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Potential of Red Ginger Rhizome (*Zingiber officinale Roscoe var. Rubrum*) as an Anti-Cancer: A Review

I Gede Y. Anggara, Aguslina Kirtishanti, Marisca E. Gondokesumo*

Faculty of Pharmacy, University of Surabaya, Universitas Surabaya, Surabaya, East Java, Indonesia 60293

Abstract

Red ginger rhizome, Zingiber officinale Roscoe var. Rubrum has long been used as a herbal medicine. Its biological properties, including anti-cancer properties, are confirmed. The chemical composition of red ginger rhizome that functions as an anti-cancer agent contains 6-gingerol, 6-shogaol, 10-gingerol, and 6-paradol, according to the findings of this literature review that was conducted. Gingerol disrupts the cell cycle, triggers apoptosis in cancer cells, and prevents the growth and spread of cells by interacting with particular proteins, gene targets, and signal transduction pathways. 6-shogaol activity suppresses NF-kB and signal transducer and activator of transcription 3 (STAT3), decreases Bcl-2 expression, and increases Bax expression, which contributes to lowering cell viability and causing autotosis. 10-Gingerol inhibits the expression of EGFR and the phosphorylation and activation of Akt and p38MAPK caused by mitogens, which inhibits breast cancer cells' proliferation and invasion. Telomerase was suppressed by paradols and shogaols found in the ginger extract, leading to telomere shortening and cellular senescence and a notable reduction in the A549 lung carcinoma's capacity to proliferate. Red ginger rhizome has been proven to have anti-cancer activity in various types of cancer that have been studied in vitro, in vivo and in silico, there are head and neck cancer, endometrial adenocarcinoma, breast cancer, lung cancer, skin cancer, colon cancer, prostate cancer, leukemia, oral and cervical cancer, brain tumor, bone cancer, and pancreatic cancer.

Keywords: 6-gingerol, 6-shogaol, Anti-cancer, Herbal medicine, Red ginger rhizome

Corresponding author: Marisca Evalina Gondokesumo. Faculty of Pharmacy, University of Surabaya.
Email: marisca@staff.ubaya.ac.id
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Introduction

Ginger rhizome, also known as *Zingiber officinale*, which belongs to the *Zingiberaceae* family and the *Zingiber* genus, has long been used as a herbal medicine[1]. According to the size and color of the rhizomes, there are three varieties of ginger: small white ginger (*Zingiber officinale. var. amarum*), giant ginger or large white ginger (*Zingiber officinale Rosc. var. officinale*), and red ginger (*Zingiber officinale var. rubrum*). Terpene and phenolic compounds, including gingerol, shogaol, and paradol are the bioactive substances that have been found in ginger[2].

In addition to being used as a food flavoring, red ginger rhizome, has biological activities that have been confirmed, including anti-inflammatory, antioxidant, antimicrobial, and anti-cancer properties. It may also be able to prevent and manage a number of diseases, including neurodegenerative, obesity, diabetes mellitus, cardiovascular disease, nausea, and vomiting brought on by chemotherapy[3]. Red ginger's mode of action in anti-cancer therapy involves stopping the growth of cancer cells and causing them to undergo apoptosis[4].

One of the many components of red ginger that have been found is 6-shogaol, which contains potent antioxidant and anti-inflammatory properties. By inhibiting NF-kB and signal transducer and activator of transcription 3 (STAT3), as well as by downregulating Bcl-2 expression and upregulating Bax expression, 6-shogaol activity contributes to the reduction of cell viability and induction of autotosis[5]. Compared to 6-gingerol, 6-shogaol is more pharmacologically appealing due to its increased cytotoxic action against lung and colon cancer cells. 6-shogaol causes colorectal cancer cells to undergo apoptosis by generating ROS, activating caspase, and expressing GADD 153. Qi et al. (2015) stated that 6-shogaol can overcome TRAIL resistance in colon cancer by inhibiting survivin and causing cell cycle arrest in G2/M. Meanwhile, 6-gingerol inhibits MAPK/AP-1 signaling, which causes caspase-dependent apoptosis and stops PMA-induced colon cancer growth[6]. 10-gingerol causes caspase-dependent apoptosis, increased intracellular Ca2+, and cell cycle arrest in colon cancer cells. AKT and p38MAPK inactivation is linked to 10-gingerol's suppression of MDAMB-231 breast cancer cell invasion and proliferation, according to a more recent study by Joo and colleagues[7]. The anticancer action of 6-paradol is achieved by inhibiting the growth, viability, invasion, and migration of pancreatic cancer cells. In terms of mechanism, 6-Paradol primarily inhibits EGFR expression and PI3K/AKT signaling inactivity through ubiquitination-mediated proteasomal degradation of EGFR[8]. In this review, we will discuss further the use of chemical compounds from red ginger rhizome as anti-cancer. The objective of this paper is to present thorough overview of anti-cancer activities and its molecular mechanism of red ginger rhizome.

Method

The method used is a literature review article (LRA) with library sources obtained through the Google Scholar data base published from 2013 to 2024 on the topic of the anti-cancer activity of red ginger rhizome. Relevant articles were collected and reviewed. The number of journals from this search resulted in 35 journals. The review was conducted using the search terms "*Zingiber officinale var. Rubrum* OR red ginger AND anti-cancer AND antitumor".

To the best of our understanding, this review article is the first on *Zingiber officinale var. rubrum rhizome*. Previous research 9 has reviewed how to extract gingerol and the use of gingerol from *Zingiber officinale Roscoe* for

the treatment of various diseases. This article review focuses on discussing the anti-cancer mechanisms of chemical composition of red ginger rhizome such as 6-gingerol, 6-shogaol, 10-gingerol, and 6-paradol. This review also provides updated research information on the anti-cancer activity of red ginger rhizome.

Result and Discussion

Plant Description

Red ginger is included in the Spermatophyta division, Angiospermae subdivision, Monocotyledoneae class, Zingiberales order and *Zingiberaceae* family. Red ginger has several synonymous names including *Zingiber amomum* L., *Zingiber officinale var. macrorhizonum Makino*, *Zingiber cholmondeleyi K. Schum*., *Zingiber officinale Roscoe var Sunti Val*., *Zingiber missionis Wall*., *Zingiber sichuanense* and *Zingiber officinale var. Rubens Makino*. In Malaysia, Indonesia, and China, red ginger is cultivated extensively[10].

It is a plant that grows annually and grows up to 5 0-100 cm high. It has thick and reddish-brown rhizomes. In terms of morphology, it resembles regular ginger. Compared to regular ginger, it is smaller and smells stronger. It has narrow and lancer-shaped leaves, 5-25 cm in length and 8-20 mm in width. The plant's rhizomes give rise to an ovoid-shaped composite, with a stem length of 10-25 cm and little leaves around the flower's base. The corollas have a funnel form, 2-2.5 cm long, and dark purple with creamy yellow spots. The petals are tridentate, tiny, and tubular. Its lip is crimson red, and its petiole is reddish, unlike common ginger (Figure 1)[10].

Chemical Composition of Red Ginger

Ginger's chemical constituents can be separated into two groups: volatiles and non-volatiles. Ginger has a distinctive flavor and perfume because of its volatile constituents, which include sesquiterpenes and monoterpene hydrocarbons. The ginger's non-volatile aromatic compounds are gingerols, shogaols, gingerdiones, zingerone, paradols, and gingerdiols[11].

Gingerols were the term given by Thresh in 1879 to the spicy chemicals found in ginger[12]. The primary aromatic component of ginger, known as gingerols, is a combination of many molecules with a 3-methoxy-4-hydroxyphenyl group. Gingerols can be divided into gingerols, zingerone, paradols, shogaols, gingerdiones and gingerdiols[13]. The average amount of gingerols in rhizomes (104.39 µg/g) is considerably greater than the average amount in their stems (0.84 µg/g) and leaf tissues (4.13 µg/g). Of the three varieties of gingerols, 6-gingerol has the highest average amount at 195.87 µg/g, but the average contents of 8-gingerol and 10-gingerol are 46.31 µg and 70.99 µg/g, respectively[14].

Red Ginger Rhizome as Anti-Cancer

Red ginger may be able to prevent the spread of malignant tumors by specifically inhibiting angiogenesis, adhesion, metastasis, and MMP synthesis. These mechanisms include the suppression of tumor metastasis through the blocking of theqPI3K/AktqandqMAPKqpathways, NF-κB and STAT3 inactivation, and the increased expression of PAI-1, plasminogen activator inhibitor[10].

Apoptosis is induced in cancer cells, the cell cycle is stopped, and cell growth and metastasis are prevented by gingerols' interactions with particular signal transduction pathways, proteins, and gene targets. Gingerols have the potential to prevent and treat cancer, because they influence a variety of cell signaling pathways. Their molecular targets include protein kinases [mitogen-activated protein

kinase (MAPK), c-Jun N-terminal kinase (JNK), inhibitor of kappa B kinase (IKK), protein kinase B (Akt), phosphatidylinositol-3 kinase (PI3K)], matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF)], transcription factors [NF-κB, activator protein-1(AP-1)], tumor suppressor gene tumor protein 53 (p53), apoptosis and anti-apoptotic proteins [B-cell lymphoma (Bcl) −2, Bcl-XL, Caspase], metastasis proteins [cyclooxygenase-2 (COX2), inducible nitric oxide synthase (iNOS), growth factors [epidermal growth factor (EGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), tumor necrosis factor (TNF)], and cell cycle proteins [CCND1, cyclin-dependent kinase (CDK) 1,2,4,6,7][15]. In these reviews, red ginger rhizome has been proven to have anti-cancer activity in various types of cancer (Table 2).

Head and Neck Cancer

Head and neck squamous cell carcinomas (HNSCCs) are the most malignant and aggressive type of cancer in the head and neck tissues. They are primarily epithelial malignancies that affect the oral cavity, larynx, and throat. Previous research has demonstrated that 6-shogaol inhibits HNSCC cell viability. 6-shogaol uses MAPK signaling pathways to cause G2/M cell cycle arrest and strengthen apoptosis in SCC-4qandqSCC-25 cells. 6-shogaol is a natural remedy that is anticipated to be a valuable, dependable, and efficient option for the adjuvant therapy of HNSCC[16].

Skin Cancer

Skinqcancerqisqtheqmostqcommon type of cancer, occurring when abnormal cells in the epidermis and outermost layer of skin proliferate uncontrollably. The second most prevalent type of skin cancer brought on by UV radiation damage to the skin is squamous cell carcinoma (SCC). In the earlier investigation, the MTT assay and molecular docking were used to assess 6-gingerol's anticancer efficacy. Docking studies demonstrated that 6-gingerol had the lowest binding energy with DDX3X, and the ADMET analysis validated 6-gingerol's drug-likeness characteristic. The 6-gingerol compound has the lowest binding energy, -7.1 Kcal/mol. Consequently, the robust binding indicates that 6-gingerol could be a useful lead chemical in the fight against skin cancer[24].

Previous study provided by Nigam et al. (2024) 25 mentioned that suppressing skin carcinogenesis is the action of 6-gingerol. As a cancer chemoprevention strategy, 6-gingerol's apoptotic potential functions in tumor tissues more than in equivalent non-tumor tissues. It can also control intrinsic apoptotic pathways by directly initiating signaling cascades that promote apoptosis. Following 6-gingerol administration, there was a drop in Bcl-2 and an increase in p53 and its downstream regulator Bax. Elevated Bax expression can cause apoptosis by inhibiting Bcl-2 activity, proving that the balance between Bcl-2 and Bax is essential for chemopreventive agent-induced apoptosis. Apoptosome formation is facilitated by the interaction of the Bcl-2 family members (Bax, Bak, Bcl-2, Bcl-X, etc.), which triggers the release of cytochrome c. Apaf1 then activates executioner caspases to orchestrate apoptosis. The essential elements of the apoptosis pathway are caspases. The activation of caspase 3 and caspase 9 is a crucial stage in the activation of the cell death mechanism.

Lung Cancer

Through different mechanisms, gingerol, shogaol, and zerumbone show anticancer action in experiments conducted on A549 lung cancer cells. It was discovered that gingerol sensitizes human lung cancer cells to apoptosis. 6-shogaol was discovered

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to promote autophagy through the AKT/mTOR pathway and suppress cancer via microsomal prostaglandin E2qsynthase 1 (mPGES-1), β-catenin, and glycogen synthase kinase 3β (GSK-3β) pathways. A prior study demonstrated that, when utilizing just subcytotoxic levels, telomerase was suppressed by paradols and shogaols found in the ginger extract, leading to telomere shortening and cellular senescence and a notable reduction in the A549qlung carcinoma's capacity to proliferate[19].

Breast Cancer

Theqmost prevalent kind ofqcancerqand the main reason why women die from cancer is breast cancer. When it comes to aggressiveness and malignancy, ER-negative breast cancer is often more common than ER-positive breast cancer. Recurrent and metastatic breast cancers are strongly associated with overexpression of either human EGFR-2 (HER2) or the epidermal growth factor receptor (EGFR). Data from an earlier study demonstrated that 10-gingerol treatment significantly reduces the growth of breast cancer cells by downregulating cell cycle regulatory proteins like Cdks and cyclins. This anti-proliferative effect of 10-gingerol appears to be unrelated to the expression level of ER. Furthermore, 10-gingerol effectively inhibits the invasion of breast cancer cells, a phenomenon that may be partially attributed to the suppression of MMP-2 activity. Additionally, prior research has shown that 6-gingerol, also known as 6-shogaol, inhibits cell invasion in a variety of cell lines, including those from liver and breast cancer, by differently modifying the activities of MMP-2 and MMP-9[21].

Individuals with ER-negative breast cancer who exhibit an aggressive phenotype and poor clinical outcomes frequently overexpress EGFR, indicating that EGFR and the signaling molecules it interacts with downstream could be valuable therapeutic targets for the management of ER-negative breast cancers. The activation of PI3K/Akt, Ras/Raf/ERK, p38MAPK, c-Jun N-terminal kinase, phospholipase Cγ, and focal adhesion kinase are examples of EGFR-dependent downstream signaling pathways that are linked to cell migration, invasion, survival, and proliferation. Treatment with LY294002 and SB203580, respectively, demonstrated that 10-gingerol-induced inhibition of breast cancer cell proliferation and invasion is mediated by inactivation of Akt and p38MAPK activity. Additionally, 10-gingerol administration significantly reduced EGFR expression in both ER-positive MCF-7 cells and ER-negative MDA-MB-231 cells[21].

Other mechanism stated by Carolina et al. (2017) 7, 10-gingerol mainly induces caspase-dependent apoptosis, which results in a marked increase in caspase-3 activation throughout primary tumors, cleavage of caspase-3 and -9 in vitro, or accumulation of cells in sub-G1, TUNEL positivity, and concentration-dependent increase in annexin-V staining in vitro. Further evidence that 10-gingerol reduces TNBC growth predominantly by causing apoptosis rather than cell cycling comes from the fact that it boosted caspase-3 activation in tumors in vivo but not proliferation, as seen by the expression of the Ki67 proliferation marker.

Colon Cancer

The fourth most common cause of cancer-related mortality worldwide is colon cancer. A popular chemotherapy medication for colorectal cancer, 5-fluorouracil (5-FU) has a high selectivity for thymidylate synthetase. In recent years, a number of research have been carried out utilizing natural substances in combination with 5-FU. Red ginger extract has been shown in earlier research to increase

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5-FU's cytotoxic effect on WiDr colon cancer cells[6]. Several recent studies on 6-gingerol's anti-cancer properties against colon cancer revealed various mechanisms by which it acts on various colon cancer cell lines. The SW-480 cell line, which is negative for COX-2, may have been impacted by 6-gingerol in a different investigation regarding other AP-1 downstream effectors, such as MMP-9 or VEGF[23].

Endometrial Cancer

Endometrial cancer cells are less susceptible to the apoptotic effects of Steam Distilled Extract of Ginger (SDGE) when p53 is inhibited. Additionally, p53neg SKOV-3 cells are not subjected to apoptosis by SDGE. These findings bolster the hypothesis that the primary mechanism by which SDGE prevents the growth of endometrial cancer cells is p53 activation. Important to note in this regard is that 6-gingerol and zerumbone, a sesquiterpene present in ginger, also cause cancer cells to die by lowering the Bcl-2/Bax ratio and raising p53 levels[17].

6-Shogaol disrupted cellular stress signaling pathways by activating certain ER response indicators in mitochondrial Ishikawa cells, and then controlled the genes and proteins linked to these cells that caused apoptosis both in vitro and in vivo. As a result, 6-shogaol can be identified as a promising natural substance that may be used to cure or prevent cancer as well as expand its use to include other cancer types. In the early stages of endometrial cancer, Ki-67, a marker of cell proliferation, also acts as a prognostic and predictive factor. This was identified by immunohistochemistry, and the group that received 6-shogaol had significantly more Ki-67-positive staining nuclei than the control group[18].

Leukemia

Rapid growth of immature and undifferentiated myeloid blood cells is a hallmark of myeloid leukemia, which is characterized by a defective hematopoietic process. Previous research has shown that 6-gingerol from Zingiber officinale Roscoe rhizome causes myeloid leukemia cells to undergo apoptosis by increasing intracellular ROS, triggering the production of miR-27b, and causing G2/M phase cell cycle arrest by DNA damage induction[26]. The first research demonstrating the anti-cancer effect of ginger extract on all mice models conducted by Najafi Dorcheh et al. (2021)[27]. 6-Shogaol is presented as a new naturally occurring small molecule that may enhance the cytotoxicity of MTX on malignant lymphoblasts in a selective and cooperative manner. 6-shogaol may have anti-neoplastic effects by causing p53 activation and ROS production, which results in cell-cycle arrest and apoptosis. Additionally, in ALL malignant cells, 6Sh may produce large cytoplasmic amounts of ROS, which could lead to FASN downregulation and cell death.

Prostate Cancer

The second greatest cause of cancer-related mortality among American males and prevalent non cutaneous neoplasm is prostate cancer. A prior study shown, for the first time, that 6-shogaol reduces the survival of prostate cancer cells in culture, both in humans and in mice. This decrease is accompanied by the induction of apoptosis. Angiogenesis, metastasis, cell proliferation, and resistance to apoptosis are all associated with constitutively active STAT3 in human prostate cancer, according to accumulating data. Jak2 and Src are examples of non-receptor tyrosine kinases that govern the activation of STAT3, but receptor tyrosine kinases, such as the EGF receptor, also play a role. 6-Jak2 and Src activation were both suppressed by 6-shogaol, indicating

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that inhibition of these kinases is probably involved in mediating the effects of 6-SHO on downstream signaling, which includes STAT3 activation[28].

All three human prostate cancer cells treated with 6-shogaol showed reduced phosphorylation of NF-kBp65, both constitutive and stimulated by TNF-α. Apoptosis, survival, and proliferation-related target genes such as cyclin D1, survivin, cMyc, and Bcl2 have different expression patterns when both STAT3 and NF-kB signaling are activated. In addition to changing the mRNA expression of a few key chemokine, cytokine, cell cycle, and apoptosis regulating genes, 6-shogaol treatment of cultured human and mouse prostate cancer cells decreased the levels of cyclin D1, survivin, and cMyc protein. Thus, suppression of STAT3 and NF-kB activity by 6-SHO was related with lower expression of their target gene products. 6-SHO presumably affects STAT3, NF-kB, and probably other signaling pathways in addition to other pathways, as evidenced by its ability to effectively limit the proliferation of prostate cancer cells regardless of STAT3 expression or activity[28].

Brain Tumor

An extremely aggressive and fatal primary brain tumor that affects adults is called glioblastoma multiforme (GBM). A previous study demonstrated that in glioblastoma cells resistant to TRAIL, gingerol can sensitize cell killing by TRAIL. Stronger apoptotic signals, such as the caspase cascade, can be sent by elevated DR5. Moreover, gingerol can induce an increase in pro-apoptotic protein (Bax) and a decrease in anti-apoptotic protein (Bcl-2 and survivin) expression by generating reactive oxygen species. Eventually, gingerol can modulate TRAIL-mediated apoptotic signaling through pro- and anti-apoptotic proteins, as well as DR5, and hence sensitize the cell death of TRAIL-resistant glioblastoma. Consequently, this work raises the prospect that noncytotoxic quantities of gingerol could be employed as an antitumor drug in combination with TRAIL to treat glioblastoma patients who are resistant to TRAIL[31].

Oral and Cervical Cancer

Previous research has demonstrated that 6-gingerol influences the proliferation, apoptosis, and cell cycle arrest of tumor cells in cervical (HeLa) and oral (SCC4, KB) cancer cell lines. 6-gingerol caused all tumor cell lines to undergo apoptosis, as demonstrated by a large rise in the sub-G1 (hypodiploid) population. KB and SCC4 were the next medications to demonstrate the largest cell population in the sub-G1 phase in HeLa cells following treatment with all the treatments, either separately or in combination. Following 6-gingerol therapy, there was an increase in PI and annexin V positive (late apoptotic) and annexin V positive (early apoptotic) cells in all tumor cell lines, which coincided with the sub-G1 population growth[29].

6-shogaol pauses the cell cycle in the G2 or M stage and promotes apoptotic cell death via mitochondrial pathways and endoplasmic reticulum (ER) stress. This syndrome prevents cervical cancer from progressing by disrupting the potential of the mitochondrial membrane of cervical cancer cells. Ginger primarily slows the progression of cervical cancer and can cure it by inducing apoptosis and inhibiting cell proliferation. Other methods that ginger extract helps cervical cancer include reducing the expression of miR-629, reducing prostaglandin synthesis, and reducing the PI3K/Akt pathway[30].

Bone Cancer

Osteosarcoma is a very dangerous primary

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bone tumor that mostly affects children and teenagers. It makes for 4% of all malignancies in this age group. Most frequently, it affects long bones like the humerus and femur/tibia. Previous research indicated that 6-gingerol exerts a growth-inhibitory effect on human osteosarcoma cells through an activation of intrinsic and extrinsic routes of apoptosis. Furthermore, sub-G1 cell cycle arrest has been linked to 6-gingerol's reduction of cell proliferation in osteosarcoma cells. 6-gingererol induced AMPK activation, which helped to prevent osteosarcoma cells from growing[32].

The creation of novel AMPK activators is essential for the advancement of anti-cancer drugs since AMPK signaling is a significant target with strong anticancer activity. 6-gingerol strongly activated AMPK and blocked the downstream mTOR, which could be a factor in the elevated Bax level. Furthermore, the inclusion of compound C, an AMPK inhibitor, reversed the inhibition of cell proliferation in both osteosarcoma cell lines caused by 6-gingerol. When combined, these results suggest that AMPK activation is essential for the 6-gingerol-induced death of osteosarcoma cells[32].

Pancreatic Cancer

A multi-step process involving invasion and migration, metastasis is the main cause of death for cancer patients. Tumor cell migration in cancer is facilitated by the extracellular matrix and basement membrane breaking down due to MMP activation, tissue remodeling brought on by the loss of the tight junction (TJ). A prior study revealed that 6-gingerol suppressed TJ proteins and mRNA levels, as well as claudin-4, ZO, and occludin, in pancreatic cells. 6-gingerol also controlled the rise in E-cadherin and fall in snail. These findings imply that 6-gingerol may have promising results when used as an antimetastatic treatment for pancreatic cancer in humans. 6-gingerol prevented snail's nuclear translocation, which is controlled by NF-KB. The mechanism by which 6-gingerol inhibits the spread of cancer cells may involve the suppression of Snail and MMP-9[33].

Conclusion

Zingiber officinale var. rubrum or red ginger rhizome confirmed to have biological activities such as anti-cancer. Red ginger's anticancer properties are mediated through a variety of mechanisms, including NF-κB and STAT3 inactivation, suppression of the MAPK and PI3K/Akt pathways, and overexpression of plasminogen activator inhibitor-1 (PAI-1), who are all involved in preventing the spread of tumors. The chemical content of red ginger rhizome which acts as an anti-cancer agent includes 6-gingerol, 6-shogaol, 10-gingerol, and 6-paradol. Red ginger rhizome has been proven to have anti-cancer activity in various types of cancer that have been studied in vitro and in silico, there are head and neck cancer, endometrial adenocarcinoma, lung cancer, breast cancer, colon cancer, skin cancer, leukemia, prostate cancer, oral and cervical cancer, brain tumor, bone cancer, and pancreatic cancer. From this review article, in the future we hoped that there will be more research into the anti-cancer activity of red ginger rhizome in vivo and clinical trials with various other types of cancer.

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Conflict of Interest

None declared.

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Table 1. The main chemical structure of red ginger rhizome

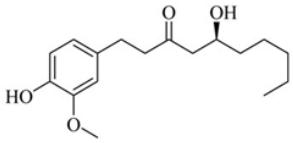
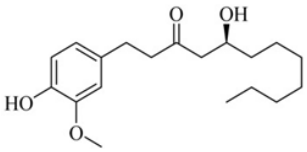
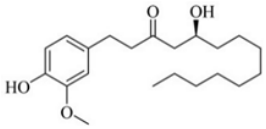
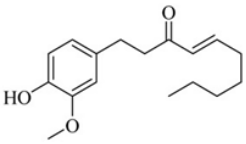
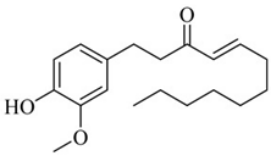
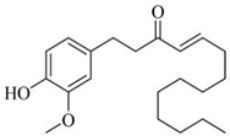
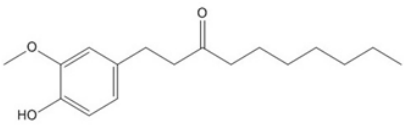
Chemical Structure	Compound
	6-gingerol
	8-gingerol
	10-gingerol
	6-shogaol
	8-shogaol
	10-shogaol
	Paradol

Table 2. Biological activity of red ginger as anticancer.

Cancer Type	Cancer Cell	Study	Content	Mechanism	Ref
Head and Neck Cancer	Squamous Cell Carcinoma Cancer	In vitro study	6-shogaol	(1) In SCC4 and SCC25, two varieties of HNSCC cells, 6-shogaol triggers apoptosis to cause their cell death and stops cell cycle progression during the G2/M phase. (2) The ERK1/2 and p38 signals control these reactions. (3) HNSCC cells may become more sensitive to cisplatin's cytotoxic effects if they are treated with 6-shogaol in addition to cisplatin.	16
Endometrial Adenocarcinoma	Ishikawa cells and ECC-1 cells	In Vitro and in vivo study	6-shogaol	6-Shogaol stimulated apoptosis, which in turn led to the formation of ROS. It subsequently activated important ER response indicators in Ishikawa cells that were linked to mitochondria, and it finally controlled relevant genes and proteins both in vitro and in vivo.	17,18
Lung Cancer	A549 lung cancer cells	In Vitro study	6-paradol, 6-shogaol	In the A549 cells, suppress hTERT expression and telomerase activity.	19

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Breast Cancer	MDA-MB-231	In Vitro and In Vivo study	10-Gingerol	(1) 10-Gingerol inhibits the expression of EGFR and the phosphorylation and activation of Akt and p38MAPK caused by mitogens, which inhibits breast cancer cells' proliferation and invasion. (2) 10-Gingerol may prevent MDA-MB-231 cells from proliferating with an IC50 value of 122.450±0.5 µM. (3) 10-Gingerol may target FASN, ADRB2, and ADRA2A to produce therapeutic benefits against TNBC. The one that showed the strongest affinity for 10-gingerol was ADRB2. (4)According to the expression of the Ki67 proliferation marker, 10-gingerol increased caspase-3 activation in tumors in vivo but not proliferation. This suggests that 10-gingerol predominantly inhibits TNBC growth by inducing apoptosis rather than cell cycling.	7,20, 21,22
Colon Cancer	WiDr colon cancer cell, Human colon cancer cell lines, SW-480 and HCT116	In Vitro study	6-gingerol, 6-shogaol	(1) 6-Gingerol stops PMA-induced proliferation in colon cancer via inhibiting MAPK/ AP-1 signaling, which results in caspase-dependent death. (2) 6-shogaol induces caspase activation, ROS production, and GADD 153 expression to induce apoptosis in colorectal cancer cells. (3) In colon cancer, 6-shogaol causes G2/M cell cycle arrest and overcomes TRAIL resistance by suppressing survivin. (4) 6-gingerol directly suggests that it has therapeutic potential against colon cancer by downregulating AP-1 transcriptional binding.	6,23

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Skin Cancer	A431 cell, mouse skin carcinogenesis model	In silico, in vivo and In vitro study	6-gingerol	(1) The ADMET analysis demonstrated the drug-likeliness of 6-gingerol, which has the lowest binding energy when paired with DDX3X. (2) In mouse skin carcinogenesis model, apoptotic potential of 6- gingerol acts in tumor tissues is higher than the corresponding non-tumor tissues and can regulate intrinsic apoptotic pathways by directly triggering apoptosis-promoting signaling cascades as mechanism of cancer chemoprevention.	24,25
Leukemia	Chronic Myeloid Leukemia (CML) cell lines; CCRF-CEM (T-ALL) and Nalm-6 (B-ALL) human cell lines; C57BL/6 nude mice	In vitro and in vivo study	6-gingerol, 6-shogaol	(1) 6-gingerol prevents MRC I from raising ROS levels. Raised ROS trigger the expression of miR-27b and DNA damage, which are essential for the cell death of myeloid leukemia. (2) Through its ability to target apoptosis and activate p53 in Nalm-6 cells, 6-shogaol may aid in cell death. (3) ASN inhibitors may cause CML cell lines to undergo apoptosis and stop proliferating. (4) 6-shogaol may act against cancer by downregulating the synthesis of fatty acids or by activating p53 and producing ROS, which causes cell-cycle arrest and apoptosis.	26,27
Prostate Cancer	Human prostate cancer cells LNCaP, DU145, and PC3	In vitro and In vivo study	6-shogaol	(1) 6-shogaol causes apoptosis and suppresses survival. (2) Additionally, 6-shogaol causes apoptosis and decreases survival in HiMyc-derived cultured mouse prostate cancer cells. (3) 6-shoagol was very successful in preventing HMVP2 cells from growing in an allograft tumor model. The suppression of NF-kB and STAT3 signaling, as well as perhaps additional signaling pathways, was linked to these actions of 6-shogaol.	28

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Oral and Cervical Cancer	Human oral squamous cell carcinoma (OSCC) cell lines KB, SCC4, and cervical cancer cell line (HeLa)	In vitro and in vivo study	6-gingerol, 6-shogaol	(1) Together with morphological alterations such cell shrinkage, detachment, and membrane blebbing, 6-gingerol also caused dose-dependent cytotoxicity in all three cell lines. 6-gingerol induces apoptosis and cell cycle arrest, which contribute its anticancer effects. (2) Stopping the progression of cervical cancer by stimulating cell proliferation inhibition and induction of apoptosis (3) Stopping the progression of cervical cancer by standing the cell cycle at G2 / M stage through mitochondrial pathways and endoplasmic reticulum stress (4) Stopping the progression of cervical cancer by stimulating the production of ROS, DNA damage and reactivating p53	29,30
Brain Tumor	Human glioma U87, U343, and T98G cells	In vitro study	6-gingerol	In U87 glioblastoma cells, gingerol effects helped to sensitize apoptotic cell death by TRAIL.	31
Bone Cancer	Human osteosarcoma cell line (143B and MG63)	In vitro study	6-gingerol	(1) 6-Gingerol induces both intrinsic and extrinsic apoptotic mechanisms in human osteosarcoma cells, hence inhibiting their development. (2) In osteosarcoma cells, 6-gingerol inhibits cell growth in a manner associated with sub-G1 cell cycle arrest. (3) 6-Gingerol caused AMPK activation, which in turn prevented osteosarcoma cells from growing.	32

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Pancreatic Cancer	Human pancreatic cancer cell line (PANC-1)	In vitro and in vivo study	6-gingerol, 6-shogaol	(1) 6-Gingerol can enhance Tight Junction (TJ) and regulate the synthesis of TJ-related proteins in human pancreatic cancer cells. It is a potent inhibitor of NF-KB activation. (2) Ginger extract caused pancreatic cancer, Panc-1 cells, to undergo autotic death by suppressing cell division. (3) In mice with Panc-1 xenografts and a Panc02 peritoneal dissemination animal model, ginger extract reduced tumor growth when given intraperitoneally without causing significant side effects.	33,34

Figure 1. Red Ginger (a) Plants and (b) Rhizomes

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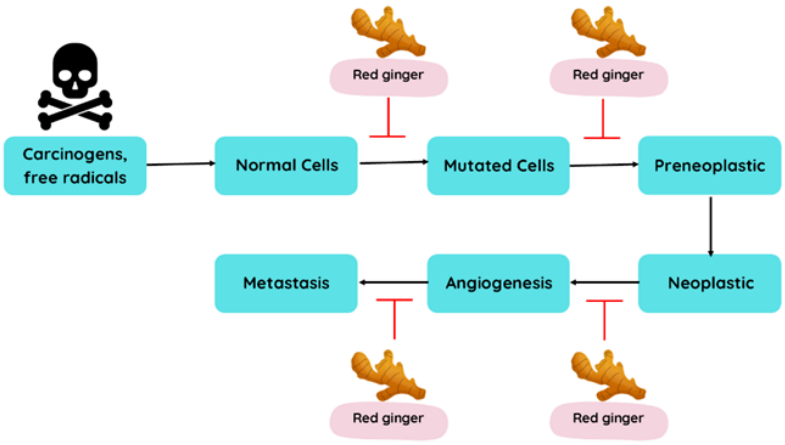

Figure 2. Red ginger prevents angiogenesis, metastasis, and the advancement of cancer[10]

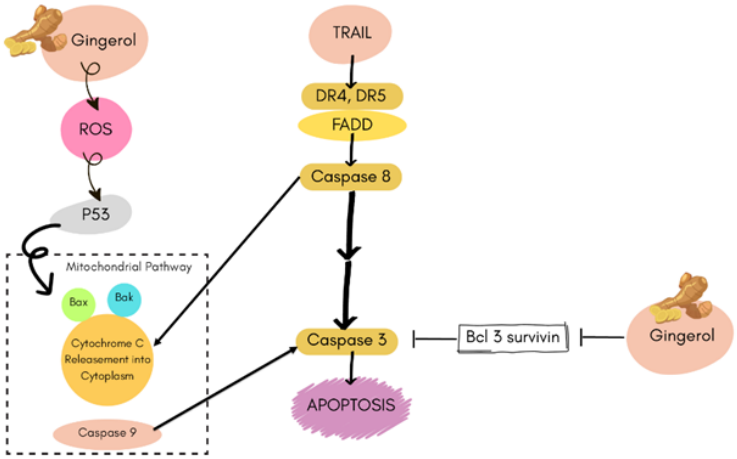

Figure 3. Schematic diagram of gingerol for sentitizing TRAIL-induced apoptosis[31]