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Zerumbone: A Magical Phytochemical

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ABSTRACT

The effect of herbal dugs has shown promising and beneficial effects which has been studied extensively and reported in literature.
One such phytochemical is zerumbone, which is derived from wild ginger possessing diverse therapeutic effects in the management of various diseases. Zerumbone has been shown to possess an anti inflammatory, analgesic, anti diuretic effect by alteration of inflammatory pathways thereby decreasing the inflammation. It has also been shown to have an anti cancer effect by altering the signalling pathways and mechanisms thereby decreasing the proliferation and growth of cancerous cells.
Key Words: Zerumbone, oral cancer, natural

INTRODUCTION

Zingiber zerumbet (L.) Smith belongs to the family *Zingiberaceae*, a native plant from the Southeast Asia which possesses potential antimicrobial activity, not fully comprehended. [1]
It has varying names depending on their area of vegetation and location. It grows in subtropical climates such as India, South-East Asian countries, South Pacific Islands and Okinawan Islands, and has been used for local folk medicine and gardening. It is called Shinkha in Manipur, North-East India.[2] Traditionally, its use has been successful in the treatment of stomach ache, toothache, fever, indigestion and ulcerative colitis.[1,3]

The roles of essential oils of Z. zerumbet have been studied by authors since 1944. The major component of the rhizome's oil varies from 12.7-73.1%. [4-9] The essential oils derived from zerumbone have promising inherent pharmacological activities, including antimicrobial, anti-inflammatory, chemo-preventive, antinociceptive, antiulcer, antioxidant, antipyretic and analgesic, however, its antimicrobial activity spectrum remains to be determined. [10,11,12,13]

This review article aims to highlight this mystic phytochemical along its properties and mechanism of action in the management of various diseases with the intention of using zerumbone widely to yield better and natural treatment modalities.

STRUCTURE AND CHEMICAL COMPOSITION

The major bioactive molecule found in the essential oil of *Zingiber zerumbet* rhizomes is the zerumbone (Figure 1), a monocyclic sesquiterpene compound (2,6,10-cy-cloundecatrien-1-one, 2,6,9,9-tetramethyl-cycloundeca-2,6,10-trien-1-one). [14]

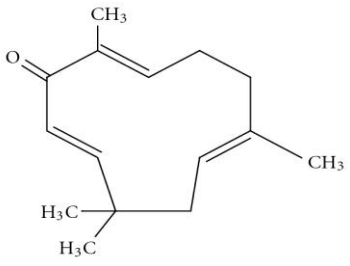

Figure 1

The present article aims to encompass all the actions of zerumbone.

1. Anti inflammatory, Anti pyretic and analgesic action:

The mechanism of anti inflammatory, analgesic and antipyretic action occurs by:

1. Inhibiting COX-2 Pathways
2. Inhibiting iNOS Pathways
3. Inhibiting matrix metalloproteinase (MMP)-13

Zerumbone acts by inhibiting inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2 expressions, Nitric oxide (NO) and prostaglandin E_2 (PGE_2) production, but induced heme oxygenase (HO)-1 expression in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells.

However, the NO inhibitory effects were reversed when zerumbone was treated with an HO-1 inhibitor (tin protoporphyrin (SnPP), proposing that zerumbone inhibited iNOS and COX-2 through induction of the HO-1 pathway. [15]

It has been postulated in various studies that matrix metalloproteinase (MMP)-13 and COX-2 expressions of interleukin (IL)-1β-stimulated primary rat chondrocytes were inhibited by zerumbone. [16, 17, 18] Several studies have also confirmed antipyretic and analgesic properties of zerumbone. [17, 19]

2. Anti cancer action:

Oral Cancer:

Zerumbone inhibits cell proliferation, migration and invasion in oral squamous cell carcinoma by suppressing the expression of CXCR4, RhoA proteins, and PI3K-mTOR signalling pathway causing G2/M cell cycle arrest followed by apoptotic activity. The inhibition of the PI3K-mTOR signalling pathway was associated with the suppression of Akt and S6 proteins. [20]

Brain Tumour:

A study by Weng et al, [21] showed that zerumbone possess anti apoptotic effect by suppressing FOXO1 and Akt phosphorylation due to inactivation of IKKα while activating caspase-3 protein and PARP, leading to decreased cell viability, and induction of apoptosis in GBM cells (human glioblastoma multiforme)

Breast Cancer:

Zerumbone has been found to increase the induction of presenilin-1 protein and transcriptional activation of Notch, causing cleavage of Notch 2. In addition, it reduces the cleaved Notch 1 and Notch 4 proteins, resulting in increased apoptosis and suppression of cellular migration. [22]

Various other studies have shown that Zerumbone decreases levels of IL-8 and MMP-3 expression by down regulation of NF-κB activity, which leads to reduction in IL-1β-induced cell migration and invasion in TNBC. It acts by inhibiting invasion and metastasis in breast cancer by downregulating the expression of CXCR4. [23, 24, 25]

Gastric Cancer:

Zerumbone causes inhibition of cell proliferation and tube formation area of human umbilical vein endothelial cells through the reduction in expression of vascular endothelial growth factor (VEGF) and NF-κB activities, thereby inhibiting angiogenesis. [26]

Leukemia:

Reduction in proliferation rate of leukemic cells has been shown by zerumbone that arrests the cell cycle at G2/M via suppression of cyclin B1/ cdk1 protein along with the phosphorylation of ATM/Chk1/Chk2, leading to apoptosis via initiation of Fas (CD95)/Fas Ligand (CD95L) expression associated with caspase-8 activation. [27, 28]

In chronic myelogenous leukemic cell proliferation, zerumbone acts by inhibiting K562 with induction of DNA damage and apoptosis via activation of pro-casase-3-9 and PARP cleavage. [29]

Lung cancer:

Zerumbone induces apoptosis through loss of mitochondrial membrane potential, release of cytochrome c, caspase-9 and -3 activation, increased expression of p53 and Bax leading to increased ROS production.[30]

A study showed that the administration of dietary zerumbone at 250 and 500 ppm to the mice for 21 weeks significantly inhibits the multiplicity of lung cancer in a dose-dependent manner. The suppression of lung carcinogenesis was caused through the reduction of growth, decreased inflammation, and decreased expression of NF-κB and HO-1, thereby causing apoptosis. [31]

Skin Cancer:

Murakami et al[32] showed that pre-treatment with zerumbone at the tumor promotion stage in mice suppressed tumor growth and the mechanism behind its effect might be due to increased expression of xenobiotic-metabolizing enzymes (GSTP1, NQO1) and mRNA levels for manganese superoxide dismutase (MnSOD) and glutathione peroxidase-1 (GPx1).

In addition, zerumbone decreased the levels of cyclooxygenase-2 (COX-2) expression, ERK1 phosphorylation, H_2O_2-induced edema formation, and leukocyte infiltration.

The treatment of epidermal cells in mice with zerumbone showed increased binding activity with the anti oxidant element leading to increased HO-1 activity, showing the antioxidant property of Zerumbone against skin carcinogenesis.[32]

Renal Cell Carcinoma:

According to Sun et al, [33] zerumbone showed its anti-cancer effects by initiating apoptosis through the activation of caspase-3 and caspase-9, leading to cleavage of PARP and down regulation of Gli-1 and Bcl-2.

Prostate cancer:

According to a study conducted by Chiang et al, [34] the management of prostate cancer cells with zerumbone significantly decreased the radiation-induced expression of phosphorylated ATM (ataxia telangiectasia-mutated) and suppressed the expression of JAK2 and STAT3, which are involved in DNA damage repair.

In addition, zerumbone selectively inhibited the IL-6/JAK2/STAT3 pathway and blocked the prostate cancer-associated genes- cyclin D1, IL-6, COX2 (cytochrome c oxidase), and ETS Variant 1 (ETV1); thereby inducing cytotoxicity through G0/G1 cell cycle arrest and causing apoptosis. [35]

Cervical and Ovarian Cancer:

The additive role of Zerumbone with cisplatin treatment has shown to stimulate apoptosis by arresting cells at the G2/M phase and decreasing the levels of IL-6 in HeLa and Caov-3 cells. [36] It is also seen that Zerumbone down regulates the expression of proliferating cellular nuclear antigen, owing to its antitumor effect on human cervical cancer cells. [37]

3. Antimicrobial activity:

Zerumbone exhibits strong antibacterial activity against Staphylococcus epidermidis, moderate activity against Escherichia coli, moderate antifungal activity against Aspergillus oryza and Aspergillus niger.[38]

H. pylori is the most prevalent bacterial infection that affects approximately half the world population. ZER also exhibits significant antibacterial action against this bacterium. [39]

A study conducted by Rana et al. has reported a significant antifungal activity against some phytopathogenic fungi, such as *Sclerotium rolfsii*, *Rhizoctonia solani* and *Macrophomina phaseolina*. [40]

4. Anti Oxidant activity:

A study conducted by Sidahmed et al, [41] showed that gastric mucosa was protected by intragastric administration of ZER from the aggressive effect of ethanol-induced gastric ulcer, in the same time with reduced

submucosal edema and leukocyte infiltration.

Mesomo et al. also reported a significant antioxidant activity of ZER (931.67 ± 2.51 mg of α-tocopherol/g of extract) using the phosphomolybdenum reduction method. [42]

5. Anti Ulcer activity:

The intragastric administration of zerumbone has been shown to protect the gastric mucosa. Several studies have shown anti ulcer activity of Zerumbone studies in rats animal models. [41, 43, 44]

6. Diuretic activity:

Studies conducted by Patonah et al and Jantan et al showed that rhizome extract of Zerumbone has diuretic activity. [45, 46]

TABULATED FORM TO DESCRIBE THE EFEFCTS OF ZERUMBONE WITH MECHANISM OF ACTION

S.No	Properties of Zerumbone	Mechanism of Action
1.	Anti inflammatory, anti pyretic and analgesic action	Inhibiting inducible nitric oxide synthase (iNOS), cyclo oxygenase-2 pathway [15-19]
2.	Anti cancer action	
	Oral Cancer	Inhibits cell proliferation, migration, and invasion in oral squamous cell carcinoma by suppressing the expression of CXCR4, RhoA proteins, and PI3K-mTOR signalling pathway, causing G2/M cell cycle arrest followed by apoptotic activity.[20]
	Brain Tumour	Exhibits anti apoptotic effect y suppressing FOXO 1 and Akt Phosphorylation leading to decreased cell viability.[21]
	Breast Cancer	Down regulates NF- B activity leading to inhibited IL-8 and MMP-3 expression causing reduction in cell migration and invasion in Triple Negative Breast Cancer.[22-25]
	Gastric Cancer	Inhibits cell proliferation , VEGF and NF-κB causing decreased angiogenesis.[26]
	Leukemia	Arrests the cell cycle at G2/M via suppression of cyclin B1/ cdk1 protein leading to apoptosis. [27-29]
	Lung Cancer	Induces apoptosis through loss of mitochondrial membrane potential, release of cytochrome c, caspase-9 and -3 activation, increased expression of p53 and Bax, and increased ROS production.[30,31]
	Skin Cancer	Increased binding activity of epidermal cells with the anti oxidant element. [32]
	Renal Cell Carcinoma	Initiates apoptosis through the activation of caspase-3 and caspase-9, leading to cleavage of PARP and down regulation of Gli-1 and Bcl-2 [33]
	Prostrate Cancer	Cell cycle arrest at G0/G1 leading to apoptosis [34,35]
	Cervical and Ovarian Cancer	Cell cycle arrest at G2/M phase leading to apoptosis [36,37]
3.	Anti microbial action	Significant antifungal and anti bacterial action.[38,39,40]
4.	Anti Oxidant action	Possess antioxidant activity due to presence of α-tocopherol in abundant quantity. [41,42]
5.	Anti Ulcer action	Protects the gastric mucosa of ulceration [41,43,44]
6.	Diuretic action	Rhizome extract of Zerumbone has a significant diuretic activity.[45,46]

CONCLUSION

Zerumbone, a monocyclic sesquiterpene, isolated from *Z. zerumbet* is a compound that possesses various activities such as anti inflammatory, anti pyretic, analgesic, anti cancer, anti diuretic, anti oxidant, gastroprotective and antimicrobial property. Most of the protective properties of zerumbone have been established via various in vitro and in vivo techniques. However, substantial clinical trials would be required to establish clinical results and its efficacy.

Abbreviations Used:

GBM: Glioblastoma Multiforme
TNBC: Triple Negative Breast Cancer
ROS: Reactive Oxygen Species
FOXO-01: Forkhead Box O1
PARP: Poly (ADP-ribose) polymerase

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