considered quite relatively effective and efficient. Emprit ginger (*Zingiber officinale* Rosc.) and tiwai onion (*Eleutherine palmifolia*) are plants that have potential anticancer properties due to their active compounds. The purpose of this literature review is to examine the various uses of these active compounds and their mechanisms of action as anticancer agents, both *in vitro* and *in vivo*, from emprit ginger and tiwai onion. The results of this literature review indicate that emprit ginger contains active compounds, namely gingerol (6-gingerol and 10-gingerol), shogaol (4-shogaol, 6-shogaol, and 10-shogaol), and paradol, which have anticancer activity. Similarly, tiwai onion contains active compounds, namely flavonoids (isoliquiritigenin), polyphenols (oxyresveratrol), and naphtoquinones (elecanacin, eleutherin, eleutherol, eleutherinol, eleutherinon, eleuthoside B, eleutherinoside A), which have anticancer activity. Pre-clinical *in vitro* and *in vivo* studies show that emprit ginger and tiwai onion have anticancer activity, including the inhibition of cancer growth through modulation of cell signaling pathways, induction of apoptosis, and cell cycle arrest.

Keywords: *anticancer activity, apoptosis, cell cycle arrest, emprit ginger (*Zingiber officinale Rosc.*), tiwai onion (*Eleutherine palmifolia*).*

INTRODUCTION

Cancer is a disease that arises from the abnormal growth of body cells and tissues, which eventually develop into cancer cells. In 2018, the prevalence of cancer in Indonesia reached 1.79 cases per 1,000 population. This increase began in 2013, reached as high as 1.4 cases per 1,000 population (Riskesdas, 2018). According to data from the Global Burden of Cancer (GLOBOCAN) in 2020, the incidence of cancer in Indonesia is nearly 400,000 new cases, with more than 230,000 deaths. This figure places Indonesia in eighth position for the highest number of cancer cases in Southeast Asia and 23rd in Asia.

Submitted: February 02, 2026
Revised: April 22, 2026
Accepted: April 24, 2026

*Corresponding author: annisakhumaira@unisayogya.ac.id

At present, efforts to prevent the spread of cancer cells continue. One of these approaches is treatment using synthetic cancer drugs; however, this method is relatively expensive and is associated with significant side effects. This encourages the search for new natural source drugs with potential anticancer properties. According to recent research, herbal plants provide many health benefits and are now being used more widely because they are more accessible to the public in terms of both price and availability.

Emprit ginger (*Zingiber officinale* Rosc.) is a plant that is still widely used to treat various diseases and has been scientifically studied for its neuroprotective, anti-inflammatory, antitumor, antiradiation, antimicrobial, antidiabetic, anti-obesity and hepatoprotective activities. The active compounds contained in this plant are gingerols, shogaols, zingerone, paradol, gingerenone, galanal, gingerdiols and ginger-diones. The active compound 6-gingerol is strongly suspected to possess anticancer activity (Wang, *et al*., 2014).

The tiwai onion (*Eleutherine palmifolia*) is a plant whose tubers are empirically efficacious in treating diseases such as jaundice, cough, stomachache, dysentery, intestinal inflammation, breast cancer, colon cancer, and as an emetic stimulant. Tiwai onion contains active compounds from the naphtoquinone group and their derivatives such as elecanacin, eleutherin, eleutherol, eleutherinol, eleutherinon, eleuthoside B, and eleutherinoside A. Naphtoquinones are known to have bioactivity as anticancer and antioxidant agents (Narko, *et al*., 2017).

According to the WHO guidelines, a substance or material used for medicinal purposes in humans and animals must undergo pre-clinical and clinical studies. An *in vitro* activity test is an evaluation of a substance conducted using specific biological culture media as the test system. The *in vivo* activity test is an experiment conducted on laboratory animals aimed at scientifically demonstrating the efficacy of drugs using the scientific method (Meles, 2010).

These issues make it necessary to conduct this literature study so that it can provide the general public and researchers with information regarding the mechanism of action of the active compounds contained in the rhizomes of emprit ginger and bulbs of tiwai onion. This literature review may later serve as a reference for future clinical studies to determine appropriate doses that can be used in humans and to provide information regarding *in vitro* and *in vivo* studies of the anticancer activity of emprit ginger rhizomes and tiwai onion bulbs through induction of apoptosis and cell cycle arrest. Apoptosis is a form of programmed cell death regulated by genetic mechanisms (DNA damage), whereas cell cycle arrest is the suspension of cell cycle progression in response to DNA damage.

Several literature studies on the potential of emprit ginger and tiwai onion as anticancer agents have been conducted; however, these studies have generally focused on a single plant species. This literature study focuses on two plants, namely emprit ginger and tiwai onion, through pre-clinical *in vitro* and *in vivo* studies, with particular emphasis on apoptosis induction and cell cycle arrest as the mechanisms of anticancer action in both plants. This review presents an integrated narrative that connects and strengthens findings from various studies, ranging from cancer pathology to the mechanism of action of active compounds derived from emprit ginger and tiwai onion as anticancer agents through apoptosis induction and cell cycle arrest.

MATERIALS AND METHODS

This literature review employed the systematic literature review with meta-synthesis method because it combines findings from

primary studies to generate a deeper understanding of the problem under investigation. This method aims to help synthesize abundant and sometimes conflicting research findins, increase analytical rigor, address uncertainty, and answer questions raised in previous studies (Utomo, 2016).

This literature review covered publications from 2002 to 2021, including scientific journals, review articles, theses, conference proceedings, articles, and books. The systematic literature search identified 135 national and international publications related to the anticancer activity of emprit ginger and tiwai onion, with a focus on apoptosis induction and cell cycle arrest.

The inclusion criteria consisted of publications reporting anticancer activity testing of emprit ginger and tiwai onion using *in vitro* and *in vivo* assays, including studies evaluating apoptosis induction and cell cycle arrest. The exclusion criteria included publications investigating activities other than anticancer effects of emprit ginger and tiwai onion, as well as studies on anticancer activity that were not available in full-text. The literature selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure (Moher, *et al*., 2009).

The database search initially yielded 135 publications. The next step involved screening the identified records using the PRISMA procedure, as shown in Figure 1. Two publications were identified as duplicates and removed. The remaining records were screened based on title, abstract, and keywords, resulting in three inaccessible articles. The remaining 130 articles then proceeded to the eligibility selection stage. After applying the inclusion criteria, 30 publications were excluded because their titles and abstracts were not relevant to the objective of this literature review. The remaining 100 full-text publications were then assessed in detail, of which 58 publications were excluded due to incomplete data or failure to meet the inclusion criteria after full-text evaluation. Following an in-depth assessment, 42 publications were included in the final review, specifically discussing *in vitro* and *in vivo* studies of anticancer activity of emprit ginger rhizomes and tiwai onion bulbs. All included publications were published between 2002 and 2021.

CANCER

Cancer is often associated with tumors; however, not all tumors are classified as cancer. A tumor is a general term for any lump or abnormal mass that appears in the body, whether visible on the body surface or hidden internally. In contrast, cancer is a disease caused by the abnormal growth of body tissue cells that subsequently develop into cancer cells (Mangan, 2005). Cancer can be characterized by four main features that distinguish cancer cells from normal cells, namely: (1) clonality, in which cancer originates from genetic changes occuring in a single cell that subsequently proliferates into malignant cells; (2) autonomy, where cell growth is no longer properly regulated by normal biochemical and physical influences from the surrounding environment, (3) anaplasia, which refers to the loss of normal and coordinated cell differentiation; and (4) metastatis, in which cancer cells continue to grow and spread to other parts of the body (Wiseman, 2007).

Carcinogenesis is the process by which neoplasms, or malignant tumors, are formed (Liu, *et al*., 2015). Most evidence suggests that cancer formation is a multistep process requiring a long latency period, commonly referred to as the initiation-promotion theory of carcinogenesis. Cancer cells arise from normal cells through a complex transformation process consisting of initiation and promotion stages. This theory states that the first step of carcinogenesis is the persistent mutation of the cell's DNA during DNA transcription. Cancers may develop from these initial events or from sustained mutations that interact over time with various promoting agents. Promoter substances

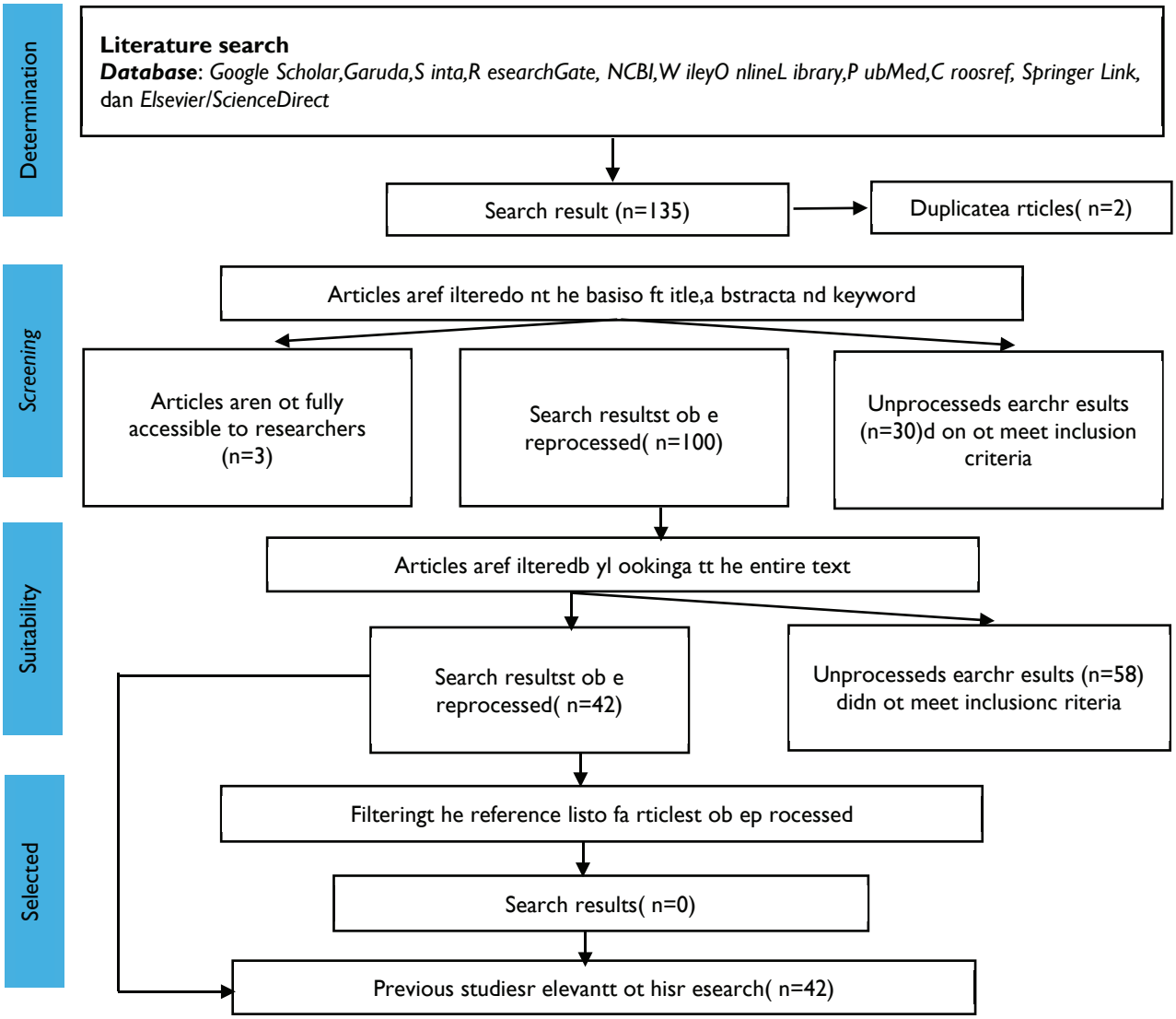

Figure 1. PRISMA flowchart in this literature review.

stimulate cell reproduction and division. In general, the carcinogenesis process includes the stages of initiation, promotion, and progression (Liu, *et al.*, 2015).

The cell cycle in eukaryotic cells can be divided into four stages: G1 (Gap 1), S (synthesis), G2 (gap 2), and M (mitosis), as shown in Figure 7. The G1 phase is the interval between the M and S phases, during which the cell continues to grow and prepares for DNA synthesis. During the S phase, DNA synthesis and chromosome replication occur. In the G2 phase, cells that have replicated their chromosomes duplicate other cellular components and synthesize mRNA as well as specific proteins. In general, the G0, G1, S, and G2 phases are known as interphase. Cell division occurs during the M phase, which consists of four sub-stages: prophase, metaphase, anaphase, and telophase. Under certain conditions, cells that are not actively dividing may exit the G1 stage and enter the G0 phase, a resting or quiescent (Murti, *et al.*, 2007). Cell cycle progression is regulated

by cyclins (D, E, A, and B), cyclin-dependent kinases (4, 6, 2, and 1), and cyclin–dependent kinase inhibitors.

Apoptosis is a form of programmed cell death that occurs through enzymatic degradation. When a cell experiences severe damage, apoptosis can be activated, making this mechanism highly efficient in eliminating cells that are unnecessary or potentially harmful, thereby protecting the organism (Nurhayati & Lusiyanti, 2014). The mechanism of apoptosis is highly complex and tightly regulated. Broadly, apoptosis can be divided into four stages. The firs stage involves the presence of death signals (apoptotic inducers), which are physiological (hormones and cytokines), biological (viruses, bacteria, and parasites), chemical (drugs), or physical (radiation and toxins). The second stage is the integration or regulation phase, involving signal transduction and induction of apoptosis-related genes. This is followed by the execution stage, in which morphological and chemical changes occur, including DNA degradation, cell disassembly, and formation of apoptotic bodies. The final stage is phagocytosis or elimination by macrophages, dendritic cells, or neighboring cells surrounding the apoptotic cells (Rastogi, *et al*., 2009).

PLANTS AS TRADITIONAL MEDICINE

Law No. 23 of 1992 concerning health states that traditional medicines are ingredients derived from plants, animals, minerals, or galenic preparations, or mixtures of these ingredients that have been used for generations for treatment based on empirical experience or through pre-clinical or clinical testing on standardized herbal medicines and phytopharmaceuticals (Kemenkes RI, 2011). Natural products are valuable in the development of anticancer drugs, especially those derived from plants (Pan, *et al*., 2012). The vast diversity of plant species represents a potential source of active compounds with antitumor and cytotoxic activities. Anticancer bioactive compounds have been identified in many plants; therefore, numerous studies have been conducted to discover and develop plant-derived anticancer drugs (Pratama & Nuwarda, 2018).

An activity (efficacy) test is conducted to determine the therapeutic effectiveness of a test substance that has been scientifically evaluated using experimental animals or certain biological materials, with the testing methodology and parameters determined based on the intended clinical use of the substance. Similar to toxicity testing, activity testing is generally classified into *in vitro* and *in vivo* assays (Yadav, *et al*., 2016). In principle, *in vitro* tests are carried out in test tubes, cell culture dishes, or other systems outside a living organism. Cell growth and viability in in vitro studies can be measured using several methods, such as the MTT assay and sulforhodamine B (SRB) assay (Avila & Pugsley, 2011). Biological *in vivo* tests usually use experimental animals to investigate effects that cannot be directly studied in the human body, based on the assumption that certain tissues, cells, and enzymatic systems in these animals share similarities with those of humans.

Emprit Ginger (*Zingiber officinale* Rosc.) and Tiwai Onion (*Eleutherine palmifolia*)

Emprit ginger is a perennial herbaceous plant that grows wild in fields with moist soil and abundant sunlight. It has an errect stem, fibrous roots, and horizontally growing rhizome bulbs. In general, the rhizome of emprit ginger contains similar phytochemicals in varying amounts, including starch, resin, malate, oxalate, gingerin, fats, carbohydrates, vitamins (A, B, and C), and bioactive compounds such as flavonoids, polyphenols, zingiberin, shogaol, gingerol, zerumbon, zingiberol, zingiberen, chavicol, geraniol, linalool, cineol, β-elemene, limonene, and camphene (Hapsoh, *et al*., 2010).

The active compound gingerol, a phenolic alkanone, can inhibit the activity of cyclooxygenase-2, the p38 mitogen-activated protein kinase (MAPK), and the transcription factor NF-κB and is therefore classified as a compound with strong antioxidant and anti-inflammatory properties (Stoilova, *et al*., 2007). Gingerol is also known to induce tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), reduce the viability of gastric cancer cells, and increase the expression of caspase-3/7, making it a potential pro-apoptotic compound (Ishiguro, *et al*., 2007). Shogaol is another phenolic compound found in emprit ginger that is known to have anti-inflammatory, anticancer, and antitumor effects. In addition to its functional health benefits, shogaol is an important constituent responsible for the characteristic taste and aroma of emprit ginger. The active compound 6-shogaol also exhibits free anti-radical scavenging activity (Abdullah, *et al*., 2010).

Tiwai onion, also known as the Dayak onion, is a plant native to Kalimantan. The Tiwai onion grows in clusters, has wet stems, reaches approximately 50 cm in height, and possesses layered, red, oval to elongated bulbs (Naspiah, *et al*., 2014). Tiwai onion contains various phytochemical constituents, including alkaloids, glycosides, flavonoids, phenolics, steroids, tannins, anthraquinones, triterpenoids, and saponins.

These active compounds, particularly alkaloids, glycosides, flavonoids, phenolics, steroids, and tannins, represent potential a source for the development of medicinal agents. Flavonoids and phenolic compounds exhibit antioxidant activity as well as α-glucosidase inhibitory effects (Febrinda, *et al*., 2014). The combination of antioxidant capacity and inhibition of the α-glucosidase enzyme suggests that tiwai onion has potential as an antidiabetic agent for the prevention and management of diabetes mellitus (Febrinda, *et al*., 2014). According to epidemiological studies, flavonoids can interact with genes and enzymes involved in antiproliferation, regulation of the cell cycle, and apoptosis (Yerlikaya, *et al*., 2017). Anticancer activity may be achieved by inhibiting cell proliferation through the K-Ras and PI3K pathways, which play important roles in cell proliferation and differentiation (Chen, *et al*., 2009).

Pre-Clinical Studies on Emprit Ginger (*Zingiber officinale* Rosc.)

Emprit ginger is a plant that has the potential to be used as an anticancer agent. The active compounds found in its rhizomes, such as gingerol (6-gingerol and 10-gingerol) and shogaol (4-shogaol, 6-shogaol, and 10-shogaol), have been shown to inhibit the growth of cancer cells in several studies conducted on cell lines and experimental animals (such as mice, rats, and hamsters). In addition, the bioactive compounds of emprit ginger can directly or indirectly suppress the growth of cancer cells through various mechanisms. Several *in vitro* and *in vivo* studies on emprit ginger as an anticancer candidate are summarized in Tables 1 and Table 2.

Mechanism of Emprit Ginger (*Zingiber officinale* Rosc.) as Anticancer

Emprit ginger is a plant with considerable potential to be developed as an anticancer agent (Zachariah, 2008). Active compounds such as gingerols (6-gingerol, 8-gingerol, and 10-gingerol), shogaols (6-shogaol and 10-shogaol), and paradol in emprit ginger have shown promising roles in cancer prevention and management through various mechanisms. The mechanisms of action of these active compounds are associated with inhibition of cell proliferation, induction of apoptosis, suppression of NF-κB activity to reduce inflammation, and induction of cell cycle arrest (Yusof, 2016).

6-gingerol is capable of inducing cell cycle arrest and cell death of cancer cells expressing p53. It also decreases the expression of cyclin

Table 1. *In vitro* studies on emprit ginger (*Zingiber officinale* Rosc.).

Elements	Study Type	Potential Mechanisms	Reference
Emprit ginger extract	*In vitro* on K-562 blood cancer cells and A-549 lung cancer cells	Able to inhibit the proliferation of K-562 cell lines and A-549 cells	Agustinisari & Zakaria, 2006
Emprit ginger extract-based on fluorescent carbon nanodots	*In vitro* on human HepG2 hepatocellular carcinoma cells	Increases *ROS* levels, upregulates p53 expression and promotes apoptosis promotion	Li, *et al*., 2014
Emprit ginger extract	*In vitro* on human colon adenocarcinoma cells, HT-29	Regulates the promotion of apoptosis, upregulates the caspase-9 gene and downregulates KRAS, ERK, Akt and Bcl-xL	Tahir, *et al*., 2015
Gingerol and shogaol	*In vitro* on blood cancer cells, K-562	Increases the cytolytic response of natural killer (NK) cells against target cancer cells K-562	Tejasari & Zakaria, 2006
Gingerol	*In vitro* on HepG2 cancer cells	Reducing levels of 8-OHdG causes oxidative stress in liver cancer cells (HepG2)	Harliansyah, 2011
6-gingerol	*In vitro* in YYT mouse colon cancer cells	Suppression of colon cancer cell growth and inhibition of tumor blood supply through angiogenesis	Brown, *et al*., 2008
6-gingerol	*In vitro* on LNCaP prostate cancer cells	Gingerol affects the cell cycle by increasing the G0 phase and is able to induce apoptosis by increasing the expression of caspase-3 in LNCaP cells	Kim, *et al*., 2011
6-gingerol	*In vitro* on human HeLa cervical cancer cells	Decreased levels of cyclin A, cyclin D1 and cyclin E1, increased caspase expression and inhibited the mTOR signaling pathway	Zhang, *et al*., 2017
10-gingerol	*In vitro* in rat and human breast cancer cells	Inhibits cell growth, reduces cell division, and induces phase S cell cycle arrest and apoptosis	Bernard, *et al*., 2017
6-gingerol, 10-gingerol, 6-shogaol dan 10-shogaol	*In vitro* on human PC3R prostate cancer cells	Inhibits prostate cancer cell proliferation, and upregulates MRP1 and GSTπ expression	Liu, *et al*., 2017

Table 2. *In vivo* studies on emprit ginger (*Zingiber officinale* Rosc.).

Elements S	tudy Type	Potential Mechanisms	Reference
Emprit ginger ethanol extract	*In vivo* in Syrian golden hamster	Upregulation of MDR1 and MRP3 against cholangiocarcinoma (CCA) resistance	Plengsuriyakarn, *et al*., 2012
Emprit ginger extract	*In vivo* with research subjects, the number of fibroblast cells in mice	Increases the number of fibroblast cells in the proliferative phase in mice with initiation wounds	Etika, *et al*., 2017
Emprit ginger extract	*In vivo* in Swiss female albino rats	Activates AMPK, reduces cyclin D1 expression, and NF-κB levels and increases p53 expression	Elashmawy, *et al*., 2018
Ginger essential oil (GSO)	*In vivo* in Swiss male albino rats	Reducing the volume of tumor development and increasing the lifespan of mice carrying tumor ascites	Jeena, *et al*., 2015
GDNPs2	*In vivo* in C57BL/6 or FVB/NJ female mice	Reduces acute colitis, improves intestinal repair and prevents chronic colitis and colitis-associated cancer (CAC)	Zhang, *et al*., 2016
Ginger oleoresin emprit-lipid nanoparticle	*In vivo* in BALB/c mice	Decreased LLC lung tumor growth and induced IL-2 and IL-10 production	Thao, *et al*., 2019
Aqueous ginger extract (AGE)	*In vivo* in adult male albino rats	Decreased mitotic index and increased MNPCE in somatic	Aziz, *et al*., 2020
Ginger extract emprit -chitosan nanoparticles (CNPS)	*In vivo* in male albino mice	Increases antioxidant activity, downregulates MDR1 and induces apoptosis	Abomansour, *et al*., 2020
Gingerol and shogaol	*In vivo* in diabetic rat models	Maintaining super oxide dismutase (SOD) levels and reducing the amount of necrosis of glomerular epithelial cells in rat kidneys	Hardiyanto, *et al*., 2018
6-shogaol rich ginger oleoresin	*In vivo* in Swiss male albino rats	Increases rat life span, controls tumor volume and normalizes hematological parameters	Kemkar, *et al*., 2018

A and CDK, leading to reduced retinoblastoma (Rb) phosphorylation, followed by blockage of entry into the S phase. As a result, cell growth is inhibited through cell cycle arrests at the G1 phase. In addition, 6-gingerol can induce significant G2/M phase arrest by increasing the levels of reactive oxygen species (ROS), p53, p27Kip1, and p21cip1, which subsequently reduces the levels of CDK1, cyclin A, and cyclin B1. These findings indicate that 6-gingerol can inhibit the growth of cancer cells by inducing cell cycle arrest at both the G1 and G2/M phases (Wang, *et al*., 2014). Furthermore, 6-gingerol suppresses cyclin D1 expression and induces NAG-1 expression through

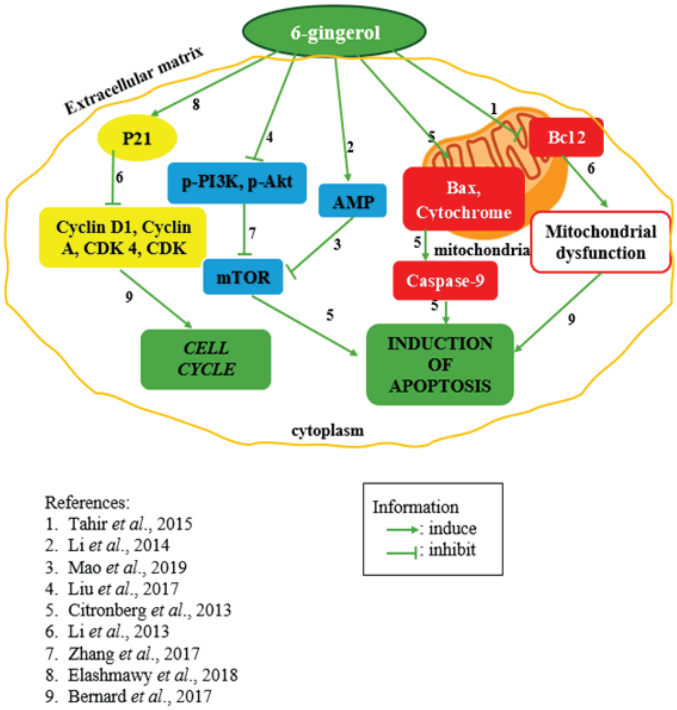

Figure 2. Mechanism of 6-gingerol in anticancer activity through induction of cell cycle arrest and apoptosis.

the PKC and glycogen synthase kinase (GSK)-3β pathways. Tumor necrosis factor-related apoptosis-inducing ligand (TNF-TRAIL) plays an important role in triggering apoptosis. In addition, 6-gingerol enhances TRAIL-induced apoptosis by increasing caspase-3/7 activity (Ashkenazi, *et al*., 2010).

Experimental studies have shown that several active compounds in emprit ginger can modulate cell cycle progression as part of their chemopreventive mechanisms (Zadorozhna & Mangieri, 2021). Among these compounds, 6-gingerol appears to exhibit the most prominent anticancer activity. Therefore, 6-gingerol has multiple anticancer mechanisms of action, including the induction of apoptosis and cell cycle arrest, as shown in Figure 2.

Apart from 6-gingerol, emprit ginger (*Zingiber officinale* Rosc.) also contains 6-shogaol, another bioactive compound with notable anticancer potential. The anticancer mechanism of 6-shogaol involves the action via ROS, ER stress, autophagy, and the MAPK and Akt signaling pathways. Interactions among these signaling networks at different cellular levels enable 6-shogaol to induce apoptosis and cell cycle arrest (Figure 3). The antiproliferative effects of 6-shogaol are mediated through the targeting of multiple signaling pathways, resulting in broad-spectrum modulation of several signaling factors, including ER stress-related proteins, GSK3β, LC3-II, MAP kinases, caspase-3 activation, ROS production, and cell cycle regulatory proteins. These effects ultimately lead to G2/M phase cell cycle arrest and apoptosis. In addition, 6-shogaol induces cyclin protein expression and promotes cleavages of protein kinase C-delta (Wu, *et al*., 2015).

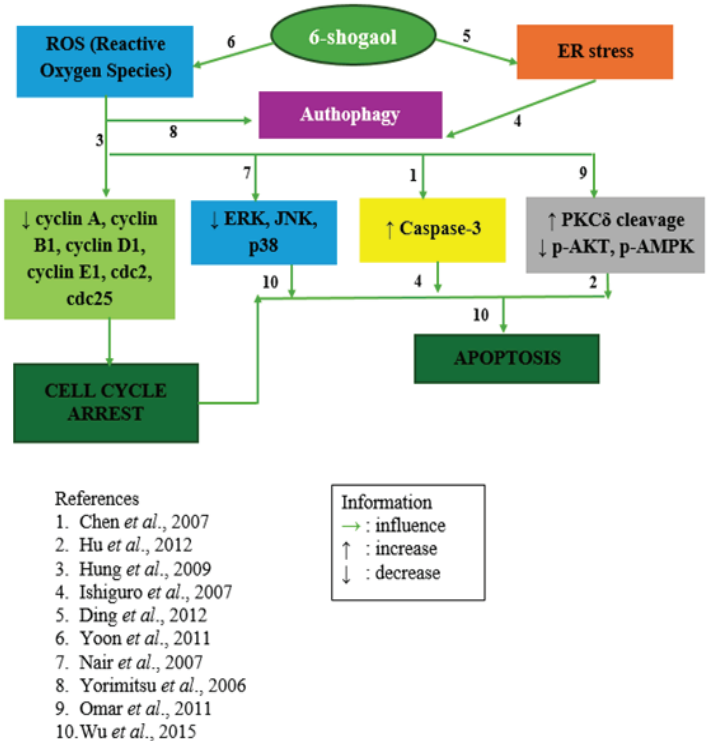

Figure 3. Mechanism of 6-shogaol in anticancer activity through induction of cell cycle arrest and apoptosis.

PRE-CLINICAL STUDY ON TIWAI ONION *(Eleutherine palmifolia)*

The tiwai onion is a plant with the potential to be developed as an anticancer agent. Active compounds found in tiwai onion, such as flavonoids and their derivatives, as well as compounds from the naphtoquinone group (eleutherinone, eleutherin, isoeleutherin and eleutherol), have demonstrated inhibitory activity against the growth of cancer cells in several studies conducted using cell lines and experimental animals (such as mice, rats and hamsters). In addition, the bioactive compounds of the tiwai onion can inhibit the growth of cancer cells directly or indirectly through several mechanisms. Several *in vitro* and *in vivo* studies on tiwai onion as a potential anticancer candidate are summarized in Table 4 and Table 5.

Mechanism of Action of Tiwai Onion (*Eleutherine palmifolia*) as Anticancer

Tiwai onion (*Eleutherine palmifolia*), also known as the Dayak onion, has several derivatives that can inhibit cancer cells through the mechanisms of apoptosis and cell cycle arrest. Some of these derivatives include flavonoid compounds and naphthoquinone compounds, such as eleutherinone, eleutherin, isoeleutherin and eleutherol (Muti'ah, *et al.*, 2018). Flavonoids are active compounds that have been shown to induce cell apoptosis and inhibit the proliferation of various cancer cells (Mardiyaningsih & Ismiyati, 2014). The mechanism of action of flavonoids in cell apoptosis induction is shown in Figure 4.

Flavonoids can act as anticancer agents by modulating both intrinsic and extrinsic

Table 4. *In vitro* studies on Tiwai Onions (*Eleutherine palmifolia*).

Elements	Study Type	Potential Mechanisms	
Naphtoquinone (Tiwai ethanol extract)	*In vitro* on colorectal cancer cells, STF293	Inhibits transcription of TCF/ß-catenin, forms topoisomerase II complex and increases c-myc for apoptosis	Li, *et al.*, 2009
Flavonoids (Tiwai onion ethanol extract)	*In vitro* on breast cancer cells, T47D	Inhibits proliferation through the inhibition of oxidative processes and inhibits the expression of the enzyme topoisomerase II	Putri & Haryoto, 2018
Flavonoids (Tiwai onion ethanol extract)	*In vitro* on cervical cancer cells, HeLa	Inhibits the estrogen/*ER-α* pathway, inhibits cancer cells through inhibition of neo angiogenesis in VEGF/VEGFR-2 and inhibits cell proliferation in the G2/M phase	Muti'ah, *et al.*, 2018
Isoliquiritigenin and oxyresveratrol	*In vitro* on cervical cancer cells, HeLa	The ethyl acetate fraction has high potential as an anticancer with an IC_{50} value of 44.335 µg/mL	Minggarwati, 2017
Isoliquiritigenin and oxyresveratrol	*In vitro* on HeLa cervical cancer cells	Antiproliferative activity, induces cell accumulation in the G2/M phase and inhibits NF-κB activity against cell lines	Muti'ah, *et a l.*, 2019
Tiwai onion ethyl acetate extract	*In vitro* on T47D breast cancer cells	Induction of apoptosis and cell accumulation in the G0/G1 phase of breast cancer	Yuniarti, *et a l.*, 2019
Flavonoids (Tiwai Onion Extract)	*In vitro* on breast cancer cells T47D	Suppresses mutant *p53* gene expression levels and induces cell cycle arrest	Sudarmawan, *et al.*, 2010
Tiwai onion extract	*In vitro* on T47D cells	Cell cycle arrest in G0 phase and causes apoptosis	Fitri & Rosidah, 2014
Hexadecanoic acid, octadecadienoic acid, linoleic acid (Tiwai onion chloroform extract)	*In vitro* on L1210 leukemia cells	The chloroform fraction has high potential as an anticancer with an IC_{50} value of 9.56 ppm	Lestari, *et al.*, 2019
Tiwai onion ethyl acetate extract	*In vitro* on colon cancer cells. WiDr	Has a toxic effect on colon cancer cells WiDr, induces cell cycle arrest and apoptosis	Lubis, *et al.*, 2018

Table 5. *In vivo* **study on Tiwai onion (*Eleutherine palmifolia*).**

Elements	Study Type	Potential Mechanisms	Reference
Isoliquiritigenin and oxyresveratrol (Tiwai onion extract)	*In vivo* in BALB/c mice CAC model	Increases TNF-α expression, induces apoptosis, and decreases colon goblet cell count and TGF-β levels	Muti'ah, *et al*., 2020
Ethanol extract of tiwai onion	*In vivo* in albino male mice BALB/c model CAIA	Reduces the incidence of arthritis and increases the regulation of inflammatory cytokines, TNF-α, IL6 and 7	Hanh, *et al*., 2018
Tiwai onion ethanol extract	*In vivo* in female Wistar rats	There was no sign of toxicity with a dose of 2000 mg/kg BW in rats	Wati, *et al*., 2021
Flavonoids and naphthoquinone (Tiwai onion chloroform extract)	*In vivo* in male white mice	Toxic effect with marked death in mice	Lestari, *et al*., 2019
Tiwai onion ethanol extract	*In vivo* in lead-induced BALB/c male mice	Maintaining testosterone and seminiferous tubule thickness	Gayatri, *et al*., 2017
Tiwai onion ethanol extract	*In vivo* in BALB/c mice	Increased macrophage activation, increased IFN-γ expression and increased number of cells expressing CD14	Toemon, 2015
Flavonoids (Tiwai onion ethanol extract)	*In vivo* in BALB/c mice	Increased serum IgG levels, increased B lymphocyte activation and increased germinal center	Carmelita, 2016
Polyphenols and flavonoids (Tiwai onion ethanol extract)	*In vivo* in mice induced by dextran sulfate sodium (DSS)	Increase levels of MDA, which are mutagenic and increase levels of tissue SOD	Wijayanti & Hasyati, 2018
Tiwai onion ethanol extract	*In vivo* in BALB/c mice	Increased number (natural killer) NK cells and CD 8+	Meiliana, 2016
In vivo tiwai onion extract	*In vivo* in DMBA-induced female Sprague Dawley rats	Inhibits the growth of neoplasms in all organs and inhibits cell proliferation	Widayati & Rompas, 2019

apoptotic pathways. The intrinsic pathway is mediated through the mitochondria, where the release of mitrochondrial protein and regulation by the Bcl-2 initiates activation of caspase-9, caspase-3, and caspase-7. In cancer cells, overexpression of oncogenes (*e.g*., c-Myc) can promote uncontrolled cell proliferation and activate the suppression of p53, an anti-apoptotic protein of the Bcl-2 family in cancer cells. In contrast, pro-apoptotic proteins and caspases can be downregulated. Flavonoids can target these apoptotic signalling pathways and thereby promote cancer cell death. The extrinsic pathway is linked to tumor necrosis factor (TNF) and other major signaling proteins. Cancer cells

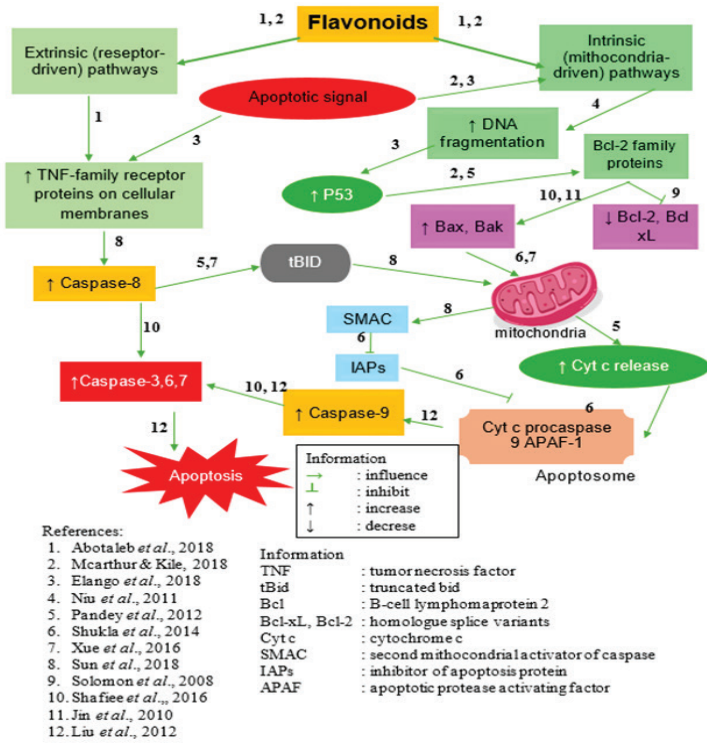

Figure 4. Mechanism of flavonoids in anticancer activity through induction of apoptosis.

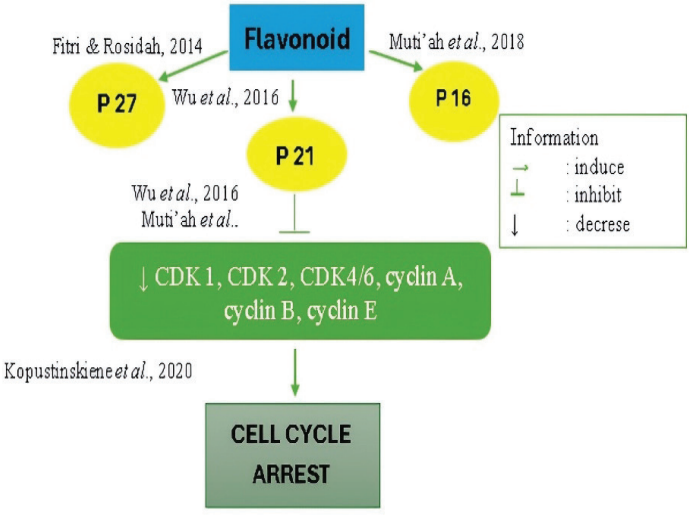

Figure 5. Mechanism of flavonoids in anticancer activity through cell cycle arrest.

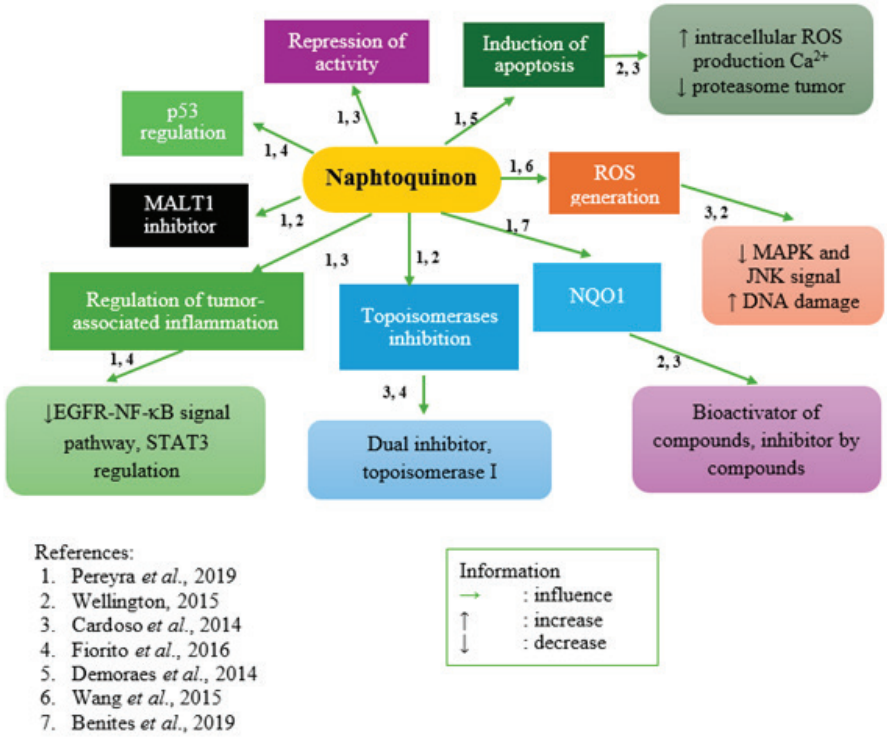

Figure 6. Mechanism of naphtoquinone in anticancer activity.

often develop resistance to programmed cell death (apoptosis) induced by a series of signal transduction pathways, as well as through altered expression of pro-apoptotic caspase proteins and Bcl-2 family proteins. Flavonoids may act as pro-oxidants, suppressing cancer cell proliferation by inhibiting the epidermal growth factor receptor (EFGR/MAPK) pathway, (PI3K), protein kinase B activation, and nuclear factor kappa-B (NF-κB) signaling. Thus, flavonoids can activate programmed cell death signaling pathways in cancer cells through dual mechanism: activating anti-apoptotic proteins while suppressing pro-apoptotic proteins and capacities (Kopustinskiene, *et al*., 2020). Cell cycle arrest may also induced by the flavonoid compounds contained in the ethyl acetate extract of tiwai onion bulbs. These compounds can increase the expression of p21 and p27, which binds to cyclin D and cyclin-dependent kinase 4/6 (CDK) complexes, thereby inhibiting PRB phosphorylation and causing cell cycle arrests (Figure 5).

In addition, tiwai onion bulbs contain active compounds from the naphthoquinone group. The mechanism of action of naphthoquinone as an anticancer agent is shown in Figure 6. Naphthoquinone can kill or induce cell death by more than one mechanism. Their cytotoxicity effects have been associated with inhibition of human DNA topoisomerase I and II, induction of DNA damage (through ROS generation and oxidative stress), activation of p53 in response to DNA damage, regulation of tumor-associated inflammation, inhibition of MALT1, induction of apoptosis through suppression of ER, repression of telomerase activity, and suppression of NQO1 (Pereyra, *et al*., 2019).

CONCLUSION

The activities of gingerol, shogaol, and their derivatives found in the rhizome of emprit ginger (*Zingiber officinale* Rosc.), as well as flavonoids, naphthoquinones, and their derivatives in the bulbs of tiwai onion (*Eleutherine palmifolia*), have been scientifically demonstrated through both *in vitro* and *in vivo* studies, indicating their potential use as anticancer medicine. Pre-clinical *in vitro* and *in vivo* studies on the rhizomes of emprit ginger (*Zingiber officinale* Rosc.) and tiwai onion (*Eleutherine palmifolia*) have also shown that these two plants are able to inhibit cell signaling pathways by inducing apoptosis and causing cell cycle arrest.

REFERENCES

Abdullah, S., Abidin, S.A.Z., Morad, N.A., Makpol, S., Zurinah, W., Ngah, W., *et al.*, 2010, Ginger Extract (*Zingiber officinale*) Triggers Apoptosis and G0/G1 Cells Arrest in HCT 116 and HT 29 Colon Cancer Cell Lines, *Afr. Journal Biochem. Res.*, **11**(8), 112-120.

Abo Mansour, H.E., El-Batsh. M.M., Badawy, N.S., Mehanna, E.T., Mesbah, N.M., and Abo-Elmatty, D.M., 2021, Ginger Extract Loaded into Chitosan Nanoparticles Enhances Cytotoxicity and Reduces Cardiotoxicity of Doxorubicin in Hepatocellular Carcinoma in Mice, *Nutrition and Cancer*, **73**(11-12), 2347-2362.

Abotaleb, M., Samuel, S.M., Varghese, E., Varghese, S., Kubatka, P., Liskova, A., and Busselberg, D. 2018, Flavonoids in Cancer and Apoptosis, *Cancers (Basel)*, **11**(1), 28.

Agustinisari, I. and Zakaria, F.R., 2006, Pengaruh Ekstrak Rimpang Jahe (*Zingiber officinale* Rosc.) Segar dan Tunas Jahe terhadap Proliferasi Beberapa Alur Sel Kanker, *Jurnal Pascapanen*, **3**(1), 50-59.

Avila, E.V. and Pugsley, M.K., 2011, An Overview of Colorimetric Assay Methods Used to Assess Survival or Proliferation of Mammalian Cells: A Review *Proc. West Pharmacol Soc.*, **54**, 10-14.

Aziz, D.Z., Kadhim, N.J., Majeed, A.A., and Abood, A.H., 2020, Protective Effects of Ginger Extract Against Methotrexate Induced Cytotoxicity in Mice, *Journal of Physics: Conference Series*, **1664**(2020), 012103.

Bernard, M.M., McConnery, J.R., and Hoskin, D.W., 2017, [10]-Gingerol, A Major Phenolic Constituent of Ginger Root, Induces Cell Cycle Arrest and Apoptosis in Triple Negative Breast Cancer Cells, *Exp. Moleculer Pathology,* **102**(2), 370–376.

Brown, A.C., Shah, C., Liu, J., Pham, J.T.H., Zhang, J.G., and Jadus, M.R., 2008, Ginger's (*Zingiber officinale* Roscoe) Inhibition of Rat Colonic Adenocarcinoma Cells Proliferation and Angiogenesis *In Vitro*, *Phytother Res.*, **23**(5), 640–645.

Chang, E., Daly, J., and Elliot, D., 2006, Patofisiologi Aplikasi pada Praktik Keperawatan, Jakarta: Buku Kedokteran EGC.

Chen, C.Y., Liu, T.Z., Liu, Y.W., Tseng, W.C., Liu, R.H., Lu, F.J., *et al.*, 2007, 6-shogaol (Alkanone from Ginger) Induces Apoptotic Cell Death of Human Hepatoma p53 Mutant Mahlavu Subline via An Oxidative Stress-Mediated Caspase-Dependent Mechanism, *Journal Agric. Food Chem.*, **55**(3), 948-954.

El-Ashmawy, N.E., Khedr, N.F., El-Bahrawy, H.A., and Mansour, H.E.A., 2018, Ginger extract Adjuvant to Doxorubicin in Mammary Carcinoma: Study of Some Molecular Mechanisms, *European Journal Nutrition*, **57**(3), 981–989.

Febrinsah, R., Putri, D.D.P., Sarmoko, Nurulita, N.A., Meiyanto, E., and Nugroho, A.E., 2014, Hesperidin as a Preventive Resistance Agent in MCF-7 Breast Cancer Cells Line Resistance to Doxorubicin, *Asian Pacific Journal of Tropical Biomedicine*, **4**(3), 228-233.

Fitri, Y. and Suwarno, E., 2014, Effects of Inhibition Cell Cycle and Apoptosis of Sabrang Onion Extract (*Eleutherine bulbosa* (Mill.) Urb.) on Breast Cancer Cells, *International Journal of*

PharmTech Research, **6**(4), 1392-1396.

Galingging, R.Y., 2009, Bawang Dayak (*Eleutherine palmifolia*) sebagai Tanaman Obat Multifungsi, Warta Penelitian dan Pengembangan.

GLOBOCAN, 2020, Estimated Cancer Incidience, Mortality and Prevalence Worldwide in 2013-2020.

Harliansyah, H., 2011, Efek Penghambatan Gingerol terhadap 8-Hidroksideoksiguanosin (8-OHdG) Penginduksi Sel Kanker, HepG2, *Majalah Kesehatan PharmaMedika*, **3**(2), 272-275.

Hapsoh, Hasanah, Y., and Julianti E., 2010, *Budidaya dan Teknologi Pascapanen Jahe*, Medan: USU Press.

Ieyama, T., Gunawan-Puteri, M.D.P.T., Gunawan, and Kawabata, J., 2011, á-Glucosidase Inhibitors from The Bulb of Eleutherine americana, *Food Chemistry*, **128**(2), 308-311.

Ishiguro, K., Ando, T., Maeda, O., Ohmiya, N., Niwa, Y., Kadomatsu, K., and Goto, H., 2007, Ginger Ingredients Reduce Viability of Gastric Cancer Cells via District Mechanisms, *Biochem. Biophys. Research Communications*, **362**(1), 218-223.

Jeena, K., Liju, V.B., and Kuttan, R., 2015, Antitumor and Cytotoxic Activity of Ginger Essential Oil (*Zingiber officinale* Roscoe), *International Journal of Pharmacy and Pharmaceutial Science*, **7**(8), 341-344.

Kemkar, K., Sathiyanarayanan, L., Sathiyanarayanan, A., and Mahadik, K., 2018, 6-shogaol from Ginger Oleoresin Loaded Liposomes using DMPG-Na as A Carrier Enhances the *In Vitro* and *In Vivo* Anticancer Activity, *Journal of Applied Pharmaceutical Science*, **8**(2), 45-53.

Kementerian Kesehatan Republik Indonesia (Kemkes RI), 2011, *Formularium Obat Herbal Asli Indonesia*, Jakarta: Departemen Kesehatan Republik Indonesia.

Kopustinskiene, D.M., Jakstas, V., Savickas, A., and Bernatoniene, J., 2020, Flavonoids as Anticancer Agents, *Nutrients*, **12**(2), 457.

Lestari, D., Kartika, R., and Marliana, E., 2019, Antioxidant and Anticancer Activity of *Eleutherine bulbosa* (Mill.) Urb on Leukemia Cells L1210, *Journal of Physics: Conference Series*, **1277**(1), 012022.

Liu, C-M., Kao, C-L., Tseng, Y-T., Lo, Y-C., and Chen, C-Y., 2017, Ginger Phytochemicals Inhibit Cell Growth and Modulate Drug Resistance Factors in Docetaxel Resistant Prostate Cancer Cell, *Molecules*, **22**(9), 1477.

Lubis, I.A., Ichwan, M.F., Mustofa, M., and Satria, D., 2018. Anticancer Activity *Eleutherine bulbosa* (Mill.) Urb. Extract on WiDr Cell Line *In Vitro*, *Advances in Health Science Research*, **9**, 167-171.

Mangan, Y., 2005, *Cara Bijak Menaklukan Kanker*, Jakarta: AgroMedia Pustaka.

Meles, K.D., 2010, *Peran Uji Praklinik dalam Bidang Farmakologi*, Pusar Penerbitan dan Percetakan UNAIR, Perpustakaan Universitas Airlangga Surabaya.

Minggarwati, T.S., 2017, Uji Aktivitas Antikanker dan Identifikasi Senyawa Aktif dari Fraksi Umbi Bawang Sabrang terhadap Sel Kanker Serviks HeLa, *ABA Journal*, **102**(4), 24-25.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and Group P., 2009, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, *PLoS Medicine*, **6**(7), e1000097.

Muti'ah, R., Listiyana, A., Suryadinata, A., Annisa, R., Hakim, A., Anggraini, W., and Susilowati, R., 2018, Activity of Inhibit The Cell Cycle and Induct Apoptosis in HeLa Cancer Cell with Combination of Sabrang onion (*Eleutherine palmifolia* (L.) Merr) and Starfruit Mistletoe (*Macrosolen cochinchinensis* (Lour.) Tiegh), *Journal of Applied Pharmaceutical Science*, **8**(10), 122-128.

Narko, T., Permana, B., Prasetiawati, R., Soni, D., and Khairiyah, F., 2017, Molecular Docking Study of Bawang Tiwai (*Eleutherine palmifolia* (L) Merr) Compound as Anti Servical Cancer, *Jurnal Ilmiah*

Farmako Bahari, **8**(2), 1-14.

Naspiah, N., Iskandar, Y., and Moektiwardoyo, M., 2014, Artikel Ulasan: Bawang Tiwai (*Eleutherine americana* Merr), Tanaman Multiguna, *Indonesian Journal of Applied Sciences (IJAS)*, **4**(2), 18-30.

Nurhayati, S. and Lusiyanti, Y., 2006, Apoptosis dan Respon Biologik Sel sebagai Faktor Prognosa Radioterapi Kanker, *Buletin Alara*, **7**(3), 57-66.

Pereyra, C.E., Dantas, R.F., Ferreira, S.B., Gomes, R.P., and Silva-Jr, F.P., 2019, The Diverse Mechanisms and Anticancer Potential of Naphthoquinone, *Cancer Cell Internation*, **19**, 207.

Plengsuriyakarn, T., Viyanant, V., Eursitthichai, V., Tesana, S., Chaijaroenkul, W., Itharat, A., and Na-Bangchang, K., 2012, Cytotoxicity, Toxicity and Anticancer Activity of *Zingiber officinale* Roscoe Against Cholangiocarcinoma, *Asian Pacific Journal of Cancer Prevention*, **13**(9), 4597-4606.

Pratama, F.E. and Nuwarda, R.F., 2018, Review: Senyawa Aktif Antikanker dari Bahan Alam dan Aktivitasnya, *Farmaka*, **16**(1), 149-158.

Puspadewi, R., Adirestuti, P., and Menawati, R., 2013, Khasiat Umbi Bawang Tiwai (*Eleutherine palmifolia* (L) Merr) sebagai Herbal Antimikrobia Kulit, *Kartika Jurnal Ilmiah Farmasi*, **1**(1), 31-37.

Rastogi, R.P., Richa, and Sinha, R.P., 2009, Apoptosis: Molecular Mechanism and Pathogenicity, *EXCLI Journal*, **8**(1), 155-181.

Riset Kesehatan Dasar (RISKESDAS), 2018, Hasil Utama Riset Kesehatan Dasar (RISKESDAS), *Journal of Physics A: Mathematical and Theoretical*, **44**(8), 1-200.

Shukla, S., Fu, P., and Gupta, S., 2014, Apigenin Induces Apoptosis by Targeting Inhibitor of Apoptosis Proteins and Ku70-Bax Interaction in Prostate Cancer, *Apoptosis*, **19**(5), 883-894.

Singh, R.L., Gupta, R., Singh, P.K., and Singh, R., 2016, Pharmacological Avtivities of *Zingiber officinale* (Ginger) and Its Active Ingredients: A Review, *International Journal of Scientific and Inovative Research*, **4**(1), 1-11.

Tahir, A.A., Sani, N.F.A., Murad, N.A., Makpol, S., Ngah, W.Z.W., and Yusof, Y.A.M., 2015, Combined ginger extract and Gelam honey modulate Ras/ERK and PI3K/AKT pathway genes in colon cancer HT29 cells, *Nutrition Journal*, **14**, 31.

Tejasari and Zakaria, F.R., 2006, Senyawa Bioaktif Rimpang Jahe (*Zingiber officinale* Rosc.) Meningkatkan Respon Sitolitik Sel Nk terhadap Sel Kanker Darah K-562 *In Vitro*, *Jurnal Teknologi dan Industri Pangan*, **XVII**(2), 97-108.

Thao, D.T., Nga, N.T., Van, N.A., and Hung, K.D. 2019, Potential Anticancer Activities of a Combination of Curcumin, Ginger Oleoresin and Rutin Solid Lipid Nanoparticle (Vietlife-Antican) in LLC Tumor-Bearing Mice, *Natural Product Communications*, 1-7.

Utomo, E.K., Wahyudi, T., Januar, M.F., Saputra, A., and Purnomo, S., 2020, *Effect Exercise on Fatigue in Patient Heart Failure: Literature Review,* International Proceedings the 2nd ISMoHIM.

Wang, S., Zhang, C., Yang, G., and Yang, Y., 2014, Biological Properties of 6-gingerol: A Brief Review, *Natural Product Communications*, **9**(7), 1027-1030.

World Health Organization (WHO), 2019, *WHO Global Report on Traditional and Complementary Medicine 2019*, World Health Organization.

Wiseman, M., 2007, *Essential of Human Nutrition*, New York: Oxford University Press.

Yadav, M., Rani, S., and Sharma, K., 2016, A Review on Awareness about Banned Drugs, *Inventi Rapid: Pharmacy Practice*, **5**(2), 11-20.

Yusof, Y.A.M., 2016, Gingerol and Its Role in Chronic Diseases, In. Chandra, S., Sahdeo, G., Bharat, P., (Eds), *Drug Discovery from Mother Nature*, **3**(5), 177-207.

Zadorozhna, M. and Mangieri, D., 2021, Mechanisms of Chemopreventive and Therapeutic Proprieties of Ginger Extracts in Cancer, *International Journal Molecular Science*, **22**(12), 6599.

Zhang, F., Zhang, J-G., Qu, J., Zhang, Q., Prasad, C., and Wei, Z-J., 2017, Assessment of Anti-Cancerous Potential of 6-gingerol (Tongling White Ginger) and Its Synergy with Drugs on Human Cervical Adenocarcinoma Cells, F*ood Chem. Toxicol.*, **109**(Pt 2), 910–922.