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REVIEW ARTICLE

Anti-cancer potential of zerumbone in cancer and glioma: current trends and future perspectives

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Abstract

Plant-derived immunomodulators and antitumor factors have appealed lots of attention from natural product scientists for their efficiency and safety and their important contribution to well-designed targeted drug action and delivery mechanisms. Zerumbone (ZER), the chief component of *Zingiber zerumbet* rhizomes, has been examined for its wide-spectrum in the treatment of multi-targeted diseases. The rhizomes have been used as food flavoring agents in numerous cuisines and in flora medication. Numerous in vivo and in vitro experiments have prepared confirmation of ZER as a potent immunomodulator as well as a potential anti-tumor agent. This review is an interesting compilation of all the important results of the research carried out to date to investigate the immunomodulatory and anticancer properties of ZER. The ultimate goal of this comprehensive review is to supply updated information and a crucial evaluation on ZER, including its chemistry and immunomodulating and antitumour properties, which may be of principal importance to supply a novel pathway for subsequent investigation to discover new agents to treat cancers and immune-related sickness. In addition, updated information on the toxicology of ZER has been summarized to support its safety profile.

Keywords Zerumbone · Anti-tumor · Immunomodulators · Glioma

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Introduction

Cancer is a major global disease and the second leading cause of death [1]. According to the GLOBOCAN report, there are projected to be 2,001,140 new cases of cancer and 611,720 deaths from cancer in the United States in the year 2024 [2]. There are many risk factors that increase cancer mortality, including environmental factors such as unhealthy diet, exposure to air pollution, toxic drugs, physical inactivity, etc. [3]. Present selective cancer treatments have non-specific toxicity [4], very low efficacy [5], high costs [6], exert a lot of adverse effects [7], and also became resistance [8]; that altogether made cancers to have more mortality and poor prognosis. Vegetables, fruits, legumes, nuts and herbs have been shown to contain an important class of phytochemicals that exert therapeutic effects on a variety of human diseases and have been used in folk medicine since ancient times for their pharmacological effects and reduced side effects [9–16].

ZER (Fig. 1), a natural crystalline cyclic sesquiterpene, is the main biological element of *Zingiber zerumbet* Smith rhizome, which is shown in a both in vitro and in vivo studies to has significant and curable effects in chemotherapy approaches [17]. ZER has been shown to have therapeutic effects such as antipyretic, anti-hypersensitive, anti-inflammatory, antibacterial, antinociceptive, antioxidant, hepatoprotective, and also has immunomodulatory functions [18]. In addition, ZER can also act as an antitumor drug due to its specific properties to suppress angiogenesis and proliferation and induce apoptosis in a variety of cancer cell lines [19]. Numerous studies have shown that ZER has anti-proliferative effects in various human cancers, including cervical, breast, colon and liver, and that it selectively affects tumor cells compared to normal cells [19–21] (Fig. 2). In this article, we have reviewed some of these effects of ZER in various human cancers.

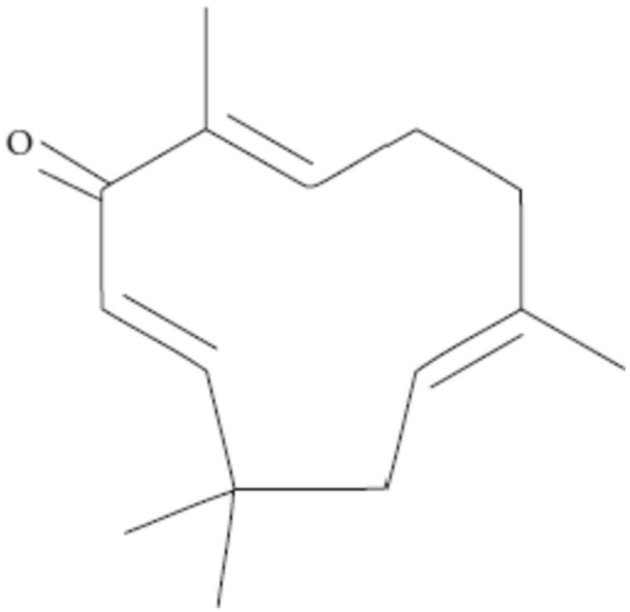

Fig. 1 Chemical structure of Zerumbone (2,6,9,9-tetramethyl-[2E,6E,10E]-cycloundeca-2,6-10-trien-1-one, MW 218.33 g/mol)

The potential mechanisms involved in cancer

Cancer, characterized by the autonomous expansion and spread of a somatic clone, is the second most common cause of death worldwide, and its prevalence is increasing [22–24]. Resistance to cell death, uncontrolled the proliferative signaling pathways, induction of angiogenesis, evasion of growth suppressors, enabling replicative immortality, and activation of invasion and metastasis are known hallmarks of cancer [25–27] Nucleotide changes, small additions and deletions, chromosomal rearrangements and copy number changes are somatic mutations that disrupt protein-coding or regulatory mechanisms of genes [28–31].

Natural products-ZER

Zingiber zerumbet Smith of the Zingiberaceae family, also known as lempoyang wild ginger, has many medicinal properties such as treating swelling, wounds, anorexia, parasitic diseases, and treating inflammation [32]. Inhibiting tumor organizer 12-*O*-tetradecanoylphorbol-13-acetate-leading to Epstein-Barr virus [33], suppressing dextran sodium sulfate-induced colitis [34], pro-inflammatory protein production, suppressing free radical generation, and cancer cell proliferation associated with apoptosis [35] are examples of hundreds of distinguishing features of this plant. ZER is a monocyclic compound with molecular formula $C_{15}H_{22}O$ is used as a food phytochemicals with anti-cancer properties [36]. The rhizomes of *Zingiber zerumbet* are abundant in Southeast Asia and tropical countries such as India, Bangladesh, Malaysia, Nepal, and Sri Lanka [37].

Anti-cancer mechanisms of ZER

Today, despite advances in cancer treatment techniques, cancer is still one of the worst diseases, causing many deaths every year [38]. Available cancer therapies are mostly infectious and have caused a lot of terrible side effects and resistance [39]. Overall, there is a need to find a novel, alternative, effective and non-toxic treatment for cancer. Studies indicate that ZER inhibits proliferation,

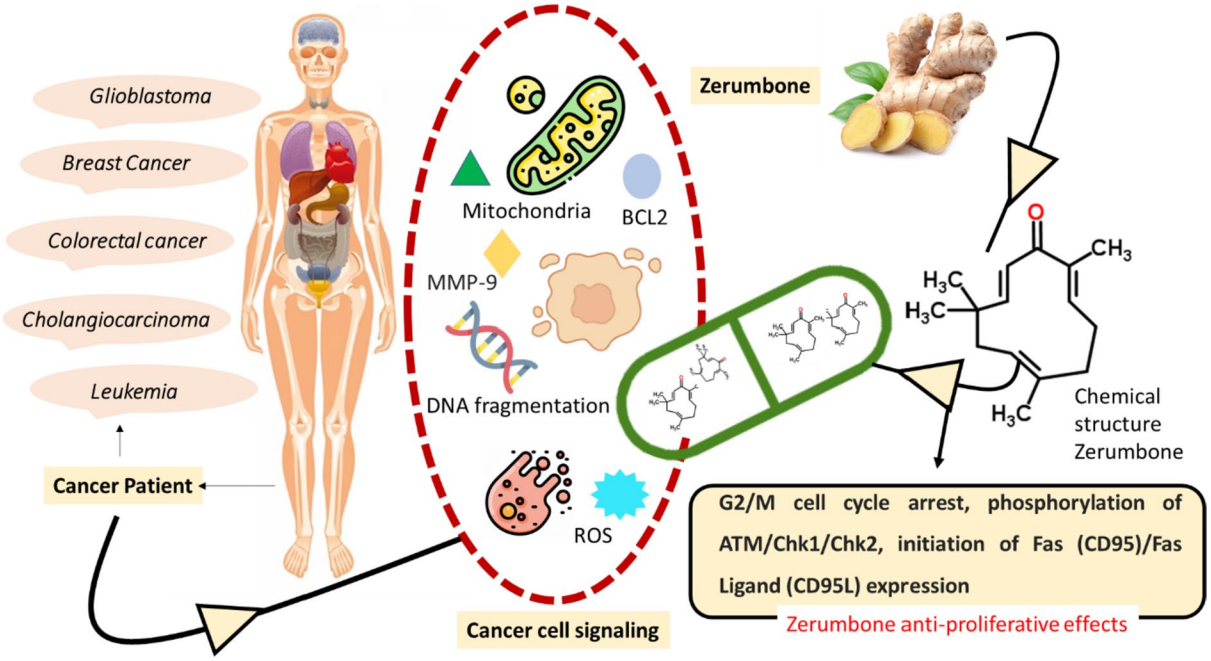

Fig. 2 Anti-proliferative effects ZER in the various human cancer categories such as cervical, breast, colon, and liver cancer

arrests the cell cycle and induces apoptosis in many types of cancer, including colon, liver, breast, lung and brain tumors, by modulating various proteins and signaling pathways [20, 40–42].

From a pathogenesis-wise perspective, the anti-cancer effects of ZER can be categorized accordingly:

1. Genetic mutations: Zerumbone shows promise in regulating genetic mutations linked to cancer, particularly by downregulating oncogenic pathways. Its ability to inhibit the expression of critical genes such as RAS and MYC suggests a potential role in impeding the oncogenic potential and promoting DNA repair mechanisms.
2. Epigenetic changes: Studies hint at Zerumbone's influence on epigenetic modifications, including DNA methylation and histone alterations. By modulating these patterns, Zerumbone could potentially affect the expression of genes involved in cancer progression by regulating their epigenetic landscape.
3. Cell signaling pathways: Zerumbone's impact on vital cell signaling pathways, such as PI3K/AKT/mTOR and MAPK/ERK, suggests its potential to disrupt aberrant cell growth and survival in cancer cells.
4. Angiogenesis: Research explores Zerumbone's anti-angiogenic effects, potentially inhibiting the formation of new blood vessels around tumors by interfering with pro-angiogenic factors like VEGF.
5. Apoptosis: Zerumbone's ability to induce apoptosis in cancer cells is noteworthy, preventing these cells from evading programmed cell death and contributing to limiting their survival.
6. Immune system evasion: Although limited, studies propose that Zerumbone might modulate immune responses, potentially enhancing the immune system's ability to recognize and eliminate cancer cells, possibly through the regulation of immune checkpoint proteins.
7. Inflammation: Recognized for its anti-inflammatory properties, Zerumbone may create an environment less conducive to cancer initiation and progression by attenuating chronic inflammation associated with cancer development.
8. Metastasis: While requiring further investigation, some studies suggest that Zerumbone may impact cell motility and invasion, crucial processes in metastasis, potentially hindering the spread of cancer cells to distant sites.
9. Metabolic reprogramming: evidence suggests that Zerumbone may influence cellular metabolism, potentially altering metabolic pathways like the Warburg effect and impacting the energy dynamics of cancer cells [31–35].

It is noteworthy that in various in vitro studies showed that ZER could also suppress the CXCR4 expression, NF-κB activity, and other proteins. In addition, this compound can also inhibit the AKT/STAT3/PI3K/mTOR/IL-6/JAK2 lines and the expression of related genetic factors such as ETV1, COX2, IL-6 and cyclin D1, thus suppressing the proliferation and angiogenesis activity of

malignant cells by inducing cell cycle arrest and apoptosis. In addition, ZER has shown anti-cancer activity against tumor growth and metastasis in various mouse models and, rarely, in clinical trials [43]. So we looked at some in vitro and in vivo trials that showed the effectiveness of ZER as a treatment for different types of cancer. ZER leads to cell detoxification of oxidative, genotoxic, and carcinogenic chemicals by induction of GSH-related enzymes of stage II, including glutathione-transferase (GST) [37]. Inhibition of tumor cell growth, induction of apoptosis, differentiation and cytoprotective activity are the mechanisms by which ZER acts as an anti-proliferative agent [44]. Studies have shown that ZER prevents the proliferation of colon adenocarcinoma HepG2 cells in a dose-dependent manner and also inhibits the activation of the primary antigen of the Epstein-Barr virus [45]. ZER reduces the production of tumour necrosis factor-alpha (TNF-α) and interleukin-4 (IL-4) and suppresses LTC4 production from lung tissue, downregulates NF-KB and NF-KB gene expression, suppresses CXCR4 and HER2-overexpressing breast cancer cells [46]. Inhibition of leukaemia cells by stimulating Fas receptors and reduction of cyclin B1/CDK1 protein levels by inhibiting the G2/M cell cycle in HL-60 cells are other protective mechanisms of ZER [20, 47]. ZER reduces the expression of NF-kB and NF-kappa regulated gene, which increases in cases of carcinogenicity. It also prevents pancreatic and invasive breast cancer by reducing the expression of the chemokine receptor CXCR4 by inducing the reduction of CXCL12 [48, 49]. It is hypothesized that the carbonyl b-unsaturated group with the depletion of intracellular glutathione (GSH) causes the therapeutic effects of ZER [41, 50].

In vitro studies of the effects of ZER on lipid peroxidation in biological systems (phospholipid and cholesterol membrane oxidation) showed that ZER induce to the accumulation of cytosolic lipid droplets and protein dynamics/altered cell membrane organization, depolarizing the mitochondrial membranes and causing alteration of nuclear morphology and apoptosis [51]. ZER with obstructing the excretion of pro-inflammatory cytokines, stimulating NF-κB p65 in LPS-activated inflammation of THP-1 cell-derived macrophages, inhibiting mRNA and protein levels of TLR-2/4 prevents diabetes, cancer and atherosclerosis [52]. ZER stimulates Hsp90 ATPase activity and modifies cysteine residues that destabilise cytotoxicity and anti-cancer efficacy [53]. ZER anti-proliferative activity on the cell lines Hep-G2 (hepatocellular carcinoma, ATCC-HB-8065), LU (lung adenocarcinoma, ATCC-HTB-57), P338 (leukaemia, ATCC-CCl-46), MCF7 (breast cancer, ATCC-HTB-22) and SW 480 (colon adenocarcinoma, ATCC-CCL-228) is evident [54]. ZER has anti-inflammatory and anti-proliferative activities by inhibiting the activation of NF-κB and NF-κB-regulated gene expression caused by carcinogens (Fig. 3) [55].

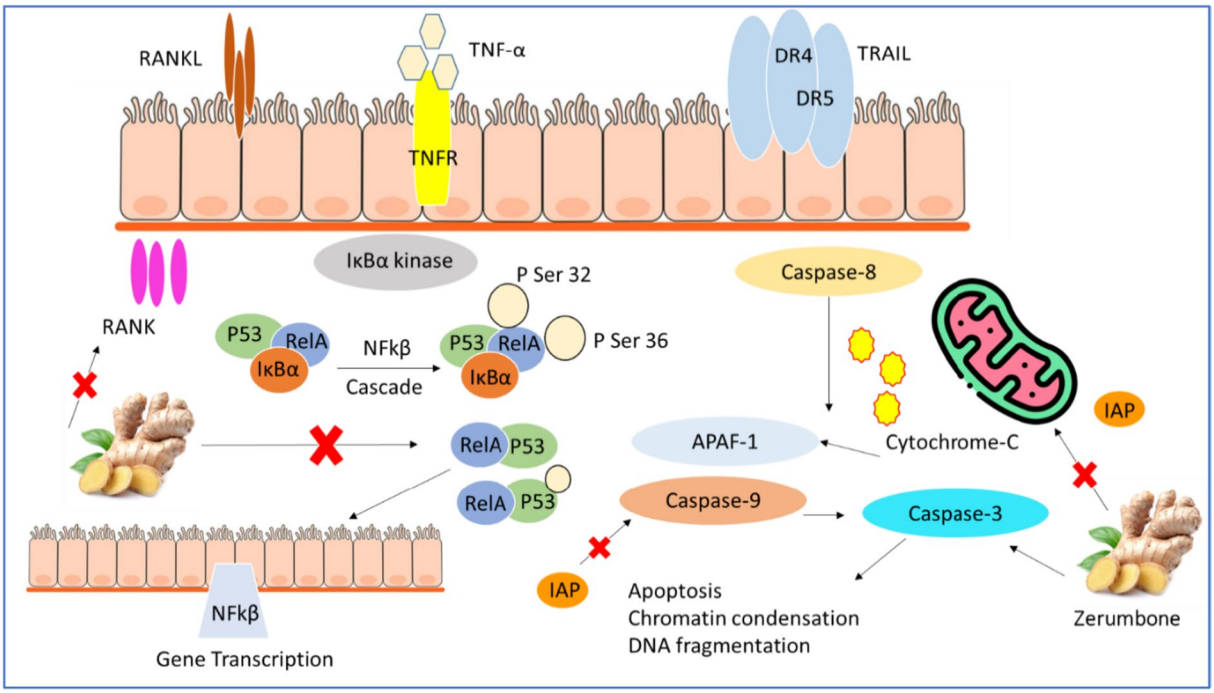

Fig. 3 Zerumbone's key signaling pathways in cancer prevention and treatment

ZER and glioma

The most common and deadly cancer of the adult central nervous system that is resistant to alkylating agents and other antineoplastic treatments is glioblastoma multiform (GBM) [56]. A number of signaling pathways have been implicated in glioma resistance to alkylating agents and/or the maintenance of brain tumor stem cells, including sonic hedgehog (SHH), Notch and Wnt-β-catenin [57]. ZER induces WOX1-overexpressed U373MG and U87MG cells, and transient overexpression of WOX1 (The WW domain-containing oxidoreductase gene) and blockade of SHH signaling can increase the radiosensitivity of GBM cells independent of p53 and WOX1 levels [58]. Activation of inhibitory κB (IκB) proteins. IκB kinase (IKK), followed by activation of the Akt-FKHR cascade and inactivation of caspase-3, contributes to the resistant to apoptotic process in GBM [59]. Apoptosis pathway of the GBM8401 cell includes inactivating IKKα that affecting to FOXO1 dephosphorylating, via Akt dephosphorylating or not, then inducing caspase-3 activation [60]. ZER treatment reduced cell viability and induced apoptosis in GBM cells by inactivating IKKα, resulting in suppressed FOXO1 and Akt phosphorylation and activation of caspase-3 protein and PARP [60].

ZER and breast cancer

Breast cancer is the second most common cause of cancer death in women and therefore requires special attention [61, 62]. Seventy percent of breast cancers are luminal carcinomas that have alpha estrogen receptor (ER) [63]. ZER binds to estrogen receptors (ERs) and mediates critical pathophysiological signaling pathways in breast cancer, known to be the most common malignancy in women worldwide [64]. The rhizome in ginger has a significant role in the care of a breast concert with inhibiting the migration of MDA-MB-231 cells [65]. The expression of integrin αvβ3 appears to play a key role in the development of bone marrow from breast cancer [66]. ZER, when co-administered with the TP5-iRGD peptide, has better antitumour activity by targeting the integrin αvβ3 [67].

ZER by inhibiting IKKβ kinase and thus preventing it from binding to NF-κB can lead to the ultimate induction of apoptosis [68]. ZER was noted that effects on the vitality of MCF-7 and MDA-MB-231 cells [69]. ZER also decrease Breast Cancer–leading to Bone Loss, inhibits Osteoclastogenesis with MDA-MB-231 breast cancer, and suppresses RANKL-leading to NF-KB Activation [70]. In a study, ZER was leading to decreased in Notch1 and Notch4 cleaved proteins, that produced in the inhibition of cellular migration and increased apoptosis. On the other hand, it caused the cleavage of Notch2 to rise the induction of presenilin-1 protein and Notch transcriptional activity [71]. Further, ZER is leading to suppressed IL-1βinduced cell invasion and migration in TNBC through the downregulation of NF-κB activity that inhibited MMP-3 and IL-8 expression [48, 72].

ZER caused a reduction in cell growth and proliferation by arresting the cell cycle in the G1 phase due to a reduction in CD1d expression and the lipid antigen presentation pathway [73]. CD44 shown to promote protumorigenic signaling and metastatic cascade [74]. ZER decreased expression of CD44 through EGFR ligands, TGF-α or EGF and also inhibited STAT3 phosphorylation that resulted reduction of tumor metastasis and progression [75].

ZER also reduced the tumor growth and caused Bax- and Bak-mediated apoptosis by inducing G2/M cell arrest [47]. The elevated levels of CXCR4 indicate that the patient has a high probability of lymph node metastasis [76]. ZER decreased CXCL12-Induced metastasis and invasion in breast cancer through downregulating the CXCR4 expression [77]. In addition, this natural compound reduce phosphorylation of TGF-β1-affected from Smad3 and Ki67 expression following that inhibit TGF-β1-induced MMP-2, FN, and MMP-9 expression, which lead to restrain the motility and tumorigenicity of triple-negative breast malignance cells [78].

In addition, Bcl-2-positive tumors with increased loss of apoptosis were associated with metastasis [79]. ZER reduced expression of Bcl-2 genes and increased Bax. ZER also N-acetyl cysteine (NAC) and elevated reactive oxygen species (ROS) which led to the NF-κB p65 activation. Therefore ZER has an apoptotic induction potential and increased cell cycle arrest at G2/M stage in GBM U-87 MG cells [80].

ZER and colorectal cancer

The incidence of colorectal cancer in the general population is about 5 to 6% and is the second most common cancer in the world [81]. The expression of miR-200c was increased in higher grade CRC and has been implicated in CRC tumor progression and aggressiveness via regulation of epithelial-to-mesenchymal (EMT) and mesenchymal-to-epithelial (MET) transition processes [82]. ZER has an important role on colorectal cancer (CRC), cancer stem cells (CSCs) and including EMT as one of the most rampant and lethal malignancies in the world by inhibiting the β-catenin pathway through miR-200c and inhibiting mesenchymal-epithelial transition and cancer stem cells characterizes [83].

This tropical ginger can increase tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), deletion of DR5 or DR4, decrease regulation of cFLIP and inhibit caspase-8 [84]. In addition, ZER has protective effects opposite bowel cancer in *Enterotoxigenic Bacteroides fragilis* (ETBF)-colonized AOM/DSS BALB/c mouse [85]. A study by Edagawa et al. demonstrated that during celecoxib and ZER treatment in human p53-deficient

colorectal cancer cells, ATF3 promotes DR5 producting and apoptotic cell death [86]. ZER induces apoptosis of colon cancer by inhibiting the formation of colonic preneoplastic ACFs, and its anti-proliferative influences were noted effectiveness as an anti-cancer agent [87].

The majority of colorectal cancers express high levels of cyclin B1 [88], that ZER inhibited DNA synthesis and cyclin B1 expression as an antitumor and anti-cancer agent, especially on human colon cancer [89]. ZER decreases the proliferation of bowel cancer cells and induced apoptosis through translocation of phosphatidylserine, mitochondrial transmembrane dysfunction, and chromatin condensation [35]. ZER Modulated Fak/PI3k/NF-κB-uPA pathway and proved its anti-metastatic potential and Suppressed Human Colorectal Cancer Invasion on HCT-116 and SW48 cells [50].

In addition, ZER increases oxidative stress in a thiol-dependent ROS-independent pathway to enhance apoptosis and radiosensitivity of colorectal cancer cells while inhibiting the expression of radiation-induced DNA repair proteins DNA-PKcs and ataxia-telangiectasia mutated (ATM) through GSH depletion, leading to cell cycle arrest (G2/M) [17].

In one study, ZER was found to stimulate the expression of interleukin (IL)-1α, IL-1β, IL-6 and production of tumor necrosis factor (TNF)-α in human colon adenocarcinoma cell lines [90]. Further ZER treatment repressed NF-κB and heme oxygenase (HO)-1 that caused inhibition of the multiplicity and inflammation in colonic adenocarcinomas, induction of apoptosis and suppression of the proliferation [21]. ZER treatment suppressed TNF-alpha and downregulated HCT116 colon cancer cells proliferation [40]. ZER increased Bax, Caspase 3, Caspase 8, Caspase 9 and also caused enhancement of cell cycle stopping at G2/M stage by down regulated Bcl2 expression, mitochondrial membrane potential and the cellular antioxidant status [91].

ZER and cholangiocarcinoma

Cholangiocarcinoma (CCA) is the most common malignancy of the biliary tract and has increased significantly in recent decades [92]. EGFR signaling is involved in cholangiocarcinoma development and progression [93]. In a study on seventeen ZER derivatives has been shown the presence of amine, hydroxylamine, epoxyamine, and nitrile groups by interacting with the molecular target EGFR have the most effective anti-proliferative activity against KKU-100 cell lines with an IC50 level of 16.44 mM which can exhibit acutely anti-cancer activities opposed to CCA cells [94].

ZER and gastric cancer

Stomach cancer is the second most common cause of cancer deaths worldwide because it is usually detected in the late stages [95]. Cyclophilin A (CypA) was expressed at abnormally high levels in several types of cancer, including gastric cancer, and was implicated in cancer cell proliferation, cell migration/invasion, drug resistance and inhibition of apoptosis in several cancer cell types [96]. ZER block the action of cyclophilin A and promote mitochondrial pathway-interceded apoptosis, as a result, produce caspase-dependent apoptosis in gastric cancer cells [97]. Gene products controlled by NF-κB include the angiogenesis modulator vascular endothelial growth factor (VEGF), which supports cell survival and leads to the acquisition of chemoresistance [91]. ZER reduces NF-κB activities and the expression of VEGF, thereby inhibiting angiogenesis, leading to suppression of cell proliferation and tube formation in human umbilical vein endothelial cells [98].

ZER and leukemia

Leukaemia is characterized by starting in the bone marrow and resulting in high numbers of abnormal blood cells, which, like other cancers, arise from mutations in DNA [93]. In research on the murine leukaemia model using WEHI-3B cells by Rahman et al, ZER also induced the mitochondrial-dependent apoptotic pathway [99]. ZER stimulates the intrinsic apoptotic proteins (Caspase-3 and Caspase-9), releases Cytochrome c from the mitochondria, and following that cleavage of poly (adenosine diphosphate-ribose) polymerase (PARP) which led to arrest the Jurkat cells at G2/M stage with inactivation of cyclin B1 protein. As a result, ZER treatment showed the anti-proliferative effect on human lymphoblastic leukemia cell line [100, 101].

ZER suppresses K562 chronic myeloid leukaemia cell proliferation and colony formation due to DNA damage and upregulation of total histone H2AX, increased calcium, generation of ROS with activation of pro-caspase-3, -9 and PARP cleavage on Western blots, termed mitochondria-mediated apoptosis [102]. ZER treatment against CEM-ss leukemic cells enhanced the number of TUNEL-positive stains and the caspase-3 level of cells and also revealed membrane blabbing holes and cytoplasmic discharges which are characteristics of apoptosis [103].

In one study, two distinct pathways [mitochondrial and Fas (CD95)-mediated] were identified in ZER-treated NB4 cells. ZER inhibits the proliferation of leukaemic promyelocytic NB4 cells by inducing G2/M cell phase arrest followed by apoptosis via the onset of Fas (CD95)/Fas ligand (CD95L) expression associated with caspase-8 action. It also reduced B1/CDK1 protein cycling along with ATM/Chk1/Chk2 phosphorylation. In this study, both caspase-8 and -9

were cleaved into their active forms by treatment with ZER. ZER also induced the cleavage of Bax and Mcl-1 proteins, but not Bcl-2 or Bcl-XL [104, 105].

ZER and liver cancer

The incidence of liver cancer has increased and it is the third most common cause of cancer and leads to death [106]. Several studies have identified alterations and dysregulated expression of the phosphatidylinositol-3-kinase (PI3K)/serine-threonine protein kinase (Akt)/mammalian target of rapamycin (mTOR) pathway in hepatocellular carcinoma (HCC) [107]. ZER decreased proliferation and clonogenic survival of HCC cells and induced apoptosis *via* stopping cells at the G2/M stage due to the significant suppression of the STAT3 and PI3K/AKT/mTOR signaling pathways [108]. ZER enhanced Bax pro-apoptotic protein and inhibited Bcl-2 anti-apoptotic protein expression and leads to inducing apoptosis [44]. In addition, ZER induced mitochondria-regulated apoptosis and inhibited proliferation by upregulating Bax, decreased Bcl-2 protein expression, reduced oxidative stress, and as a result, lessening DEN/AAF-caused carcinogenesis in rat liver [109].

HCC is characterized by marked vascular abnormalities, arteriogenesis and capillarisation [110]. Another in vitro study about the anti-tumor effect of ZER on HCC demonstrates suppression angiogenesis in cells of HepG2 through suppression the expressions of VEGF, MMP-9, and VEGFR [86]. In a study noted that to prevent the proliferation and migration of HepG2 cell in a dose-dependent method, ZER decreased tube formation through HUVECs inhibits new blood vessel and tissue matrix formation and also reduces expression of molecular effectors of angiogenesis, MMP-9, VEGF, and VEGF receptor proteins [111]. Further ZER influence on nuclear localization of the transcription factor (Nrf2) that activated the Nrf2/ARE-dependent detoxification pathway and therefore showed the antioxidant role in the lipid peroxidation neutralization in hepatocytes [112]. ZER encapsulated by hydroxypropyl-β-cyclodextrin (HPβCD) recognized induced apoptosis and G2/M stage stopping in HepG2 cells beside the release of cytochrome c and damage of mitochondrial membrane potential and also increased Caspase 3/7, Caspase 8, and Caspase 9 with the depletion of BID divided by Caspase 8 [113]. ZER increased apoptosis and cell cycle arrest at G2/M stage in HepG2 cells via upregulated cytochrome c, p27, p38, Bcl-2, caspase-3 and-9 expression through MAPK signaling pathway [114].

ZER and lung cancer

Lung cancer is the leading cause of cancer death worldwide [115]. Lipopolysaccharide (LPS) increased the expression of haem oxygenase (HO-1) and Nrf2 and lipid peroxidation, activation of antioxidant enzymes and activation of MMP-9 and myeloperoxidase (MPO), which was suppressed by ZER and led to a reduction in acute lung injury [116]. NF-κB and HO-1 signaling pathways reduce ROS production in lung cancer cells which followed by chemoresistance [117] and ZER decreased growth, inflammation, and expression of NF-κB and HO-1, which caused apoptosis, suppression of lung carcinogenesis, and inhibited the multiplicity [21].

In addition, ZER leads to loss of mitochondrial membrane potential resulting in cytochrome c production, activation of caspase-3 and -9, promotion of Bax and p53 expression and upregulation of ROS production. Thus, ZER induces increased susceptibility to cisplatin and mitochondrial apoptosis in non-small cell lung cancer (NSCLC) cells [118]. LIM kinase (LIMK) is a serine/threonine protein kinase that includes members LIMK1 and LIMK2, which protect cancer cells from death and promote cell proliferation and chemotherapeutic resistance. LIMK2 expression was also upregulated in radioresistant NSCLC cells [119] and in vitro showed that ZER suppressed LIM kinase 1 and 2 and AKT and FAK phosphorylation Non-Small Cell Lung Cancer A549 Cells and also reduced osteopontin through blocking ROCK1 expression [120].

ZER and oral cancer

Oral squamous cell carcinoma (OSCC) is one of the ten most common cancers worldwide, with high mortality and poor response to treatment [121]. Regarding the distant metastasis from the oral cancer and as over activation of PI3K/Akt signaling pathway in human oral cancers [122], A study of ZER treatment in oral squamous cell carcinoma by Zainal et al. showed that ZER suppressed OSCC proliferation, migration and invasion, and induction of G2/M cell phase exit and apoptosis by downregulating the expression of RhoA, CXCR4 proteins, and also decreased the PI3K-mTOR signaling pathway via inactivation of S6 and Akt proteins [123]. Regarding the apoptosis-resistant of oral cancer cells, ZER induced apoptosis via S and G2/M stages of cell cycle arrest due to its antiproliferative, antioxidant, anticancer, and anti-inflammatory effects on Human Laryngeal Carcinoma Cell Line Hep-2 [41].

ZER and cervical and ovarian cancer

Cervical cancer is known to be a major problem in most developing countries and the second most common cancer in women worldwide [124]. Ovarian cancers have the highest occurrence and mortality rate among gynecologic cancers that, unlike cervical cancer, there is no proper prevention program [125]. Thirteen percent of women with cervical cancer are diagnosed at an advanced stage of the disease that in contrast to localized type, there is no standard treatment

for patients with metastatic cervical cancer and median survival is only 8 to 13 months [126]. ZER is an active agent that induces apoptosis, cytotoxicity and anti-migratory effects in cervical cancer cells by preventing cell migration of HeLa cells, reducing the production of MMP-2/9 and proangiogenic factor VEGF, and stimulating programmed cell death in HeLa cells through phosphatidylserine translocation, increased caspase 3 activity, DNA fragmentation, upregulation of the expression of pro-apoptotic protein Bax, cleaved caspase 3, cleaved PARP and downregulation of anti-apoptotic protein Bcl-2 [38].

In a study on ZER treatment in Cervical Intraepithelial Neoplasia (CIN) of Female BALB/c mouse, noted ZER reduced immunoexpressions of proliferating cell nuclear antigen and proved an anti-cancer effect on cervical cancer cells [127]. Regarding the overexpression of Bcl-2 and Bax in CIN [128], ZER modulated the expression of Bcl-2 gene and Bax protein and induced mitochondria-regulated apoptosis through the regression of CIN tissues [129]. IL-6 was significantly upregulated in ovarian cancer and subsequently promote a pro-inflammatory tumor microenvironment [130]. ZER suppressed the IL-6 levels secreted by both Caov-3 and HeLa cells and induced apoptosis by stopping cells at the G2/M phase [131]. ZER also upregulated the Caspase-3 cellular level in HeLa cells and originated distinctive morphological features of apoptosis concluded chromatin and nuclear condensation, multinucleation, cell shrinkage, membrane blebbing, holes, abnormalities of mitochondrial cristae, cytoplasmic extrusions and formation of apoptotic bodies [132].

ZER and pancreatic cancer

Pancreatic cancer has poor prognosis among solid tumors. And the response to chemotherapy is not so good [133]. CXCR 4/CXCL12 is associated with tumor invasion and metastasis in pancreatic cancer also induced chemoresistance [134] that ZER treatment decreased CXCR4 expression and inhibited CXCL12-induced invasion in pancreatic tumor cells, which leads to suppressed cancer metastasis [77]. Similar to CXCR4, IL8/CXCL8 could play an important role in tumor progression and angiogenesis [135], ZER reduced the mRNA expression and protein secretion of the main angiogenic factors VEGF and IL-8 in PaCa cells and blocked the PaCa-associated angiogenesis through the suppression of NF-κB and NF-κB-dependent proangiogenic genesis which leads to suppressed tube structure of human umbilical vein endothelial cells [136]. In a study using the pancreatic cancer cell lines AsPC-1, SW1990 and PANC-1, ZER treatment resulted in upregulation of p21 expression, p53 protein levels and ROS production. Therefore, ZER decreased cell viability and induced apoptosis via the p53 pathway [137].

ZER and prostate cancer

Prostate cancer in men has a significant prevalence and a good prognosis with early detection through prostate specific antigen (PSA) in the blood for and improved procedures with radiotherapy and surgical intervention [138]. Ataxia telangiectasia mutated (ATM) kinase is a 350 kDa nuclear protein kinase that is activated by DNA double-strand breaks to activate DNA repair, but is down-regulated in prostate cancer that induces resistance to radiotherapy [139]. In research on PC3 and DU145 prostatic cancer cells, emphasized that ZER increased the radiation effect on prostate cancer cells and reduced the radiation-caused expression of phosphorylated ATM. ZER also suppressed the expression of STAT3 and JAK2, which are implicated in DNA damage repair signaling [140].

A primary sensor and master regulator of ER stress is glucose-regulated protein 78 (GRP78), overexpression of which confers resistance to a variety of chemotherapy drugs [141]. In a study on anti-proliferative and apoptotic effects against DU-145 and PC-3 cell lines, ZER induced (ER) stress and mitochondrial damage by upregulation of GRP-78 and CHOP/GADD153 expression and the loss of mitochondrial membrane potential [142]. ZER also increased intracellular Ca^{2+} levels, which related to the structure of the active calpain I fragment and induced autophagy and apoptosis in human hormone-refractory prostate cancers (HRPCs) through tubulin binding and a Caspase-dependent way and dramatic LC3-II formation.

In addition, ZER suppressed microtubule assembly and increased MPM-2 expression, Mcl-1 protein expression, phosphorylation of Bcl-xL and Bcl-2, leading to the tubulin-binding effect. ZER also downregulated Cdc25C and increased the expression of C/EBP homologous protein (CHOP)/growth arrest and GRP-78 and DNA damage 153 (GADD153) [143]. Furthermore, ZER induced apoptosis via cell cycle arrest at the G0/G1 stage, and also ZER decreased the JAK2/STAT3/IL-6 signaling pathway and blocked the prostate cancer-associated genes including: IL-6, cyclin D1, COX2 (cytochrome c oxidase) and ETS variant 1 (ETV1) [144].

ZER and renal cell carcinoma

Renal cell carcinoma (RCC) accounts for approximately 3% of adult cancers and is characterized by resistance to conventional cancer treatments [145]. ZER treatment induced apoptosis in human renal cell carcinoma through inhibition of Bcl-2 and Gli-1, which caused chemoresistance of RCC, inhibition of cell viability and DNA fragmentation. On the other hand, stimulation of caspase-3 and -9 led to PARP cleavage [146]. STAT3 is aberrantly activated in several types of malignancy, including RCC, where it regulates

the expression of genes involved in cell survival, proliferation and angiogenesis [147]. ZER stimulates JAK 1/2 and upstream kinases c-Src. It therefore inhibits the activation of STAT3 in RCC cells in a time- and dose-dependent manner. As a result, ZER suppresses proliferation and induces apoptosis in RCC. ZER induced the expression of the tyrosine phosphatase SHP-1, which is associated with its ability to block STAT3 activation [148].

ZER and skin cancer

One of the most common types of cancer, especially in fair-skinned populations, is skin cancer, which is divided into melanoma and non-melanoma skin cancers (NMSCs), affecting the skin in the form of basal cell carcinoma and squamous cell carcinoma (BCC and SCC, respectively) [149]. Mice genetically deficient in Nrf2 are highly susceptible to chemically induced skin tumorigenesis. They are also less responsive to the cytoprotective effects of some chemopreventive phytochemicals [150]. ZER with suppressed nuclear Nrf2 activation in HSF cells prevents from aging skin cells [151]. Reactive oxygen species such as NOX, iNOS, COX-2 play a key role in skin tumorigenesis [150] and ZER decrease NOX, iNOS, COX-2 with inhibiting mRNA expression. This mechanism is also seen in the colon [152]. Melanoma is known as a high malignancy tumor. ZER with suppressing the migration and proliferation of the melanoma cell line CHL-1, also decreasing mitochondrial activity that leads to the subsequent raising in ROS generation, decrease in MMP, and a reduction in mtDNA and ATP levels can be a valuable treatment option [42].

The xenobiotic-metabolizing enzymes (NQO1, GSTP1) and mRNA levels for manganese superoxide dismutase (MnSOD), glutathione *S*-transferase-P1, glutathione peroxidase-1 (GPx1), and NAD (P) H quinone oxidoreductase are examples on antioxidant that protect in cells the epidermis from tumorigenesis and could be upregulated over ZER treatment. ZER also reduced cyclooxygenase-2 (COX-2) expression, H2O2-induced oedema formation, ERK1 phosphorylation and leukocyte infiltration, suppressing the initiation and promotion stages of skin cancer [153]. ZER induced HO-1 expression via stimulation of Nrf2, which led to an antioxidant effect on skin carcinogenesis [43]. In a study on UVA-irradiated damages that caused skin cancer, noted ZER increased expression of c-glutamyl cysteine ligase (c-GCLC) and HO-1 genes and also upregulated antioxidant response element (ARE) and Nrf2 nuclear translocation that related to the PI3K/AKT, p38 MAPK, and PKC signaling [149]. In addition, ZER suppressed the expression of microphthalmia-associated transcription factor (MITF) and downregulated melanin aggregation in α-melanocyte stimulating hormone (α-MSH), leading to the induction of melanogenesis [154].

ZER and esophageal cancer

Adenocarcinoma and esophageal squamous cell carcinoma (SCC) of the esophagus is a serious malignancy with a poor prognosis and the eighth most common cancer in the world [155]. ZER can be useful in on the proliferation and apoptosis of the esophagus cancer EC-109 cells by downregulating the Bcl-2 protein expression and upregulating the P53 protein expression [156]. The results showed that Rac-1 was upregulated at the protein and mRNA levels in ESCC cancer and associated with lymph node metastasis were two independent factors for poor survival [157]. ZER decreased Rac1 protein by enhancing Rac1 ubiquitination through the proteasome-dependent inhibition pathway, which led to suppressed migration in human esophageal squamous cell carcinoma KYSE-150 and KYSE-30 cells [158] and may be a potential agent for targeting and therapy of ESCC.

Future directions

As reviewed above, many in vitro studies have shown the significant effect of ZER on various human cancers, but only a few in vivo studies on breast, lung, cervical, renal cell, colorectal and skin cancers have been conducted to demonstrate these effects. There are also no relevant clinical trials to test the safety and efficacy of ZER, so there is a paucity of in vivo evidence. In addition, some studies are needed to analyze the pharmacokinetic properties of this product, such as distribution, solubility, etc. As an example, previous research designed to improve the solvability of ZER and it was investigated to evaluate its relationship with hydroxypropyl-β-cyclodextrin (HPβCD) in containing compounds and demonstrated that the solvability of ZER dramatically improved with an increase in the release of HPβCD at 20 °C, thus indicating that this product could be consumed in this drug formation [159]. Therefore, in this field of medicine on cancer therapy with ZER, we urgently need to more studies in both in vivo and clinical trials and also pharmacokinetic features, to accredit its clinical use in various human cancers.

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Data availability The data supporting the conclusions of this article are all online.

Declarations

Competing interests The authors declare that they have no competing interests.

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