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CURRANT REVIEW ON PHYTOCHEMICAL & PHARMACOLOGICAL IMPORTANCE OF ZINGIBER ZERUMBET L.

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Abstract:
Populations around the world use medicinal plants to treat numerous diseases and ethnopharmacological information serves as a starting point for developing new drugs. The evidence of the therapeutic properties of zerumbone from bitter ginger, which are mainly secondary metabolites, is important information that can help in the search to discover new drugs. From a commercial point of view, a positive aspect is that ginger is easy to cultivate and it has a lot of pharmacological properties. This review article highlights the phytochemical & pharmacological aspects of Zingiber zerumbet. The results from all the studies and research mentioned in this review paper are definitive evidences that ZER is a powerful compound in the treatment of cancer and several other diseases and it possesses different beneficial in vitro and in vivo biological activities. It is nevertheless essential to do more animal studies and human clinical trials to determine the efficacy, safety and usefulness of Zingiber zerumbet as an intended pharmaceutical drug.

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INTRODUCTION:

Zingiber zerumbet (L) Smith is part of the Zingiberaceae family, one of the largest families of the plant kingdom. *Z. zerumbet* is a perennial, aromatic and tuberose plant that grows in humid locations where its center of distribution is located in the South-East Asia region. The rhizomes of Zingiberacea family are vegetables widely used in many Asian countries, and their medicinal functions have been broadly discussed and accepted in many traditional recipes. Members of Zingiberaceae are usually aromatic in all or most parts or at least one of the plant parts and many species are known to be rich in terpenoids (Chen *et al*.,2008; Bokyung *et al*., 2008).

This plant has been traditionally used in foods and beverages and for ornamental purposes. *Z. zerumbet* has been used traditionally for the treatment of stomach ache, toothache, fever, sprain and indigestion. Besides, it is also used as the spice ginger and a novel factor for mitigating experimental ulcerative colitis. Many major metabolites that have been reported to contain anti-allergic properties are terpene compounds which can be found in the essential oil extracted from the rhizomes of *Z. zerumbet*, such as zerumbone, limonene, and humulene. The rhizome is among the part of *Z. zerumbet* that has been widely used for many studies due to its exceptional biomedical applications (Singh *et al*., 2012; Sharifah *et al*., 2007).

BOTANICAL DESCRIPTION:

Zingiber zerumbet (L.) Sm. is an erect herbaceous, perennial plant, 0.6 to 2 m high. Its rhizomes are large, tuberous, and pale yellow within. The leaves are distichous, ovate-lanceolate, acuminate, 15 to 40 cm long and 4 to 9 cm wide, short-petioled, and hairy beneath. Each leaf has a prominent ligule which is erect, elongate, obtuse, membranaceous, hairy, and about 1.5 to 3.5 cm long. The flowering scape is produced directly from the rhizomes. The peduncle is about 25 cm long and 9 mm wide; covered with 4 to 8 pubescent sheaths which are slightly two-lobed at the apex, about 5 cm long, and reddish at the base. The inflorescence is a spike, ovoid to oblong with an obtuse apex, 10 to 15 cm long and 4.5 to 5.5 cm wide. The bracts are numerous, obovate, imbricate, with mucronate apices, about 3 to 3.5 cm long and 2.5 cm wide, persistent, with a membranaceous margin, slightly hairy, greenish and pink-edged when they are young but turn red after flowering, and hold a mucilaginous substance. The bracteoles are thin, about 2.5 cm long and 1.3 cm wide (Sabu, 2003).

The sessile flower is cream-colored, irregular, and about 5 cm long, Its calyx is 13 to 17 mm long and its corolla tube 2 to 3.5 cm long. Its dorsal lobe is 1.5 to 2.5 cm long and 1 to 2 cm wide. Its lateral lobes are narrower, ovate, and acuminate. The labellum is almost orbicular and slightly cleft at the apex, the middle lobe about 2 cm wide and long, and the side lobes smaller, ovate, and almost entirely separate from the middle lobe (Nalawade & Sagare,2003).

The stamen is as long as the labellum, 8 to 20 cm long, with the appendage shorter than the anther. The basal flowers open ahead of the terminal flowers in the inflorescence.

The fruit is a capsule, white, thin-walled, glabrous, dehiscent, and 8 to 12 mm long. The seeds are numerous, ellipsoidal, black, 5 to 6 mm long, and covered with white aril (Holttum,1950)

Figure 1: *Zingiber zerumbet* plant

Taxonomy:
Scientific name: *Zingiber zerumbet*
Rank: Species
Family: Zingiberaceae
Kingdom: Plantae
Order: Zingiberales

Common names of *Zingiber zerumbet:*

Country	**Common name**
India	Ghatian, Yaiimu, Narkachur
Hawaii	Awapuhi
Haeo dam" or "Hiao dam	Northern Thailand
Lempoyang	Malaysia and Indonesia
Jangli adha	Bangladesh
Hong qiu jiang	China
Zurunbah	Arab

(Huang *et al*.,2005; Bhuiyan *et al*., 2009; Zakaria *et al*., 2010)

Historical & Traditional uses:
The rhizome has been extensively used with remarkable therapeutic effects for the treatment of inflammation, diarrhea, stomach cramps, bacterial infections, fever, flatulence, allergies and poisoning. Powdered rhizome is used to treat ear infections, toothache and to treat stomach disease. The leaves are also used in therapies for joint pain. The juice of cooked rhizome was reported to be effective in combating worms in children. The creamy substance present in the mature inflorescence, is rich in surfactants and serves as a natural shampoo (Ghosh *et al*., 2011; Prakash *et al*., 2011; Somchit, & Shukriyahet, 2003; Yu *et al*., 2008).

Z. zerumbet has a wide spectrum of traditional uses, as well as biological and pharmacological properties. The cone-shaped flowers are long-lasting and are employed in craft arrangements for ornamental purposes. The rhizome is used as a tonic and as a stimulant. The rhizome serves as a seasoning in foods, while the floral buds are consumed as vegetables (Sakinah *et al*., 2007; Sirirugsa, 1999; Devi *et al*., 2014).

Phytochemical constituents of *Zingiber zerumbet:*
Z. zerumbet is a rich source of different classes of compounds that belong to a wide variety of chemical metabolites, such as polyphenols, alkaloids and terpene.

Zerumbone and acaryophyllene have been reported as major constituents in oils as well as in almost all the leaves and rhizome oil of the world. There is report on the isolation of aromatic compounds and Kaemferol derivatives from the chloroform soluble fraction of the methanol extract of the rhizomes of *Z. zerumbet*. Jang and Seo (2005) reported potentially bioactive two new natural sesquiterpenoids (6-methoxy-2E, 9E-humuladiene-8-one Stigmast-4- en-3-one) from the rhizome of *Z. zerumbet* (Nigam & Levi, 1963; Jang & Seo, 2005).

A complete analysis of the essential oil from the rhizomes of *Z. zerumbet* Smith.was given and the isolation of several new humulene-based sesquiterpenoidswas described. Humulenol-II, a minor component of the volatile oil from the rhizomes of *Z. zerumbet*, was shown to possess the absolute stereostructure I and had been directly correlated with (-)-humulene epoxide-II. Two new oxygenated derivatives of humulene, viz., humulene monoxide (II and humulene dioxide (VIII) have been isolated from the sesquiterpene fractions of wild ginger oil (Damodaranm & Dev, 1968).

Three new acetylated and one known kaempferol glycosides have been isolated from the rhizomes of *Zingiber zerumbet* and their structures determined to be the 3-O-(2-O-acetyla-l-rhamnopyranoside), 3-O-(3-O-acetyl-a-l-rhamnopyranoside), 3-O-(4-O-acetyl-a-l-rhamnopyranoside) and 3-O-a-l-rhamnopyranoside on the basis of spectroscopic methods (Ramaswami & Bhattacharyya, 1962; Masuda *et al*., 1991).

Pharmacological activity of *Zingiber zerumbet:*
Anti-microbial activity:
The *Z. zerumbet* oil showed significant inhibitory activity against the bacteria, Staphylococcus aureus (1.2 cm), *Lactococcus lactis* (0.8 cm), and the fungus *Aspergillus awomori* (1.5 cm), *Fusarium oxysporum* (1.0 cm), *Aspergillus accularatus* (0.9 cm), *Candida albicans* (0.8 cm), *Tricoderma viridae* (0.8 cm), *Rhodotorula sps.* (0.8 cm) and *Aspergillus niger* (0.6 cm) (Helen *et al*., 2009)

Extracts were screened for dengue-2 virus protease inhibitory activities and the results show that the methanol fractions of Curcuma longa and *Zingiber zerumbet*, and both the methanol and hexane fractions of CM were most potent against Den2 virus NS2B/NS3 protease activity and may provide potential leads towards the development of anti-viral agents. The percentage inhibition of Den2 virus NS2B/NS3 protease cleavage of the substrate showed linear dose-dependent increment for all the samples tested (Kiat & Richard,2006)

Anti- inflammatory activity:
Zingiber zerumbet cause reduction of pain and inflammation. *Z. Zerumbone* have great anti-inflammatory capabilities. *Z. zerumbet* have tissue compatibility on type II cells in osteoarthritic joint synovial stratum so *Z. zerumbet* could prevent antigen-presenting cells (APCs) of immune and also decrease the osteoarthritis inflammatory process. *Z. zerumbet* powerfully could prevent inflammation via lambda carrageenan and dinoprostone which was comparable to the nonsteroidal anti-inflammatory drug of the oxicam class. Additionally, it could prevent pain just alike to the NSAIDs. It has the capability of prevention of prostaglandin-endoperoxide synthase (PTGS) and nitric oxide synthase (iNOS) in addition with dinoprostone (Koga *et al*., 2016; Hosseinpour *et al*., 2014)

The application of *Z. zerumbet* could increase the proliferation and polarization of T cell via endotoxin motivated the soft gelatinous tissue inside some bones derived dendritic cells within an allogeneic test of mixed lymphocyte reaction. It can acts as anti-allergic agents upon viamodulation of cytokines of T-cell subsets. Their outcomes proved that the application of *Z. zerumbet* could decrease the osteo arthritis symptoms and improve the reaction of immune (Al-Saffar *et al*., 2011)

Immunomodulatory activity:
The chloroform extract of RZZ (Rhizome of *Z. zerumbet*) (EEZZ) (Ethanol extract of RZZ) (significantly stimulated T lymphocytes to express CD69 antigen by 31.6% as compared to the control group (6.2%). The MEZZ (Methanol extract of *Z. zerumbet*) and AEZZ (Aqueous extract of RZZ) gave percentage stimulation of CD69 antigen of 5.8% and 2.3%, respectively. None of the crude extracts stimulated the migration of polymorphonuclear cells but CEZZ and MEZZ did suppress polymorphonuclear cells migration. Phytohemagglutinin (PHA), at the concentration of 5 μg/mL, was used as positive control drug to stimulate the CD69 expression on lymphocytes with an incubation period of 4 h and gave an approximately 46% stimulation of lymphocytes. However, no positive control was used to compare the polymorphonuclear migration rate potential of those extracts (Vuddhakul *et al*., 2004).

Antipyretic and cytotoxic activity:
The ethanol and aqueous extract of *Z. zerumbet* elicitate moderate to marked antipyretic activities which was dose dependent. Further added that the ethanol extract revealed dose dependent analgesic property which was significantly different than control. The aqueous extract was devoid of any analgesic effects 50 and 100 mg/kg. The analgesic activity of 10 mg/kg Z. zerumbet ethanol extract was similar to 0.8 mg/kg morphine. Zerumbone has been found to exhibit cytotoxic activities on Hepatoma Tissue Culture (HTC), a neoplastic rat liver strain cultured in vitro and was found to be selective against normal mouse fibroblast (Murakami et al. 2002).

The carbonyl group at the 8-position in zerumbone is the important structural element for its chemopreventive potential. Combination of both Cisplatin and toxol induce apoptosis in epithelial ovarian cancer (Havrilesky *et al*., 1995; Ormerod *et al*., 1996).

Hepatoprotective activity:
The hepatoprotective activity of ZER may be through the enhancement of drug-metabolising enzyme activity. It is postulated that in the hepatocytes, the antioxidant effect of ZER is through the neutralisation of lipid peroxidation (Nakamura *et al*. 2004).

Anti-cancerous activity:
Z. zerumbet has demonstrated that zerumbone is a potential drug for the treatment of several cancers as well as leukemia. Kaemferol derivatives components of Z. zerumbet is a scaffold for developing agents that reverse P-gp-mediated Multi Drug Resistant (MDR) in human cancer chemotherapy. The compound 2,6,9,9-tetramethyl from Z. zerumbet. Further reported that the extract decreased the release of tumour necrosis factor-alpha and interleukin-4 (IL-4) in vitro and effectively suppressed LTC4 release from lung tissue in vivo. Zerumbone has been found able to exert anti-tumour activity. Zerumbone suppressed the activation of NF-KB and NF-KB regulated gene expression induced by carcinogens, and reported that this inhibition may provide molecular basis for the prevention and treatment of cancer (Han *et al*. 2005; Kinghorn *et al*. 1997).

Zerumbone is an active principal of *Z. zerumbet* and is potentially a lead compound for the development of anticancer drugs. Zerumbone Downregulates Chemokine Receptor CXCR4 Expression Leading to Inhibition of CXCL 12-Induced INVASION of Breast and Pancreatic Tumor Cells (Ohigashi & Murakami, 2002).

Anti -gastric ulcer activity:
In rats, ZER has gastroprotective effects against an ethanol-induced gastric ulcer model. The ethanol-induced gastric ulcers have an aggressive effect on gastric mucosa and ZER can protect them by reduced submucosal edema and leukocyte infiltration. Their results also showed that ZER promoted the protection of ulcers, which might be attributed to the mucus integrity maintenance and induction of HSP-70 (Baiubon, *et al*., 2016).

In another study, the gastroprotective activity of ethanol extract of *Z. simaoense* rhizome was investigated in rats. The *Z. simaoense* extract strongly inhibited the formation of gastric ulcers in all gastric ulcer models (Chantharangsikul *et al*., 2016).

Immunomodultory activity:
the use of ZER leads to activated mice splenocytes, thymocytes and PBMC in an amount dependent assay with 7.5 µg/mL as the optimum concentration. A prominently upregulation at 24 h and decrease from 48 h to 72 h were observed in the production of human interleukin-2 and human interleukin-12 cytokines in culture supernatant of ZER-activated lymphocytes. The progression and induction of cytokine (IL-2 and IL-12) are affected by ZER. This was demonstrated by the proliferation of ICFmice thymocytes and splenocytes and human peripheral blood mononuclear cells (PBMC). Entrance of high population of PBMC to G2/M phase is caused by ZER treatment (Keong, *et al*., 2010).

The ZER has effect on the proliferation, cell cycle progression, and induction of cytokine (IL-2 and IL-12) of immune cells in vitro. This was demonstrated by the proliferation of ICF mice thymocytes and splenocytes and human peripheral blood mononuclear cells (PBMC). ZER highly increases the visible gastric mucus secretion and showed a tendency to increase the secretory rate of soluble gastric mucus (Sriphanaa *et al*., 2013).

Hypoglycemic activity:
The ethanolic extract of *Z. zerumbet* in its ability to attenuate streptozotocin-induced diabetic nephropathy. Bitter ginger can promote glucose homeostasis and, therefore, it can be used as a therapeutic to control diabetic complications. The ethanolic extract (95%) was prepared by the maceration method. Male Wistar rats were used in the experiments and diabetes was induced by injecting streptozotocin (plasma glucose equal or higher than 350 mg/dl. A reduction in body weight was observed during the experimental period. The other parameters, such as glycated hemoglobin fasting glucose, were reduced during the eight weeks of treatment with *Z. zerumbet* when compared with the control group (Kim *et al*., 2009; Chang *et al*., 2012).

Z. zerumbet inhibits the glycation of hemoglobin and promotes normoglycemia. So, extract of bitter ginger can reverse the effects of hyperglycemia. The ability to reverse insulin resistance may be attributed to the presence of bioactive compounds such as quercetin, curcumin and kaempferol (Tzeng *et al*., 2013).

Antinociceptive activity:
The essential oil of Z. zerumbet was obtained by hydrodistillation and for the experiments male ICR rats were divided into groups. The antinociceptive activity was performed using the methods of writhing induced by acetic acid, capsaicin-induced nociception, glutamate and phorbol 12- myristate 13-acetate (PMA). Aspirin was used as a positive control. The results showed that the systemic administration of essential oil of ginger caused a significant dose-dependent inhibition in all the models of nociception tests: writhing induced by acetic acid, capsaicin, glutamate and PMA (Khalid *et al*., 2011).

Anti-oxidant activity:
ZER has antioxidant activity through two main pathway, which include reactive oxygen (RO) attenuation and N_2 species generation. Hamdi et al. used NG108-15 neuroblastoma-rat glioma hybridoma cells for investigation of the ZER-epoxide effect on H_2O_2-induced oxidative stress. In assessment of oxygen radical antioxidant capacity (ORAC), a strong antioxidant activity was observed. In a recent study, the gastroprotective effect of ZER was evaluated on an ethanol-induced gastric ulcer model in rats. First, the authors did a pre-treatment by ZER on rats and then exposed them to acute gastric ulcers induced by absolute ethanol administration. The findings showed that ZER can promote ulcer protection that might be related to mucus integrity maintenance, antioxidant activity, and HSP-70 induction. Moreover, 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 (Hamdi *et al*., 2015; Sidahmed *et al*., 2015).

Anti-AD (Alzheimer's disease):
Bustamam et al. (2008), had done a study where the inhibitory effect of ZER towards acetyl cholinesterase was evaluated using thin layer chromatography (TLC) bioautography and compared concurrently to tacrine, as positive control. The results obtained showed that ZER had an enzymolytic effect towards AChE (Acetyl Cholinesterase). It could be suggested that ZER might be a potential candidate for the development of antiAD (Alzheimer's disease) treatment (Bustamam *et al*., 2008).

Antiplatelet aggregation activity:
The MEZZ (Methanol extract of *Z. zerumbet*) was also reported to exhibit strong antiplatelet aggregation activity at 100 μg/mL in human whole blood *in vitro*, with all extracts exhibiting 100% inhibition. ASA, used as a positive control at the concentration of 25 μg/mL, exhibited inhibitory effects of 100%, 31% and 43% against arachidonic acid-, collagen- and ADP-induced platelet aggregation. Interestingly, compound isolated form RZZ, zerumbone, at the concentration of 100 μg/mL, exerted strong inhibition on platelet aggregation induced by arachidonic acid, collagen and ADP with inhibitory effects of 100%, 68%, and 100%, respectively (Jantan *et al*., 2008).

CONCLUSION:

Natural compounds are small molecules from biological sources, such as animals, microorganisms, plants and marine organisms Herbs and spices are considered safe and effective against certain deceases. These useful compounds have been used in many disease treatments. The study of *Z. zerumbet* and its compounds offers many oppurtunities to investigate the various functions and prospects in various pharmaceutical studies. Zerumbone gained certain significances as pharmaceutical compounds. It become more evident about its potential from the bioactivities reviewed above based on the work of various researchers. Developed analytical tools and the effective action on various in vitro and in vivo studies may bring numerous opportunities to further unravel the potential bioactivies. As compounds of *Z. zerumbet* are effective against many types of cancer and because cancer is one of the dreaded disease prevalent in the world and even it was found effective against HIV, it is worthwhile studying the accumulation of zerumbone and other different compounds in different parts of the *Z. zerumbet.* The results from all the studies and research mentioned in this review paper are definitive evidences that ZER is a powerful compound in the treatment of cancer and several other diseases and it possesses different beneficial in vitro and in vivo biological activities. It is nevertheless essential to do more animal studies and human clinical trials to determine the efficacy, safety and usefulness of *Zingiber zerumbet* as an intended pharmaceutical drug.

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