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THE POTENTIAL OF GINGEROL ACTIVE COMPOUNDS IN ZINGIBER OFFICINALE AS ANTI-CANCER AGENTS

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ABSTRACT

Cancer is a type of chronic disease which is the main cause of death in the world with 19.3 million new cases in 2020. Current cancer treatment includes surgery, chemotherapy, radiotherapy, hormone therapy, antiangiogenesis inhibitors, stem cell therapy, and others. Long-term cancer treatment can cause other health problems, so alternative anti-cancer therapy with the fewest side effects is needed. One natural ingredient that is known to prevent and act as anti-cancer therapy is Zingiber officinale. Zingiber officinale contains gingerol which functions as an anti-oxidant, anti-inflammatory, anti-bacterial, anti-cancer, anti-tumor and anti-mutagenic. The anticancer effects of gingerol are known to be effective in cancers of the liver, stomach, mouth, prostate, breast and ovaries. This literature aims to delve deeper into the role of gingerol as an anti-cancer compound. The strategy employed in the article search involved using electronic databases such as Google Scholar and PubMed. Keywords utilized included "cancer," "red ginger," "gingerol," "Zingiber officinale," and "anticancer." The articles selected were those published within the last 10 years. The study results indicate that gingerol is beneficial in oral, breast, lung, colorectal, cervical, and prostate cancers. The mechanism of action of gingerol involves pathways such as the PI3K/AKT, JAK/STAT, apoptosis, and ROS proliferation pathways. Gingerol is known to be effective as an anti-cancer agent and has the potential to become one of the alternative anti-cancer treatments.

Keywords: *Zingiber officinale, Gingerol,* anticancer

ABSTRAK

Kanker merupakan satu diantara jenis penyakit kronis yang menjadi penyebab kematian utama di dunia dengan 19,3 juta kasus baru pada tahun 2020. Pengobatan kanker saat ini meliputi pembedahan, kemoterapi, radioterapi, terapi hormon, inhibitor antiangiogenesis, terapi stem sel, dan lainnya. Pengobatan kanker tersebut dalam jangka panjang dapat menimbulkan masalah kesehatan lainnya sehingga diperlukan adanya alternatif terapi anti-kanker dengan efek samping paling sedikit. Salah satu bahan alami yang diketahui dapat mencegah dan sebagai terapi anti-kanker adalah Zingiber officinale. Zingiber officinale memiliki kandungan gingerol yang berfungsi sebagai anti-oksidan, anti-inflamasi, anti-bakteri, anti-kanker, anti-tumor, dan anti-mutagenik. Efek antikanker gingerol diketahui efektif pada kanker hati, lambung, mulut, prostate, payudara dan ovarium. Literature ini betujuan untuk membahas lebih dalam mengenai peran gingerol sebagai senyawa anti kanker. Strategi yang dilakukan dalam pencarian artikel adalah dengan menggunakan database elektronik dari Google Scholar, dan PubMed. Kata kunci yang digunakan adalah "kanker", "jahe merah", "*gingerol", "zingiber officinale",* "antikanker. Artikel yang idgunakan adalah artikel dalam kurun waktu 10 tahun terakhir. Hasil studi menunjukan bahwa gingerol berguna pada kanker mulut, payudara, paru, kolorektal, serviks, dan prostat. Mekanisme kerja gingerol adalah melalui jalur proliferasi PI3K/AKT, JAK/STAT, apoptosis, dan ROS. Gingerol diketahui efektif sebagai antikanker dan berpotensi untuk menjadi menjadi salah satu alternatif pengobatan antikanker.

Kata kunci: *Zingiber officinale, Gingerol,* antikanker

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1. INTRODUCTION

Cancer is one of the chronic diseases that are a leading cause of death worldwide. Data obtained from the Global Burden of Cancer indicates that the incidence and mortality of cancer have increased globally.[1] In 2020, the Global Burden of Cancer estimated 19.3 million new cancer cases and 10 million cancer deaths worldwide.[2] The incidence and mortality of cancer in Indonesia, according to the Cancer Country Profile 2020, showed 348,000 cancer cases and 207,000 cancer deaths in 2018. The most common cancer incidence in Indonesia in 2018 was breast cancer, with the highest mortality being lung cancer, followed by breast cancer.[3] Current cancer treatments include surgery, chemotherapy, radiotherapy, hormone therapy, antiangiogenesis inhibitors, stem cell therapy, and others.[4] However, these treatments have side effects such as alopecia, weakness, and pain in the radiotherapy area.[5,6] Long-term cancer treatment can lead to other health problems and drug resistance, necessitating alternative therapies with the fewest side effects.[7]

Currently, the use of natural ingredients, such as spices, is increasing due to their beneficial effects on human health and their anti-cancer properties.[7] One natural ingredient that plays a role in cancer prevention and therapy is red ginger, also known as Zingiber officinale.[8] Ginger is a rhizome plant with many benefits, including as a traditional medicine, culinary spice, and herbal remedy. Ginger can be distinguished by its shape, size, and rhizome color. Emprit ginger has small rhizomes and is generally used in beverages, elephant ginger has large rhizomes and is typically used in confectionery, and red ginger is commonly processed as an herbal medicine.[9] Ginger belongs to the Zingiberaceae family. Today, ginger can be found almost all over the world.[10] Zingiber officinale var. Rubrum, or red ginger, contains phenolic compounds with antioxidant properties. These compounds function to inhibit free radicals in the body. Additionally, red ginger contains gingerol compounds that serve as antioxidants, anti-inflammatory, antibacterial, anti-cancer, anti-tumor, and anti-mutagenic agents.[11]

2. METHOD

The method used in this literature review involves utilizing electronic databases, namely Google Scholar and PubMed. The keywords used include "cancer," "Zingiber officinale," "red ginger," "gingerol," and "anti-cancer." The inclusion criteria are articles in Indonesian and English that discuss the effects of gingerol on cancer. The exclusion criteria include dissertations/theses, letters to the editor, and articles discussing mechanisms other than cancer. The articles reviewed and included in this study consist of 24 studies, comprising 8 types of reviews, 6 in vivo studies, 6 in vitro studies, 2 observational studies, and 2 reports.

3. RESULTS

Gingerol is a phenolic compound predominantly found in ginger. Gingerol and shogaol are the main components that give ginger its spicy flavor.[12] Gingerol is a homologous compound with different unbranched alkyl chains. Shogaol is also a homolog derived from the dehydration of gingerol at C4 and C5.[7] Gingerol compounds are one of the main polyphenols in oleoresin, consisting of 6-gingerol, 8-gingerol, and 10-gingerol. The concentration of gingerol in red ginger

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is higher compared to other types of ginger.[13] Generally, gingerol is the most commonly found compound in ginger, and reports indicate that this compound has various therapeutic potentials, including tumor prevention.[7] In addition to gingerol and shogaol, red ginger also contains other phenolic compounds such as gingerenone-A, 6-dehydrogingerdione, zingerone, quercetin, and paradol.[13]

3.1. Gingerol Effect in Oral Cancer

An important global cancer that affects the head and neck is oral cancer, and the AMPK/mTOR pathway plays a key role in its development. In contrast to mTOR, which is involved in cell proliferation and biosynthesis, AMPK functions as a metabolic tumor suppressor. AMPK inhibits mTORC1 through specific phosphorylation processes. Zhang et al. discovered that 6-gingerol caused G2/M phase cell cycle arrest, triggered apoptosis, and greatly reduced cancer cell migration, invasion, and proliferation on YD10B and Ca9-22 oral cancer cells. At concentrations of 100 μM and 150 μM, the reduction in cell viability was approximately 50% to 70% after treatment. Mechanistically, [6]-gingerol activated AMPK and suppressed the AKT/mTOR signaling pathway, leading to reduced cancer cell growth. [14]

3.2. Gingerol Effect in Breast Cancer

Breast cancer is caused by several risk factors, including lifestyle, radiation, hormonal therapy, and genetic mutations. Previous studies have found that the activity of gingerol can inhibit growth, migration, invasion, and stimulate apoptosis by targeting the PI3K/Akt signaling pathway in MDA-MB-231/IR cells. Gingerol is known to cause a 16% reduction in MDA-MB-231 cells. Gingerol works by affecting the structure of lipid rafts in MDA-MB-231 IR cells and reducing the activity of key signaling pathways within the lipid rafts.[15–17]

3.3. Gingerol Effect in Lung Cancer

The most prevalent kind of lung cancer, non-small cell lung cancer, has a poor prognosis. 6-gingerol has been shown to stop the growth of non-small cell lung cancer (NSCLC) cells by causing apoptosis, cell cycle arrest, and a DNA damage response, according to research by Kang et al. (2023). The investigation results demonstrated that an intrinsic apoptosis pathway dependent on mitochondria causes cell death. Furthermore, 6-gingerol inhibits iron transport in cancer cells, which is essential for its anticancer effects. It does this by either upregulating p53 and downregulating the expression of PD-L1 or downregulating EGFR/JAK2/STAT5b signaling. Moreover, 6-gingerol upregulates the expression of miR-34a and miR-200c, indicating that it controls the expression of PD-L1. Moreover, 6-gingerol prevents the EMT pathway from being activated and HIF-1α from moving to the nucleus. At a dosage of 100 μM 6-gingerol, Kim et al. observed that H460 cell growth dropped by almost 50%. These findings suggest that 6-gingerol may have a major effect on cancer immunotherapy and be a viable medication choice for the treatment of NSCLC.[18,19]

3.4. Gingerol Effect in Hepatocellular Carcinoma

Salama et al.'s (2024) study indicates that taking gingerol and sorafenib together dramatically lowers lipid peroxidation, improves antioxidant status, and heightens anti-hepatocellular carcinoma (HCC) action. Gingerol and sorafenib can reduce serum albumin levels and decrease bilirubin, AST, ALT, and ALP levels. Gingerol also reduces the formation of pro-inflammatory compounds by inhibiting the COX-2/NF-κB pathway and affects oxidative

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stress. This indicates that gingerol can prevent the initiation and progression of cancer and is a viable therapeutic option for HCC.[20]

3.5. Gingerol Effect in Colorectal Cancer

A number of genetic alterations in oncogenes, tumor suppressor genes, and signaling pathways, including the epidermal growth factor receptor (EGFR) and its constituent parts, are the cause of colorectal cancer. The activity of 8-gingerol strongly prevents colorectal cancer cell models from proliferating. There is a dose-dependent reduction in the migration and invasion of cancer cells when 8-gingerol is administered. 8-gingerol inhibits the development of CRC cells by increasing apoptosis and causing cell cycle arrest. 8-gingerol inhibits the signaling of the epidermal growth factor receptor (EGFR). 8-Gingerol, whose actions are reliant on EGFR expression, blocks the growth and migration of colorectal cancer cells by focusing on the EGFR/STAT3/ERK pathway. In addition, 8-gingerol lowers 5-fluorouracil's toxicity and effective dose when used in combination medication therapy.[21] Hu et al. reported that increasing concentrations of 8-gingerol can decrease the viability of CRC cell lines HCT116 and DLD1. The IC50 of 8-gingerol for HCT116 was 118.2±7.37 μM at 24 hours, 77.4±4.70 μM at 48 hours, and 61.8±3.57 μM at 72 hours. Meanwhile, the IC50 of 8-gingerol for DLD1 cells was 100.3±6.32 μM at 24 hours, 53.7±2.24 μM at 48 hours, and 34.5±2.33 μM at 72 hours.[21] Gingerol can also inhibit cell viability in LoVo cells at concentrations of 10 and 15 μg/mL by 68.7 ± 4.3% and 24.6 ± 2.1%, respectively.[22]

3.6. Gingerol Effect in Cervical Cancer

Women with human papillomavirus (HPV) infection are more likely to develop cervical cancer. If this cancer is discovered quickly, it may be treated early on. Chemotherapy is typically one of the primary therapies for cervical cancer available today. For the treatment of cervical cancer, some studies recommend a triage of chemotherapy, surgery, and radiation. However, there are a number of difficulties in treating patients with this approach, particularly when the disease is advanced, such as weakness, toxicity from chemotherapy drugs, and therapeutic failure. Patients may also develop medication resistance. Consequently, complementary therapies with low adverse effects and the ability to enhance patients' quality of life.[7] The activity of 6-gingerol enhances the treatment of HPV-induced cervical cancer by suppressing cell proliferation and stimulating apoptosis. 6-Gingerol produces reactive oxygen species (ROS), which slow the progression of cervical cancer by activating p53 in response to DNA damage. Additionally, 6-gingerol supports the inhibitory effects of cisplatin (a cancer drug) on cell proliferation.[7]

3.7. Gingerol Effect in Prostate Cancer

Prostate cancer cells' migration, adhesion, and invasion are significantly suppressed by 6-gingerol. Biomarker proteins for the epithelium-mesenchymal transition (EMT), including as zonula occludens-1, E-cadherin, N-cadherin, and vimentin, were shown to have changed. Furthermore, 6-gingerol increases the expression levels of Beclin-1 and LC3B-II proteins, which in turn triggers autophagy. In DU145 cells, 6-gingerol and the autophagy inhibitor LY294002 dramatically boosts cell viability. Moreover, 6-gingerol dramatically lowers the nuclear factor erythroid 2-related factor 2 and glutathione (GSH) peroxidase 4 protein expression levels in prostate cancer cells. Prostate cancer cells treated with 6-gingerol exhibit a substantial increase in ROS levels.[23] Kim et al. reported that 6-gingerol can reduce cell viability at concentrations of

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100 µM, 200 µM, and 300 µM by 29.9%, 40.6%, and 72%, respectively, in LNCaP human prostate cancer cells.[24]

The limitations of this study are that the scope is restricted to certain types of cancer, potentially overlooking other cancers where gingerol might be effective. The variability in gingerol concentration across different studies and the lack of standardized dosing protocols also pose challenges in drawing definitive conclusions. Additionally, the long-term safety and potential side effects of gingerol use in humans remain underexplored, warranting further investigation before it can be recommended as a reliable alternative cancer therapy.

4. CONCLUSION

Zingiber officinale var. Rubrum, or red ginger, contains active ingredients such as phenols as antioxidants and gingerol known for its anti-oxidant, anti-inflammatory, anti-bacterial, anti-cancer, anti-tumor, and anti-mutagenic properties. The active compound gingerol in Zingiber officinale has been proven to have anti-cancer effects against various types of cancers including oral, breast, lung, colorectal, bladder, cervical, and prostate cancers. Gingerol exerts its anti-cancer effects by inhibiting cell proliferation, suppressing colony formation, migration and invasion of cancer cells, and enhancing apoptosis protein expression.

REFERENCES

1. Hanggoro Putro DU, Ike Darmayanti AR, Tandiola R, Aulawi K. Pengendalian Infeksi pada Pasien Kanker: Literature Review. J Kesehat Vokasional. 2023;8(1):46.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
3. WHO. Indonesia. Cancer Ctry Profile 2020. 2020;
4. Abbas Z, Rehman S. An Overview of Cancer Treatment Modalities Chapter. In: Neoplasm. 2016. p. 279–96.
5. Harun HM, Jannah N, Idawati, Ahmad ZF. Evaluasi pengobatan radioterapi pada pasien kanker. J Syifa Sci Clin Res [Internet]. 2022;4(3):662–70. Available from: https://ejurnal.ung.ac.id/index.php/jsscr/article/view/15794
6. Rafli R, Abdullah D, Sinulingga BY. Gambaran Efek Samping dan Terapi Suportif Pasien Kanker Payudara Pasca Kemoterapi CAF di RSUP M.Djamil Padang. Baiturrahmah Med J. 2021;1(1):8–13.
7. Zivarpour P, Nikkhah E, Maleki Dana P, Asemi Z, Hallajzadeh J. Molecular and biological functions of gingerol as a natural effective therapeutic drug for cervical cancer. J Ovarian Res. 2021;14(1):1–13.
8. de Lima RMT, dos Reis AC, de Menezes AAPM, Santos JV de O, Filho JWG de O, Ferreira JR de O, et al. Protective and therapeutic potential of ginger (Zingiber officinale) extract and [6]-gingerol in cancer: A comprehensive review. Phyther Res. 2018;32(10):1885–907.
9. Novitasari R, Harsadi P, Hasbi M. Klasifikasi Jenis Jahe Berdasarkan Ciri Statistik Orde Satu Dari Warna Rimpang. J Inform Upgris. 2022;8(1).
10. SARI D, NASUHA A. Kandungan Zat Gizi, Fitokimia, dan Aktivitas Farmakologis pada Jahe (Zingiber officinale Rosc.): Review. Trop Biosci J Biol Sci. 2021;1(2):11–8.
11. Rukhayyah KK, Kawareng AT, Sastyarina Y. Studi Literatur: Uji Aktivitas Antioksidan Ekstrak Jahe Merah (Zingiber officinale var. Rubrum) Menggunakan Metode 2,2-

diphenyl-1-picrylhydrazyl (DPPH). Proceeding Mulawarman Pharm Conf [Internet]. 2021;(April 2021):135–8. Available from: file:///C:/Users/ASUS/Downloads/R+MPC+15+Khusnul+Khatimah+R.pdf
12. Srikandi S, Humaeroh M, Sutamihardja R. Kandungan Gingerol Dan Shogaol Dari Ekstrak Jahe Merah (Zingiber Officinale Roscoe) Dengan Metode Maserasi Bertingkat. al-Kimiya. 2020;7(2):75–81.
13. Siregar PNB, Pedha KIT, Resmianto KFW, Chandra N, Maharani VN, Riswanto FDO. Review: Kandungan Kimia Jahe Merah (Zingiber officinale var. Rubrum) dan Pembuktian In Silico sebagai Inhibitor SARS-CoV-2. J Pharmascience. 2022;9(2):185.
14. Zhang H, Kim E, Yi J, Hai H, Kim H, Park S, et al. [6]-gingerol suppresses oral cancer cell growth by inducing the activation of AMPK and suppressing the AKT/mTOR signaling pathway. In Vivo (Brooklyn). 2021;35(6):3193–201.
15. Smolarz B, Zadrożna Nowak A, Romanowicz H. Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). Cancers (Basel). 2022;14(10):1–27.
16. Ediriweera MK, Moon JY, Nguyen YTK, Cho SK. 10-Gingerol targets lipid rafts associated PI3K/Akt signaling in radio-resistant triple negative breast cancer cells. Molecules. 2020;25(14):1–13.
17. Lee HS, Seo EY, Kang NE, Kim WK. [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. J Nutr Biochem. 2008;19(5):313–9.
18. Kang DY, Park S, Song KS, Bae SW, Lee JS, Jang KJ, et al. Anticancer Effects of 6-Gingerol through Downregulating Iron Transport and PD-L1 Expression in Non-Small Cell Lung Cancer Cells. Cells. 2023;12(22):1–17.
19. Kim MJ, Ku JM, Choi YJ, Lee SY, Hong SH, Kim HI, et al. Reduced HIF-1α Stability Induced by 6-Gingerol Inhibits Lung Cancer Growth through the Induction of Cell Death. Molecules. 2022;27(7).
20. Salama AF, El-Far AH, Anbar EA, El-Naggar SA, Elshazli RM, Elmetwalli A. Gingerol and/or sorafenib attenuates the DAB-induced HCC and hepatic portal vein dilatation via ATG4/CASP3 and COIIV/COX-2/NF-κB expression. Med Oncol [Internet]. 2024;41(2):1–16. Available from: https://doi.org/10.1007/s12032-023-02284-3
21. Hu SM, Yao XH, Hao YH, Pan AH, Zhou XW. 8-Gingerol regulates colorectal cancer cell proliferation and migration through the EGFR/STAT/ERK pathway. Int J Oncol. 2020;56(1):390–7.
22. Lin C Bin, Lin CC, Tsay GJ. 6-gingerol inhibits growth of colon cancer cell LoVo via induction of G2/M arrest. Evidence-based Complement Altern Med. 2012;2012.
23. Liu CM, An L, Wu Z, Ouyang AJ, Su M, Shao Z, et al. 6-Gingerol suppresses cell viability, migration and invasion via inhibiting EMT, and inducing autophagy and ferroptosis in LPS-stimulated and LPS-unstimulated prostate cancer cells. Oncol Lett. 2022;23(6):1–11.
24. Kim HW, Oh DH, Jung C, Kwon DD, Lim YC. Apoptotic Effects of 6-Gingerol in LNCaP Human Prostate Cancer Cells. Soonchunhyang Med Sci. 2011;17(2):75–9.