Research Article

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ZERUMBONE MOLECULE ON BREAST CANCER

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Abstract

Cancer is a significant danger to general wellbeing universally, causing roughly ten million deaths globally in 2018. Regardless of advances in regular therapy in modalities of the malignant growth treatment, there are, as, yet, scarcely any effective therapies accessible because of the absence of selectivity, unfavourable results, toxicity levels, and tumour relapse. Hence, there is a quick requirement for fundamental elective therapeutics, which can be helpful and protect against the said disease. Different phytochemicals derived from natural sources have been discovered to show practical restorative actions against different human infections. One such chemical is Zerumbone, extracted from *Zingiber zerumbet Smith* that has various pharmacological properties, including cell reinforcement, antibacterial, antipyretic, immunomodulatory, and is also hostile to neoplastic growths. Zerumbone has demonstrated anti-cancer potential by causing critical concealment of multiplication, survival, angiogenesis, and metastasis through various pathways. NF-kB, Akt, and IL-6/JAK2/STAT3 (Interleukin-6/Janus Kinase-2/Signal Transducer and Activator of Transcription 3) are a few examples with their downstream objective proteins. The present audit momentarily sums up the activity and helpful capability of zerumbone against breast malignancy.

Abbreviations	Full form
ZER	Zerumbone
BC	B-cells
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
IL	Interleukin
miRNA	MicroRNA

Keywords: Zerumbone, Breast Malignancy, Cancer.

Introduction

Breast cancer is a prevalent and leading type of cancer worldwide, eliciting high mortality rates, especially among women. Breast cancer prognosis is poor because of its advanced metastasis and heterogeneity[1] . However, the armamentarium of breast cancer alignment relies on chemotherapy, which has faced many drawbacks, such as low concentration of the chemotherapeutic drug at the tumor target site and the adverse effects in the body that indistinctively target other undamaged body parts. Therefore, there are other potential therapeutic interventions such as Zerumbone, with advanced anti-breast cancer properties revealed by several studies, and works by repressing the invasive properties of ductal/breast carcinoma cell lines - MCF-7 and MDA-MB-231.

The structure representing the functioning head of Z. zerumbet cells that is Zerumbone is shown in Fig.1-

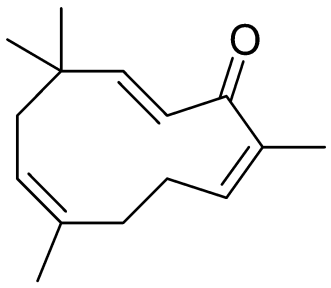

Fig.1 Molecular structure of Zerumbone

Zerumbone and its Biomedical Application in Breast Cancer

Zerumbone is a sesquiterpene derivative found in rhizomes from the wild ginger plant, *Zingiber zerumbet*[1] demonstrated by several studies to have various biological effects, including anti-inflammatory properties and ameliorating impairment abilities. Zerumbone is the functioning head of Z. zerumbet and is possibly a lead compound for the discovery of potential anticancer agents. Previous studies indicated that the therapeutic management of BC by Zerumbone affected the proliferation of cells and also caused the Hep-2 (human laryngeal carcinoma) cells to undergo cell cycle arrest. For BC, it suppresses and blocks the invasion of breast cancer cells and induces cell death[2]. Additionally, other than inducing apoptosis, Zerumbone activates Bak and Bax, Bax and its homolog Bak are key governors of the mitochondrial pathway of apoptosis, and also, its administration inhibits Ki-67 proteins, which play a role in BC growth. According to[1], ZER suppresses and blocks activation of CD44 induced by EGF (epidermal growth factor) through suppressing a signal transductor and activator for the BC signaling pathway. This means that STAT-3 transcription and SKBR3, a human breast cancer cell line responsible for signaling in BC, are suppressed and inactivated. Thus, tumor formation does not occur[1]. ZER has various desired pharmacological effects, such as anti-inflammatory and anti-cancer, which are beneficial interventions. However, its potency, mechanism, and effectivity

on BC remain unknown. Zerumbone also biologically activates miRNAs. Recent studies have demonstrated that decreased expression of miR-708 and its up-regulation in breast cancer suppressed the growth of tumors and inactivate resistance to therapeutic drugs.

There are various subsets of breast cancer, which have been associated with high mortalities and morbidities. Triple-negative breast cancer (TNBC), which accounts for roughly 15–20 percent of all occurrences, is a very aggressive disease with the poorest prognosis of any breast cancer subtype [3,4]. TNBC is distinguished by a lack of expression of the oestrogen receptor (ER), progesterone receptor (PR), and human-epidermal growth factor receptor-2 (HER2) expression[3,4.] TNBC patients have a high risk of recurrence during the first three years, a high risk of cancer-related mortality within the first five years, and a high incidence of distant metastases [5, 6.] Interleukins (ILs) are pro-inflammatory cytokines generated by monocytes, macrophages, and epithelial cells. The interleukin-1 (IL-1) family includes the cytokines IL-1, IL-1, and an interleukin-1 receptor antagonist (IL1RA) [8,9,10]. Due to the lack of recognized targets, such as the oestrogen receptor and HER2, conventional systemic chemotherapy is the sole therapeutic choice for TNBC patients[7]. ZER inhibits cell migration and invasion by inhibiting IL-8 and MMP-3 production, and it lowers TNBC motility and tumorigenicity by inhibiting the TGF-1 signalling pathway. Furthermore, ZER reduces cell development by inducing apoptosis and cell cycle arrest, as well as suppressing IL-6 release in ovarian and cervical cancer cells. ZER has also been demonstrated to block tumour angiogenesis in gastric and pancreatic cancer cells by down-regulating proangiogenic genes such as VEGF and IL-8. Beyond surgery, radiotherapy, and chemotherapy, other treatment methods have been invented and show improved BC prognosis in patients with increased recovery and curative rates. An experimental study on MTT viability and data obtained from colony assay formation demonstrates that ZER suppresses BC cells' proliferation as concentration-dependent[2]. For Transwell assays, ZER demonstrated its effectivity by targeting the migration of BC cells and causing inhibition. qPCR, luciferase tests and immunoblotting further showed that ZER has anti-breast tumor effects through the axis of miR708-BACH1. All these describe the anti-tumor activities upon the target tumor cites of BC development[2] ; the drug exerts anti-tumour effects through various pathways such as its multiple effects on cellular processes that target microRNAs. Here, ZER suppresses transition in the epithelial-mesenchymal by β-catenin signalling inhibition; by regulating miR-200. Moreover, it’s interesting how ZER administration for BC prognosis down-regulates miR-708, which, when unregulated, leads to proliferation of BC cells and increases metastasis. Therefore, present studies emulate that miR-708 expression regulated by ZER highly suppresses the progression of BC tumor cells[2]. The oncogene BACH1 is responsible for the formation and proliferation of different types of cancer cells in humans, such as colorectal cancer. However, it is also a biomarker of BC prognosis, demonstrating migration of BC tumors and apoptosis. ZER interferes with the proliferation of breast cancer cells, their migration, and invasion to target sites by focusing on inhibiting miR-708 and oncogene BACH1[2]. The explanation, therefore, suggests that tracing BACH1 inhibitors is an effective intervention strategy important for breast cancer. Poor penetrating ability through the biological membrane is the leading factor that reduces the efficacy of various anticancer agents, an obstacle for tumor management. Therefore,

studies have proven that enhancing ZER's in vitro activity upon BC cells with TP5-iRGD peptide co-administration induces early apoptosis. Furthermore, encapsulation of ZER in hydroxypropyl-b-cyclodextrin, forming a compound ZER-HPβCD inhibits MCF-7 BC cell growth. Additionally, it also inhibits the growth of other cells responsible for the formation of BC tumours, including MDA-MB-231 cells[1]. Most importantly, unlike chemotherapy, ZER+TP5-iRDG peptide does not display any viable toxicity towards other normal basal cells since it is highly effective with significant selectivity on BC cells and inhibiting their target sites. For ZER-HPβCD, the complex shows advanced effectivity and selectivity of up to 92% against estrogen receptors that induce the proliferation of breast cancer cells. Interestingly administration of a double ZER complex, ZER-HCPBD, and TP5-Irgd, slightly increases the anti-tumor proliferation activity[1]. This indicates that the co-administration has a way in which it interferes with various pathogenesis signalling pathways of estrogen receptors for BC cells, with MDA-MB-231 activity remaining uninterred.

Conclusion

ZER has promising anti-breast tumour activity with high specificity for estrogen receptors for BC cells, whose administration leads to apoptosis. However, co-administration with other compounds forms more effective and advanced complexes in fighting BC tumor progression. The suppression by ZER is in vitro, as it regulates and inhibits the invasion and migration of tumor cells for BC. Thus, Zerumbone is a promising therapeutic intervention for breast cancer.

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