Ad-Dawaa' Journal of Pharmaceutical Sciences
ISSN: 2654-7392, E-ISSN: 2654-6973
Vol. 6, No. 2, December 2023, p. 103 – 125
DOI: https://doi.org/10.24252/djps.v6i2.39968

Antioxidant Activity of Zerumbone and Its Pharmacological Prospects in Oxidative Stress Conditions: A Narrative Review

Haeria Doloking[1,2*], Subehan[1], Marianti A. Manggau[1], and Yusnita Rifai[1]

[1]Faculty of Pharmacy, Universitas Hasanuddin, Makassar, Indonesia
[2]Department of Pharmacy, Faculty of Medical and Health Sciences, UIN Alauddin Makassar, Gowa, Indonesia

Article history:
Submited: 26-7-2023
Revised: 28-8-2023
Accepted: 16-9-2023

Corresponding author e-mail: haeria.doloking@uin-alauddin.ac.id

Cite this article: Doloking, H., Subehan, Manggau, M.A., Rifai, Y. (2023). Antioxidant Activity of Zerumbone and Its Pharmacological Prospects in Oxidative Stress Conditions: A Narrative Review. Ad-Dawaa' J. Pharm. Sci. 6(2): 103-125.

ABSTRACT

Introdiction*: Oxidative stress is a condition caused by an imbalance between the level of oxidants in cells and tissues and the ability of the biological system to detoxify these reactive products. To compensate for the excess oxidant molecules, the human body requires the intake of antioxidant compounds through diet or medicinal plants to overcome the deficiency of these endogenous antioxidants. Zerumbone is the main bioactive compound of the Zingiber zerumbet L. Smith rhizome that was reported to have antioxidant activity and different pharmacological effects, like anti-inflammatory, anti-cancer, antidiabetic, immunomodulatory, anti-neurodegenerative disease, hepatoprotective, and gastroprotective.* ***Aims****: This review aims to gather available scientific research data regarding the antioxidant activity of zerumbone and its pharmacological prospects under conditions of oxidative stress. This paper is an overview of previous research on the various pharmacological activities of zerumbone and studies of its mechanism of action related to oxidative stress at the molecular level. The selected articles are related research reports for the 2010–2022 period, which can be accessed online through NCBI, Science Direct, MDPI, and Google Scholar.* ***Result****: The research results mentioned in this review paper can summarize knowledge to explain the pharmacological potential of zerumbone so that it can be used as a starting point or comparison in designing further research.* ***Conclusion****: The results of the reviews show that the various pharmacological prospects of zerumbone are related to oxidative stress conditions through various modes of action.*

KEYWORDS*: Zerumbone, antioxidant, antiinflammation, oxidative stress, and narrative review.*

INTRODUCTION

Oxidants are various highly reactive molecules that oxidize specific substrates under favorable conditions. Oxidant molecules can be free radicals or non-radical derivatives of oxygen, nitrogen, and sulfur (Ali et al., 2020). The metabolism of oxygen and nitrogen produces highly reactive molecules known as reactive oxidant species (ROS) and reactive nitrogen species (RNS). ROS and RNS can be free radicals such as superoxide radicals (O_2•-), hydroxyl radicals (OH•), and nitric oxide (NO•). However, other non-free radicals can also exist, including peroxynitrite (ONOO•) and hydrogen peroxide (H_2O_2) (García-Sánchez et al., 2020). The human body can

produce endogen antioxidants to compensate for the presence of these various oxidant molecules. However, when an excess of oxidant molecules and endogenous antioxidants cannot neutralize them, oxidants and antioxidants are out of balance called the oxidative stress phenomenon (Pizzino et al., 2017).

Oxidative stress activates several inflammatory mediators implicated in several chronic diseases. According to clinical evidence, oxidative stress and inflammation brought on by an excess of ROS are likely to play a crucial part in the development of several diseases, including chronic inflammation-related disease (Hussain et al., 2016). Oxidative stress lead a major role in the development of certain pathophysiological conditions such as inflammation (Mittal et al., 2014), carcinogenesis (Ziech et al., 2011), diabetes mellitus, neurodegenerative diseases (He et al., 2017; Vigneron & Vousden, 2010), etc. (García-Sánchez et al., 2020). These various conditions can be inhibited by the intake of antioxidants through supplements, functional foods, or medicinal plants.

Antioxidant compounds commonly known to be used in treating various chronic diseases are N-acetylcysteine, Paricalcitol (vitamin D), retinol, ascorbic acid, and α-tocopherol, or coenzyme Q10 (García-Sánchez et al., 2020). In comparison, the antioxidant compounds obtained from medicinal plants are polyphenols and carotenoids (D.-P. Xu et al., 2017). Numerous sesquiterpenes with promising anti-inflammatory, antiparasitic, and anticarcinogenic properties have been discovered recently through efforts in the research and development of new drugs derived from natural products (Shoaib et al., 2017). One of the sesquiterpenes that have been widely studied and reported regarding their antioxidant activity and other pharmacological prospects is zerumbone.

Zerumbone is a secondary metabolite found in various Zingiberaceae plants with many potentials. Suk Dev isolated zerumbone from the *Zingiber zerumbet* rhizome's essential oil in 1956 (Dev, 1960), and the compound's structure was then determined using NMR and X-ray analysis (Dev et al., 2002). As shown in Figure 1, Zerumbone is a sesquiterpene with an isolated double bond and a cross-conjugated dienone system (Ajish et al., 2014). This substance is classified as a potential cytotoxic sesquiterpene ketone. The pentadienone group of a particular sesquiterpene ketone in this compound plays a significant role in its bioactivity (Truong, Duy et al., 2015).

The pharmacological prospects of zerumbone for various conditions related to oxidative stress have been reported, such as anticancer (Girisa et al., 2019), anti-inflammatory (Su et al., 2021), hepatoprotector (Abuzahra et al., 2021), immunomodulator, anti-gastric ulcer, even antibacterial (Kalantari et al., 2017). This review aims to gather available scientific research data regarding the antioxidant activity

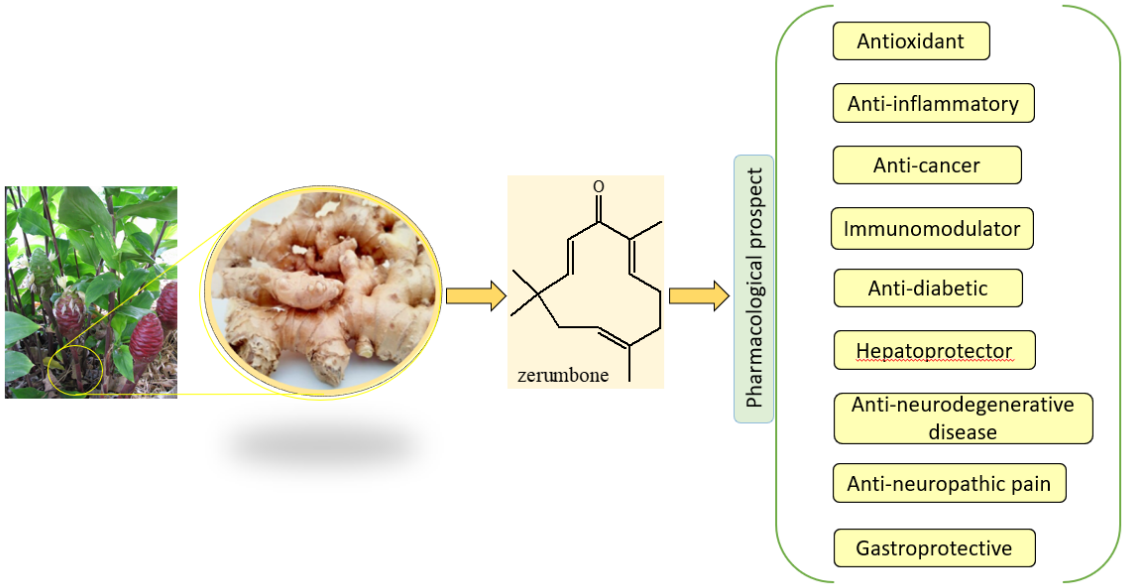

Figure 1. Zerumbone isolated from Zingiber zerumbet (L) Smith with various pharmacological prospective.

of zerumbone and its pharmacological prospects under conditions of oxidative stress. Currently, a number of previous authors have published review articles that touch on the biomedical aspects of zerumbone (Girisa et al., 2019; Kalantari et al., 2017; Rahman et al., 2014; Yeh, et al., 2022). The novelty value that we highlight in this article is associated with zerumbone's pharmacological potential based on its antioxidant activity. As a result, the information provided in this review is extremely relevant for upcoming investigations into the mechanism of action of zerumbone in a variety of disease conditions linked to oxidative stress.

METHODS

Several journals from NCBI, Science Direct, MDPI, and Google Scholar were gathered for this journal review using the keywords "bioactivity of zerumbone", "zerumbone as antioxidant", "zerumbone as anticancer", "zerumbone as anti-inflammatory", "zerumbone as immunomodulator", "zerumbone as antidiabetic", zerumbone as hepatoprotector", "anti-neurodegenerative of zerumbone", "anti-neuropathic pain of zerumbone" and “Gastroprotective of zerumbone”. The journals taken are those published from 2010 to 2022. The journals used as references are international journals.

RESULTS AND DISCUSSION

Zerumbone as Antioxidant

Several scientists investigated zerumbone's antioxidant activity by conducting both enzymatic and non-enzymatic methods. The enzymatic methods target enzymes involved in cell redox reactions, such as CAT (catalase), GSH (glutathione), MDA (malonaldehyde), and SOD (superoxide dismutase). In comp-

arison, the FRAP (Ferric reducing antioxidant power) method, which has been reported so far. MDA can indirectly reflect the severity of oxygen-free radical attacks on tissue cells, whereas CAT, GSH and SOD remove intracellular oxygen-free radicals and protect cells from injury (M. Xu et al., 2017).

CAT and SOD activity, as well as GSH levels, significantly increased in the zerumbone group, according to research on the drug's impact on CAT, SOD, MDA, and GSH levels in the gastric tissue of rats with chronic gastritis. On the other hand, the MDA content fell by a statistically significant amount. The findings show that zerumbone, through its antioxidant effect, can increase the capacity to capture oxygen free radicals, protecting gastric mucosal cells from free radical attack and thus reducing gastric tissue injury (Liqing Li et al., 2017). In line with these results, zerumbone was demonstrated to reduce oxidative stress and protect the liver from CCl_4-induced acute liver injury (ALI) by replenishing GSH reservoirs, restoring antioxidant enzyme activity, and reducing lipid peroxidation (M. Wang, Niu, Ou, et al., 2019).

Elevated MDA levels due to lipid peroxidation with high ROS and low antioxidant levels have been consistently connected to hypercholesterolemia, increased circulating ox-LDL, and decreased plasma HDL-C levels. In order to prevent and treat atherosclerosis, oxidative stress tests and studies of antioxidant biomarkers revealed that zerumbone is a powerful antioxidant in inhibiting the formation of free radicals (Hemn et al., 2015). The antioxidant potential was revealed in this study by restoring the redox balance, where zerumbone increases E-SOD levels while decreasing MDA levels. Because zerumbone decreases free radical formation from inflammatory cells, this dual effect significantly reduces free radical generation and lipid peroxidation.

When exposed to oxidative stress, Nrf-2 can form a protein dipolymer with the corresponding protein, activating the HO-1 gene's transcription and translation. Liqing et al. (2017) investigated how zerumbone affected the expression of the proteins HO-1 and Nrf-2 in the gastric tissues of rats to understand better the mechanism underlying the drug's protective effect on gastric mucosal tissues. They also looked at CAT, SOD, GSH, and MDA. The outcomes demonstrated that HO-1 and Nrf-2 expressions in tissues of the gastric mucosa could be significantly increased by zerumbone, enhancing CAT and SOD activities, raising GSH levels, and lowering MDA levels (Liqing Li et al., 2017). Furthermore, according to their findings, zerumbone protects rats from chronic gastritis by boosting the ability of antioxidants of stomach mucosal tissue and avoiding lipid peroxidation.

In line with those findings, zerumbone's protective properties in preventing lipopolysaccharide-induced acute lung injury was investigated using mouse model conditions. This effect involves the mechan-

ism of antioxidant enzymes and Nrf2/HO-1. It was discovered in this study that zerumbone pretreatment increased the expression of Nrf2 and HO-1 that LPS caused to be associated with erythroid and restored the GPx, SOD, and CAT activities that LPS had decreased. The results of this study show that zerumbone increases antioxidant enzymes and the Nrf2/HO-1 pathway, protecting against LPS-induced ALI (Leung et al., 2017).

Non-enzymatic antioxidant activity was tested using the FRAP method by comparing its reducing power activity with ascorbic acid. The results show that the reducing power of zerumbone was better than ascorbic acid, which had values of 58.3 ± 2.08 s μM Fe (II)/g and 215.5 ± 3.11 s μM Fe (II)/g (Sidahmed et al., 2015).

According to the findings of this study, zerumbone works as an antioxidant by reducing free radical levels and has a synergistic effect in increasing antioxidant enzyme levels in various types of diseases related to oxidative stress. The cellular antioxidant pathways are more robust due to zerumbone's antioxidant activity.

Zerumbone as Anti-Inflammatory

In oxidative stress situations, NF-B can provide protection by preventing the buildup of ROS (Lingappan, 2017). It has been assumed that oxidative stress and nuclear factor (NF)-κB, a redox-sensitive factor, are closely related. Oxidative stress and the NF-κB pathway have been shown to interact in a vicious cycle. The NF-B signaling pathway's activation depends on oxidative stress. However, following the activation of this pathway, a number of inflammatory cytokines are produced, which exacerbate oxidative stress. NF-κB signaling pathway is one of the primary factors involved in the inflammatory pathway. Therefore, the mechanism of zerumbone's action on NF-KB is closely related to its antioxidant activities.

In addition to the NF-κB signal transduction cascade, oxidative stress has been shown to cause inflammation through the activation of cyclooxygenase-2 (COX-2), inducibility of nitric oxide synthase (iNOS), and high expression of inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and chemokines (CXC chemokine receptor 4), in addition to changes in specific microRNA expression, additionally shown to play a part in the inflammation brought on by oxidative stress (Arulselvan et al., 2016). Several researchers have reported zerumbone's anti-inflammatory activity based on the effect of zerumbone administration on the activity of various inflammatory signaling pathways related to oxidative stress, which is summarized in Table 1.

Zerumbone as Anticancer

Cancer is one of the diseases with the worst prognosis today (Kalantari et al., 2017). Uncontrolled cell growth and cell signalling abnormalities caused by genetic or epigenetic changes in cells trigger cancer (Jiang et al.,

Table 1. Anti-inflammatory activity of zerumbone

Method	Dose	Result	Ref
In Vivo Enterotoxigenic Bacteroides fragilis (ETBF) infection-induced colitis in mice	60 mg/kg	Zerumbone reduced ETBF-induced colitis by inhibiting NF-κB signaling.	(S. Hwang et al., 2019)
In Vivo acute necrotizing pancreatitis in rats	20 mg/kg	Zerumbone inhibits NF-κB activation and reduces the expression of ICAM-1 and IL-1β in rats, reducing the severity of acute necrotizing pancreatitis and pancreatitis-induced hepatic injury.	(Wenhong et al., 2012)
In Vivo female ICR mice	100 mg/kg	Zerumbone may offer protection against UVB-induced cataractogenesis by lowering lipid peroxides and raising the levels and activity of the body's own antioxidants GSH and GR.	(Chen et al., 2011)
In Vivo Male ICR mice	0, 0.1, 1, or 10 mmol/kg	Zerumbone inhibits NF-kB activation, Akt phosphorylation, and the release of proinflammatory cytokines like TNFa and IL-6. It also reduces the expression of proinflammatory mediators like iNOS and COX-2.	(Ho et al., 2017)
In Vitro murine J774A.1 cells, murine peritoneal macrophages, and murine bone marrow-derived macrophages.	10,20,30,40,50 μM	preventing the activation of the NLRP3 inflammasome, ERK-MAPK, and NF-κB signaling pathways.	(Su et al., 2021)
In Vitro The murine macrophage cell line, RAW 264.7	(2.5~20 μM)	Zerumbone activated the HO-1 pathway, which reduced the activity of iNOS and COX-2.	(Chien et al., 2016)
In Vivo Abdominal writhing response of acetic-acid induces in mice.	Zerumbone (50 mg/kg) positive control (PC) was morphine (5 mg/kg) zerumbone (5 mg/kg PC= indomethacine 1 mg/kg	inhibited the number of writhing instances	(Chien et al., 2016)
paw-edema in rat		reduced paw edema	
In Vivo male Sprague Dawley rats	ZER: 0.4% w/v of diluted in corn oil. CS: 20% in normal saline. celecoxib = 30 mg/kg diluted in 5% CMC	zerumbone significantly increased the synovium's immunoreactivity in rat knees with monosodium iodoacetate (MIA)-induced arthritis.	(Al-Saffar et al., 2011)
In Vivo Syrian golden hamsters fed on high-fat diet (HFD)	Zerumbone 300 mg/kg PC= lipanthyl 100 mg/kg	zerumbone has a beneficial effect in inhibiting fat accumulation in liver, improves insulin resistance, possesses a repressive effect on hepatic lipogenesis and inhibits inflammation, which are linked to the suppression of SREBP-1c and induction of PPARα.	(Tzeng et al., 2013a)
In Vivo carrageenan-induced paw edema and cotton pellet-induced granuloma tissue formation test in mice.	5, 10, 50 and 100 mg/kg	Zerumbone resulted in significant dose-dependent inhibition of carrageenan-induced leg edema and, at the same dose, significantly suppressed granulomatous tissue formation in a cotton pellet-induced granuloma assay.	(Sulaiman et al., 2010)

2019). In addition, factors such as genetics, environment, free radicals and oxidative stress also contribute to cancer development (Esquivel-Chirino et al., 2016). Multiple endogenous and exogenous factors can produce reactive oxygen species, which can have various biological consequences. ROS is also a double-edged sword in cancer immunity, acting as an intracellular second messenger at low levels. Moderate ROS levels benefit cancer cells by increasing cancer metabolism and signalling and inhibiting antioxidants, which contribute to oncogenesis. High levels of ROS, on the other hand, can cause cell death caused by DNA damage (Nakamura & Takada, 2021). Antioxidants defend cells against free radical damage by interacting with them, stabilising them, and preventing cell damage. Zerumbone has antioxidant activity and can inhibit inflammatory reactions caused by oxidative stress in cancer. Thus, zerumbone can assist cancer treatment and other methods, such as chemotherapy and immune modification.

Studies have reported zerumbone's biological activity as an anticancer in various organs and its inhibition mechanism, as shown in Table 2.

The cells use signaling pathways involved in cell proliferation, metastasis, apoptosis, and cell cycle regulation, all of which are targets for anticancer therapy to respond to various potentially DNA-damaging exogenous and endogen stimuli (Kabeer et al., 2017). The tumour suppressor p53 acts as a transcription factor that allows genes involved in the stress response to be activated, and most types of cancer in humans are associated with defects in the p53-mediated stress response (Duronio & Xiong, 2013). In this case, by activating p53, zerumbone also prevents the proliferation of cancer cells in various cancer types (Ma et al., 2018; Zhang et al., 2012b).

Many studies reveal the antiproliferative effect of zerumbone on various types of cancer. The underlying mechanisms include up-regulating P53 in esophageal cells to promote apoptosis (Ma et al., 2018), pancreatic(Zhang et al., 2012a), and lung cancers (Truong, Nam, et al., 2015). In addition, apoptosis occurs by downregulating Bcl-2 in oesophagal (Ma et al., 2018), CNS (Jalili-Nik et al., 2020), and gastric cancers (D. Wang et al., 2016). Meanwhile, in breast (Sehrawat et al., 2012), CNS (Jalili-Nik et al., 2020), and gastric cancer cells (D. Wang et al., 2016), zerumbone induces Bax/Bak-mediated apoptosis. Zerumbone can also induce apoptosis in human gastric cancer cells through the Cyp A regulatory and mitochondria-mediated pathways (D. Wang et al., 2016). IKK inactivation, followed by Akt and FOXO1 phosphorylation and caspase-3 activation, contributes to zerumbone-mediated GBM cell death. Zerumbone inhibits cancer cell growth by inducing apoptosis, stops the cell cycle in the G2/M phase, and reduces IL-6 secretion in ovarian, cervical, and liver cancer cells (Abdelwahab et al., 2012).

Zerumbone can inhibit angiogenesis by inhibiting the αvβ3 integrin signaling pathway in breast cancer. This compound also suppresses TGF-β1-induced expression of FN, MMP-2, and MMP-9 through smad3 inactivation and inhibits triple-negative breast cancer (TNBC) cell tumorigenicity. In TNBC, tumor invasion is also reduced by zerumbone by inhibiting the formation of IL-1β and NF-κB activation. Zerumbone can also inhibit angiogenesis by blocking NF-κB activity in gastric, central nervous system, and pancreas cancer.

Zerumbone also suppresses Rac1 expression, inhibiting oesophagal cancer cell migration (M. Wang, Niu, Gao, et al., 2019). Inhibition of cancer cell migration to the pancreas by zerumbone is mediated by inhibiting the JAK2/STAT3 signaling pathway (Jorvig & Chakraborty, 2015). Lung cancer metastasis and migration are inhibited by zerumbone by inhibiting TGF-β-induced EMT through up-regulation of E-cadherin and down-regulation of the Smad2 signaling pathway (Hseu et al., 2015).

Zerumbone as Immunomodulator

Reactive oxygen species, as an agent with direct cytotoxic effects on cells, triggers the autoimmune response. Furthermore, antioxidant systems, which include enzymatic and nonenzymatic antioxidants, regulate ROS levels (Tavassolifar, Vodjgani, Salehi, & Izad, 2020). In immune-related diseases, immunomodulators can increase or decrease the immune response of the innate and adaptive immune systems (T. Behl et al., 2021). The cells of the innate immune system, especially those with phagocytic activity like neutrophils and macrophages, are used in in vitro cellular functional tests to assess the effect of drugs or chemicals on immune system function (Bilitewski, 2008). Several studies related to the immunomodulatory activity of zerumbone have been reviewed and presented below.

When activated by endogenous or exogenous chemoattractants, phagocyte migration to the infection site is inhibited, which serves as a mechanism for a sample's anti-inflammatory activity. According to a study by Akhtar et al. (2019), the effects of extract, oil of *Zingiber zerumbet* rhizome, and zerumbone on CD18 integrin expression were moderately inhibited with a dose-dependent pattern. An extract from *Z. zerumbet* inhibited phagocytic engulfment to the greatest extent, with a percentage of phagocytic cells for PMN (Polymorphonuclear Neutrophils) of about 55 %. Zerumbone inhibited PMA (Phorbol myristate 13-acetate) and zymosan-induced neutrophil oxidative sequences significantly. Zerumbone has activity comparable to aspirin in inhibiting the production of extracellular ROS in PMN with an IC_{50} of 17.36 M (Akhtar et al., 2019). concentration-dependent results. Zerumbone inhibited the release of Th1 and Th2 cytokines and significantly reduced T and B lymphocyte proliferation. Zerumbone significantly

Table 2. Anticancer activity of zerumbone on various organs, cell lines and targets.

Organ	Cell line	Dose	Mechanism	Ref.
Esophagus	Esophageal Cancer EC-109 Cells	30; 40; 50 µM	Apoptosis is induced by increasing the expression of P53's mRNA and decreasing the expression of Bcl-2's mRNA, as well as by increasing the expression of P53's protein and decreasing the expression of Bcl-2's protein.	(Ma et al., 2018)
	KYSE-30 Cells and KYSE-150 Cells	5; 10; 20; 40; 80 µM	Rac1 expression is suppressed by Zerumbone, which prevents cell migration. Rac1 is suppressed by encouraging its ubiquitination and destruction.	(M. Wang, Niu, Gao, et al., 2019)
Breast	MCF-7 and MDA-MB-231 and (Hs27)	3,125; 6,25;12,5; 25; 50; 100, µg/mL	On coadministration with the TP5-iRGD Peptide, by explicitly targeting αvβ3 Integrin, Zerumbone causes apoptosis.	(Eid et al., 2019)
	(TNBC) Cell	20 mg/kg	Smad3 deactivation and inhibition of tumorigenicity in TNBC cells.	(Kim et al., 2016)
	(TNBC) Cell	20 µM	Zerumbone reduces TNBC cell invasion by inhibiting IL-1β production through inhibiting NF-κB activation.	(Jeon et al., 2016)
	Various BCS	20 and 40 µM	Zerumbone affects CD1d expression and lipid antigen presentation pathways	(Shyanti et al., 2017)
	MDA-MB-231, MCF-7, and MCF-10A cells. Wild-type HCT-116 cell line	20 µM	Zerumbone prevented MDA-MB-231 xenograft growth in vivo by causing G2/M cell cycle arrest and Bax/Bak-mediated death in human breast cancer cells.	(Sehrawat et al. 2012)
Central nerve system	GBM U-87 MG cell	12.5; 25; 50; 100; 200; and 400 µM	Zerumbone upregulates proapoptotic Bax gene expression while suppressing antiapoptotic Bcl-2 gene expression. Zerumbone causes cytotoxicity via the production of ROS.	(Jalili-Nik et al. 2020)
	(GBM8401) cells	10; 30; 50 µM	Zerumbone-mediated GBM cell death was influenced by IKK inactivation, Akt and FOXO1 phosphorylation, and caspase-3 activation.	(Weng et al., 2012)
Ovaries	HeLa Sel cells	0, 5; 10; 15 µM	With an IC50 of 14.2 ± 0.5 mol/L, Zerumbone specifically inhibits HeLa cell growth.	(Ashraf et al., 2019)
	HeLa and Caov-3 cells	10; 20; 30 µM	Zerumbone arrested the cell cycle in the G2/M phase, decreased the level of IL-6 release, and inhibited the development of both cancer cells by inducing death.	(Abdelwahab et al., 2012)
Liver	Hepatoma HepG2 cells	0; 2; 5; 10; 20; 50; 100 µM	In HepG2 hepatoma cells, zerumbone caused apoptosis and inhibited invasion and metastasis.	(Lv et al., 2018
	HepG2 Cells	6.25; 12.5; 25 µg/mL	HepG2 cell migration and proliferation are both inhibited by zerumbone.	(Samad et al., 2017)
	(PaCa)	0,5;1;5;10;25; 50 µM	By suppressing NF-1D705B and NF-B-dependent proangiogenic gene products, zerumbone reduces angiogenesis linked to PaCa.	(Shamoto et al., 2014)

Tabel 2. Continue…

Organ	Cell line	Dose	Mechanism	Ref.
Colorectal	Human CRC cell lines; HCT116 cells; HT29; SW620 cells	10;20;30; 40; 50 µM	Zerumbone generates more significant radiation-induced DNA damage; however, zerumbone-mediated radiosensitisation is achieved by cellular glutathione (GSH) depletion rather than ROS.	(Deorukhkar et al., 2015)
Pancreas	(PaCa)	3; 10; 30; 100 µM	The expression of p53 and p21 proteins were both markedly increased.	(Zhang et al., 2012a)
	(PaCa)	0,5;1;5;10;25; 50 µM	By suppressing NF-1D705B and NF-B-dependent proangiogenic gene products, zerumbone reduces angiogenesis linked to PaCa.	(Shamoto et al., 2014)
	(PaCa)	20; 40; 60; 80; 100 µM	An effective Jak2/Stat3 inhibitor that prevents the proliferation of pro-migration genes and cancer cell expression and migration.	(Jorvig & Chakraborty, 2015)
	TGF-β1- (A549) cells	10 or 20 µM	In A549 lung cancer cells stimulated with TGF-1, zerumbone showed anti-EMT and anti-metastatic effects.	(Hseu et al., 2015)
Lung				
Skin	CHL-1	0; 1; 2; 4; 8; 16 µg/ml.	Alterations in mitochondrial function decrease proliferation and migration.	(Yan et al., 2017)
Stomach	SGC-7901	0,1; 1;5;10; 20; 50 µM	the levels of Cyp A and Bcl-2 are decreased, Bax is increased, and Caspase-3 is activated by cytochrome c (Cyt-C) being released.	(D. Wang et al., 2016)
	VEGF	500 nM,; 1; 5; 10 µM.	In AGS cells, zerumbone treatment decreased VEGF expression and NF-B activity, which restricted angiogenesis.	(Tsuboi et al., 2014)
Mouth	OSCC cell lines	3; 10; 30 µM	inhibits the CXCR4-RhoA and PI3K-mTOR signalling pathways, decreasing cell viability.	(Zainal et al., 2018)
Blood	murine leukaemia induced with WEHI-3B cells	20; 40; 60; 80; 100 µg/mL	Zerumbone-NLC induces apoptosis in leukaemia cells.	(Rahman et al., 2015)
	CEM-ss cells	5; 10; 20; 30; 40; 50; 60; 70; 80; µg/mL	In acute T-lymphocytic leukaemia, CEM-ss and Zerumbone can induce apoptosis.	(Abdelwahab et al., 2011)

reduced sRBC-induced delayed-type hypersensitivity (DTH) rat-paw swelling. Anti-sRBC immunoglobulin antibody titers were significantly reduced in mice immunised with zerumbone and treated with it (Jantan et al., 2019). Based on these various research reports, further investigation and application of zerumbone's immunomodulatory potential is recommended.

Zerumbone as Antidiabetic

Diabetes mellitus (DM) is a severe, chronic, and complicated metabolic disorder with many etiologies that can have immediate and long-

term adverse effects (Salehi et al., 2019). ROS are produced during euglycemic, natural insulin-regulated glucose metabolism; their levels are regulated by factors that regulate cellular respiration, such as the availability of NAD-linked substrates, succinate, and oxygen; and antioxidant enzymes that maintain cellular redox balance. Under normal reduced conditions, only about 1-2% of total oxygen consumption results in the formation of superoxide anion and hydrogen peroxide. However, under hyperglycemic conditions, free radicals may account for up to 10% of the respiratory oxygen consumed (Black, 2022). Several investigators have reported the activity of zerumbone in reducing the severity of inflammation associated with hyperglycemic conditions in animal models of diabetes mellitus.

Reduced creatinine clearance, elevated blood glucose, blood urea nitrogen, proteinuria, and a markedly higher kidney-to-body weight ratio are all signs of renal dysfunction in diabetic mice. Zerumbone therapy significantly enhanced the diabetic kidney's histologic architecture. Mitogen-activated protein kinase p38 activation by hyperglycemia increases macrophage infiltration and interleukin-1, IL-6, and TNF levels. In diabetic kidneys, zerumbone treatment reversed all these abnormalities and decreased fibronectin expression, transforming growth factor 1, intercellular adhesion molecule 1, and monocyte chemoattractant protein-1 (Tzeng et al., 2013b).

In streptozotocin-induced diabetic rats, Liu et al. (2016) looked into the impact of zerumbone administration on repairing retinal damage. They achieved this by obstructing the receptors for advanced glycation end products. According to the results of this study, zerumbone decreased the expression of retinal angiogenic genes and inflammatory cytokines and chemokines in the retina of diabetic rats. In addition, zerumbone prevented NF-κB p65 nuclear translocation and decreased p38 MAPK phosphorylation in the retina of diabetic mice. Zerumbone reduced the severity of retinal inflammation and angiogenesis in diabetic mice by blocking the p38 MAPK and NF-κB signalling pathways. Zerumbone's antihyperglycemic and antihyperlipidemic qualities are to thank for this benefit for DR (Liu et al., 2016).

The majority and noticeable diabetic microvascular complication is a retinal condition called diabetic retinopathy (DR). In 2016, Tzeng et al. published a study on zerumbone's ability to protect diabetic rats' retinas from damage brought on by the disease. Their research revealed that giving zerumbone to diabetic rats resulted in markedly lower plasma glucose and glycosylated haemoglobin levels. The treatment with zerumbone for diabetic rats reversed the irregularity and loss of retinal layer thickness, according to retinal histopathological findings. In the retina of

diabetic rats, zerumbone prevents upregulation of advanced glycosylation end products (AGEs) and elevated levels of AGE receptors (RAGE). Additionally, zerumbone decreased the upregulation of the cytokines interleukin (IL)-1, IL-6, and tumour necrosis factor connected to diabetes. Zerumbone also inhibits nuclear factor (NF)-κB activation, apoptosis, and the overexpression of VEGF and ICAM-1 in the retina of streptozocin diabetic mice (Tzeng et al., 2016).

Wang et al. (2015) found that zerumbone prevents apoptosis in INS-1 pancreatic cells primarily by inhibiting ROS production and activating p38 and JNK in a study on the impact of zerumbone administration on high-glucose-induced pancreatic cell cytotoxicity. In INS-1 cells exposed to high glucose, zerumbone significantly reduced ROS production and the activation of the JNK, p38 and MAPK pathways (C. Wang et al., 2015). These findings imply the potential therapeutic value of zerumbone in treating beta-cell degeneration in diabetic patients.

Zerumbone as Hepatoprotector

ROS and reactive nitrogen species greatly impact cellular structures such as hepatocytic proteins, lipids, and DNA. The process causes structural and functional abnormalities in the liver (Cichoż-Lach & Michalak, 2014). The painkiller paracetamol can damage liver cells if used excessively. This is caused by the production of N-acetyl-para-benzo-quinone imine, a reactive, poisonous metabolite of paracetamol (Hinson et al., 2010). The metaboliteN-acetyl-para-benzo-quinone imine interacts with mitochondrial proteins in hepatocytes to produce oncotic necrosis, which is thought to be a factor in the elevated levels of ALT and AST (Jaeschke & Bajt, 2006). Furthermore, PCM-induced liver damage could result from mitochondrial permeability changes, which can lead to mitochondrial oxidative stress and ATP depletion. Hamid et al. (2018) investigated zerumbone's hepatoprotective properties against paracetamol-induced acute hepatotoxicity in rats (Hamid et al., 2018). Zerumbone administration significantly lowered ALT, AST, and total liver protein levels compared to paracetamol-induced animals. Hepatocyte structure was typical in mice given zerumbone, with no vacuolisation or necrosis. However, the number of neutrophils significantly decreased (Hamid et al., 2018).

Carbon tetrachloride (CCl_4) is a well-known hepatotoxin. The most popular *in vivo* experimental model is acute CCl4 administration to rodents, which quickly causes oxidative stress and inflammatory response (Dai et al., 2018). The trichloromethyl peroxy radical, a toxic CCl_4 metabolite, promotes lipid peroxidation and oxidative stress (Reyes-Gordillo et al., 2017). Zerumbone will reduce the inflammatory response and oxidative stress, which will have a hepatoprotective effect against acute liver injury (ALI) (M. Wang, Niu, Ou, et al., 2019).

Their findings verified that zerumbone reduces oxidative stress by restoring antioxidant enzyme activity, restoring GSH reservoirs, and reducing peroxidation of lipids in particular to protect the liver from CCl_4-induced ALI. SOD, GSH-Px, GSH, and MDA were among the oxidative stress indicators in the liver tissue that were evaluated. Research regarding the hepatoprotective activity of zerumbone has yet to be widely reported. Therefore, it is recommended that research be carried out using other methods.

Anti-neurodegenerative Effect of Zerumbone

Oversecretion of ROS in the brain causes oxidative stress, which, if not suppressed or inhibited, can cause oxidative damage to critical components of the central nervous system. This condition can also start or speed up reactions that harm the brain's physiological functions and health. Suppose these reactions, such as neuroinflammation and progressive neuronal cell loss via apoptosis, are not suppressed. In that case, they can exacerbate protein misfolding and the formation of protein aggregates, resulting in neurodegeneration and associated neurobehavioral incompetence (Oladele, Oladiji, Oladele, & Oyeleke, 2021).

The most typical type of neurodegeneration and the leading cause of dementia is Alzheimer's disease. Language, learning and memory, executive function, complex attention, visuospatial function, praxis, gnosis, and social and behavioural issues are the symptoms of this condition (Long & Holtzman, 2019). The formation of senile plaques composed of extracellular amyloid (A) peptide accumulation is among the most notable neuropathological characteristics of Alzheimer's disease (Serrano-Pozo et al., 2011). The A peptide may contribute to memory loss, behavioural problems, and neurodegenerative diseases (Klein et al., 2004). Neuroinflammation also contributes to the pathogenesis of Alzheimer's disease. Microglial and astroglial activity and the production of different inflammatory mediators are characteristics of neuroinflammation that are incredibly close to amyloid plaques (Heneka et al., 2015; Hensley, 2010).

Zerumbone inhibits the nf-κB/MAPK signalling cascade, which reduces the pro-inflammatory cytokine expression and changes microglia from a typically inflammatory phenotype to an alternative anti-inflammatory phenotype, according to research by Li et al. published in 2020. After a 20-day treatment period, zerumbone significantly enhanced cognitive and non-cognitive behaviour in APP/PS1 transgenic miceZerumbone reduced amyloid buildup significantly in the cortex and hippocampus and suppressed pro-inflammatory microglial activation. The percentage of among all activated microglia, anti-inflammatory microglia increased with the use of zerumbone, suggesting that it may encourage

phagocytosis to aid in reducing amyloid deposition and preventing the accumulation of amyloid. Zerumbone inhibits the synthesis of crucial MAPK pathway molecules like p38 and extracellular signal-regulated kinases (ERKs) (Lei Li et al., 2020).

Cholinergic transmission is carried out by acetylcholine (ACh), the most prevalent neurotransmitter in the brain. Acetylcholine is broken down by the cholinesterase enzymes butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) (Reid et al., 2013). According to this theory, as Alzheimer's disease progresses, cholinergic insufficiency develops, resulting in widespread cognitive impairment and deterioration. According to a recent study by Hwang et al., 2020, an essential possibility for zerumbone's physiological and pharmacological efficacy in preventing Alzheimer's disease is that it is a rare dual AChE and BChE inhibitor with strong BBB permeability (J. Hwang et al., 2020).

Early stages of memory loss have been associated with hippocampus and cerebral cortex cholinergic deficits (P. Behl et al., 2014). Scopolamine impairs learning and memory in rats by causing the degeneration and dysfunction of cortical cholinergic neurons and by causing the expression of a large number of genes related to cell differentiation, apoptosis, and muscarinic receptor signalling pathways. Studies have shown a correlation between a high levels of lipid peroxidation and low levels of antioxidant in the brain and the memory-decreasing effects of scopolamine. As part of their investigation into the impact of zerumbone on these outcomes, Jafarian and associates (Jafariana et al., 2019) looked at the impact of scopolamine on scopolamine-induced memory impairment and anxiety-like behaviour in rats. According to their research, scopolamine-induced learning and memory deficits can be reversed with zerumbone therapy. Last but not least, their research demonstrates that zerumbone has a beneficial effect on dementia-like behaviour in the animal model they used, which may be helpful in future studies on hyperactivity, anxiety, and learning difficulties.

Anti-neuropathic pain Activity of Zerumbone

Several studies have suggested that GABA neurons are vulnerable to oxidative stress. For example, superoxide, a type of ROS, contributed to angiotensin's presynaptic inhibition of GABA release in the paraventricular nucleus of the hypothalamus, indicating the vulnerability of GABA neurons to oxidative stress (June Yowtak, Kim, Jigong Wang, Chung, & Chung, 2011). In order to simulate neuropathic pain, chronic constriction injury (CCI), a common method of causing peripheral neuropathy, is used (Safakhah et al., 2017). Changes in mitochondrial dynamics brought on by oxidative stress result in increased production of ROS, which is the cause of mitochondrial

dysfunction (Ilari, Giancotti, Lauro, Dagostino, et al., 2020). As with neurodegenerative diseases, neuropathic pain is also triggered by oxidative stress conditions. Ilari, Giancotti, Lauro, Gliozzi, et al. (2020) specifically showed that oxidative stress, caused by the buildup of lipid peroxidation and malondialdehyde, alters mitochondrial activity and is responsible for post-translational modifications and the inactivation of important mitochondrial proteins.

The effects of zerumbone on the mechanisms underlying neuropathic pain have been the subject of numerous studies. For instance, Gopalsamy et al.'s (2020) study into how potassium channels and opioid receptors interact to cause zerumbone to induce analgesia in a rat model of neuropathic chronic constriction injury (CCI) is one example. They concluded that zerumbone's antiallodynic and antihyperalgesic effects in a mouse model of CCI-induced neuropathic pain were caused by K^+ channels, specifically V_K, K_{ATP}, BK_{Ca}, and SK_{Ca} channels (Gopalsamy et al., 2020). Furthermore, zerumbone's modulation of neuropathic pain is linked to μ-, δ-, and κ-opioid receptor subtypes.

Gopalsamy et al. 2017 used a rat model of CCI neuropathic pain to study the prophylactic effects of zerumbone treatment on hyperalgesia and allodynia. They found that IL-1, IL-6, and TNF-α production in blood plasma and bone marrow tissue was successfully inhibited by zerumbone, but IL-10 production was not affected. According to the findings, zerumbone may have antiallodynic and antihyperalgesic effects by reducing nociceptor neurons' sensitivity to pain by inhibiting inflammatory mediators. Zerumbone was successful in providing analgesia at an effective dose of 10 mg/kg as a prophylactic dose (Gopalsamy et al., 2017).

The transmission of pain signals can be slowed down or altered by various receptors and pathways. The serotonin 5-HT receptor was previously connected to the serotonergic system and zerumbone's anti-neuropathic properties in an animal model of CCI. They demonstrated the availability of the neurotransmitter serotonin and the inhibitory effect of 5-HT receptor subtypes 1A, 1B, 2A, 3, 6, and 7 interacting with zerumbone in modulating nociception (Chia et al., 2016). In a recent study, it was examined whether zerumbone could modulate the SH-SY5Y neuroblastoma model in vitro and vivo, as well as TRPV1, NMDA NR2B, adrenergic receptor plasticity, and neuropathic pain caused by CCI. Zerumbone interacts with the noradrenergic system, TRPV1, and NMDA receptors to produce antiallodynic and antihyperalgesic effects in a mouse model of neuropathic pain. Furthermore, zerumbone's impact on the expression of 2A-adrenoceptor receptors, TRPV1, and NMDA NR2B sheds light on the drug's mechanism of action. Prior studies on zerumbone for the treatment of neuropathic pain indicate that zerumbone has a high potential as an antinociceptive substance (Chia et al., 2020).

Given these findings, we suggest future research studies to investigate other possible mechanisms of action needed to fully characterize the anti-neuropathic properties of zerumbone.

Gastroprotective Activity of Zerumbone

The gastrointestinal (GI) tract is vulnerable to ROS attack because it is exposed to the outside environment, which contains immune cells that are already present, intestinal flora, and dietary components that could all be ROS sources. In the GI tract, ROS are primarily produced by the HX/XO system and the NADPH oxidase system. The body's highest XO concentration is found in the GI tract, where it is combined with a significant number of phagocytic cells to produce a significant amount of O2. ROS has been linked to a number of inflammatory GI conditions, such as gastric cancer, ulcers, and gastroduodenal inflammation (Bhattacharyya et al., 2014).

A rat model of gastric ulcers caused by ethanol or nonsteroidal anti-inflammatory drugs, such as indomethacin, can be used to study an ingredient's gastroprotective effects. Through the oxidative stress and inflammation induction, ethanol can directly or indirectly damage cell membranes, exfoliation, dehydration, and cytotoxicity. Furthermore, ethanol makes mast cells, macrophages, and blood cells release vasoactive substances, which increases gastric acid mucosal permeability. As mentioned above, the effects lead to necrosis, which in turn triggers the ulcer development (Aziz et al., 2019; Shams & Eissa, 2022). Meanwhile, NSAIDs cause mucosal damage via ROS-mediated leukocytes produced, besides inhibiting cyclooxygenase and decreasing prostaglandin production. ROS-mediated mitochondrial damage and lipid, protein, and DNA oxidation cause apoptosis and mucosal injury (Suzuki et al., 2012).

According to animal studies, intragastric ethanol administration causes extensive submucosal oedema, long hemorrhagic bands, mucosal ossification, inflammatory cell infiltration, and epithelial cell death. Shidamed et al. (2015) reported that zerumbone has antioxidant, anti-helicobacter pylori, gastroprotective, and antisecretory properties. They discovered that mucus integrity, antioxidant activity, and HSP-70 activation are related to the anti-ulcer properties of zerumbone. As an antimicrobial, zerumbone has also successfully combated *Helicobacter pylori* (Sidahmed et al., 2015).

CONCLUSION

Oxidative stress has been implicated in many chronic diseases. Inflammation and oxidative stress are two pathophysiological processes that are intimately linked and that can be easily induced by one another. Then both take part in the pathogenesis of many chronic diseases, including cancer, metabolic diseases, immune-related diseases, neurodegenerative diseases, and others. The results of the reviews show that the various

pharmacological prospects of zerumbone are related to oxidative stress conditions through various modes of action. This review will provide scientific knowledge about the development of the natural product zerumbone for various diseases and disorders related to oxidative stress. Because most commonly used test methods are still limited to in vitro methods, more in vivo research and clinical trials are required to complete scientific data on the pharmacological potential of zerumbone in overcoming various oxidative stress-related conditions.

REFERENCES

Abdelwahab, S. I., Abdul, A. B., Mohan, S., Taha, M. M. E., Syam, S., Ibrahim, M. Y., & Mariod, A. A. (2011). Zerumbone induces apoptosis in T-acute lymphoblastic leukemia cells. *Leukemia Research*, *35*(2), 268–271. https://doi.org/10.1016/J.LEUKRES.2010.07.025

Abdelwahab, S. I., Abdul, A. B., Zain, Z. N. M., & Hadi, A. H. A. (2012). Zerumbone inhibits interleukin-6 and induces apoptosis and cell cycle arrest in ovarian and cervical cancer cells. *International Immunopharmacology*, *12*(4), 594–602. https://doi.org/10.1016/J.INTIMP.2012.01.014

Ajish, K. R., Dhanya, B. P., Joseph, N., Rani, M. P., Raghu, K. G., Vineetha, V. P., & Radhakrishnan, K. V. (2014). Synthesis of novel zerumbone derivatives via regioselective palladium catalyzed decarboxylative coupling reaction : a new class of a -glucosidase inhibitors. *Tetrahedron Letters*, *55*(3), 665–670. https://doi.org/10.1016/j.tetlet.2013.11.110

Akhtar, N. M. Y., Jantan, I., Arshad, L., & Haque, M. A. (2019). Standardized ethanol extract, essential oil and zerumbone of Zingiber zerumbet rhizome suppress phagocytic activity of human neutrophils. *BMC Complementary and Alternative Medicine*, *19*(1), 331. https://doi.org/10.1186/S12906-019-2748-5

Al-Saffar, Ganabadi, S., Fakurazi, S., & Yaakub, H. (2011). Zerumbone significantly improved immunoreactivity in the synovium compared to Channa striatus extract in monosodium iodoacetate (MIA)-induced knee osteoarthritis in rat. *Journal of Medicinal Plants Research*, *5*(9), 1701–1710. http://www.academicjournals.org/JMPR

Ali, S. S., Ahsan, H., Zia, M. K., Siddiqui, T., & Khan, F. H. (2020). Understanding oxidants and antioxidants: Classical team with new players. *Journal of Food Biochemistry*, *44*(3), 1–13. https://doi.org/10.1111/jfbc.13145

Arulselvan, P., Fard, M. T., Tan, W. S., Gothai, S., Fakurazi, S., Norhaizan, M. E., & Kumar, S. S. (2016). Role of Antioxidants and Natural Products in Inflammation. *Oxidative Medicine and Cellular Longevity*, *2016*. https://doi.org/10.1155/2016/5276130

Ashraf, S. M., Sebastian, J., & Rathinasamy, K. (2019). Zerumbone, a cyclic sesquiterpene, exerts antimitotic activity in HeLa cells through tubulin binding and exhibits synergistic activity with vinblastine and paclitaxel. *Cell Proliferation*, *52*(2). https://doi.org/10.1111/CPR.12558

Aziz, R. S., Siddiqua, A., Shahzad, M., Shabbir, A., & Naseem, N. (2019). Oxyresveratrol ameliorates ethanol-induced gastric ulcer via downregulation of IL-6, TNF-α NF-κB, and COX-2 levels, and upregulation of TFF-2 levels. *Biomedicine and Pharmacotherapy*, *110*(November 2018), 554–560. https://doi.org/10.1016/j.biopha.2018.12.002

Behl, P., Edwards, J. D., Kiss, A., Lanctot, K. L., Streiner, D. L., Black, S. E., & Stuss, D. T. (2014). Treatment effects in multiple cognitive domains in Alzheimer's disease: a two-year cohort study. *Alzheimer's Research & Therapy*, *6*(4), 48. https://doi.org/10.1186/ALZRT280

Behl, T., Kumar, K., Brisc, C., Rus, M., Nistor-Cseppento, D. C., Bustea, C., Aron, R. A. C., Pantis, C., Zengin, G., Sehgal, A., Kaur, R., Kumar, A., Arora, S., Setia, D., Chandel, D., & Bungau, S. (2021). Exploring the multifocal role of phytochemicals as immunomodulators. *Biomedicine and Pharmacotherapy*, *133*(November 2020), 110959. https://doi.org/10.1016/j.biopha.2020.110959

Bhattacharyya, A., Chattopadhyay, R., Mitra, S., & Crowe, S. E. (2014). Oxidative stress: An essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiological Reviews*, *94*(2), 329–354. https://doi.org/10.1152/physrev.00040.2012

Bilitewski, U. (2008). Determination of immunomodulatory effects : focus on functional analysis of phagocytes as representatives of the innate immune system. *Anal Bioanal Chem*, 1545–1554. https://doi.org/10.1007/s00216-008-2089-6

Black, H. S. (2022). A Synopsis of the Associations of Oxidative Stress, ROS, and. *Antioxidant*.

Chen, B.-Y., Lin, D. P.-C., Su, K.-C., Chen, Y.-L., Wu, C.-Y., Teng, M.-C., Tsai, Y.-T., Sun, C.-Y., Wang, S.-R., & Chang, H.-H. (2011). Dietary zerumbone prevents against ultraviolet B-induced cataractogenesis in the mouse. *Molecular Vision*, *17*, 723. /pmc/articles/PMC3060159/

Chia, J. S. M., Izham, N. A. M., Farouk, A. A. O., Sulaiman, M. R., Mustafa, S., Hutchinson, M. R., & Perimal, E. K. (2020). Zerumbone Modulates α2A-Adrenergic, TRPV1, and NMDA NR2B Receptors Plasticity in CCI-Induced Neuropathic Pain In Vivo and LPS-Induced SH-SY5Y Neuroblastoma In Vitro Models. In *Frontiers in Pharmacology* (Vol. 11). https://doi.org/10.3389/fphar.2020.00092

Chia, J. S. M., Omar Farouk, A. A., Mohamad, A. S., Sulaiman, M. R., & Perimal, E. K. (2016). Zerumbone alleviates chronic constriction injury-induced allodynia and hyperalgesia through serotonin 5-HT receptors. *Biomedicine and Pharmacotherapy*, *83*, 1303–1310. https://doi.org/10.1016/j.biopha.2016.08.052

Chien, T.-Y., Huang, S. K.-H., Lee, C.-J., Tsai, P.-W., & Wang, C.-C. (2016). Antinociceptive and Anti-Inflammatory Effects of Zerumbone against Mono-Iodoacetate-Induced Arthritis. *International Journal of Molecular Sciences*, *17*(2), 249. https://doi.org/10.3390/IJMS17020249

Cichoż-Lach, H., & Michalak, A. (2014). Oxidative stress as a crucial factor in liver diseases. *World Journal Gastroenterology*.

Dai, C., Xiao, X., Li, D., Tun, S., Wang, Y., Velkov, T., & Tang, S. (2018). Chloroquine ameliorates carbon tetrachloride-induced acute liver injury in mice via the concomitant inhibition of inflammation and induction of apoptosis. *Cell Death and Disease*, *9*(12). https://doi.org/10.1038/s41419-018-1136-2

Deorukhkar, A., Ahuja, N., Mercado, A.-L., Diagaradjane, P., Raju, U., Patel, N., Mohindra, P., Diep, N., Guha, S., & Krishnan, S. (2015). Zerumbone increases oxidative stress in a thiol-dependent ROS-independent manner to increase DNA damage and sensitize colorectal cancer cells to radiation. *Cancer Medicine*, *4*(2), 278. https://doi.org/10.1002/CAM4.367

Dev, S. (1960). Studies in sesquiterpenes—XVI : Zerumbone, a monocyclic sesquiterpene ketone. *Tetrahedron*, *8*(3–4), 171–180. https://doi.org/10.1016/0040-4020(60)80027-0

Dev, S., Anderson, J. E., Cormier, V., Damodaran, N. P., & Roberts, J. D. (2002). Nuclear magnetic resonance spectroscopy. The conformational mobility of humulene and zerumbone. *Journal of the American Chemical Society*, *90*(5), 1246–1248. https://doi.org/10.1021/JA01007A024

Duronio, R. J., & Xiong, Y. (2013). Signaling Pathways that Control Cell Proliferation. *Cold Spring Harb Perspect Biol*. https://doi.org/10.1101/cshperspect.a008904

Eid, E. E. M., Alanazi, A. S., Koosha, S., Alrasheedy, A. A., Azam, F., Taban, I. M., Khalilullah, H., Al-Qubaisi, M. S., & Alshawsh, M. A. (2019). Zerumbone Induces Apoptosis in Breast Cancer Cells by Targeting αvβ3 Integrin upon Co-Administration with TP5-iRGD Peptide. *Molecules*, *24*(14). https://doi.org/10.3390/MOLECULES24142554

Esquivel-Chirino, C., Esquivel-Soto, J., Morales-Gonzales, J. A., Sanches, D. M., Ventura-Gallegos, J. L., Hernandes-Mora, L. E., & Zentella-Dehesa, A. (2016). Inflammatory Environmental, Oxidative Stress in Tumoral Progression. *Intech*, *i*(tourism), 13.

García-Sánchez, A., Miranda-Díaz, A. G., & Cardona-Muñoz, E. G. (2020). The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- And Antioxidant Properties in Chronic Diseases. *Oxidative Medicine and Cellular Longevity*, *2020*. https://doi.org/10.1155/2020/2082145

Girisa, S., Shabnam, B., Monisha, J., Fan, L., Halim, C. E., Arfuso, F., Ahn, K. S., Sethi, G., & Kunnumakkara, A. B. (2019). *molecules Potential of Zerumbone as an Anti-Cancer Agent*. https://doi.org/10.3390/molecules24040734

Gopalsamy, B., Chia, J. S. M., Farouk, A. A. O., Sulaiman, M. R., & Perimal, E. K. (2020). Zerumbone-Induced Analgesia Modulated via Potassium Channels and Opioid Receptors in Chronic Constriction Injury-Induced Neuropathic Pain. *Molecules*, *25*(17), 3880.

https://doi.org/10.3390/MOLECULE 25173880

Gopalsamy, B., Farouk, A. A. O., Mohamad, T. A. S. T., Sulaiman, M. R., & Perimal, E. K. (2017). Antiallodynic and antihyperalgesic activities of zerumbone via the suppression of IL-1β, IL-6, and TNF-α in a mouse model of neuropathic pain. *Journal of Pain Research*, *10*, 2605. https://doi.org/10.2147/JPR.S143024

Hamid, A., Lee, L. S., Karim, S. R., & Jufri, N. F. (2018). Hepatoprotective Effects of Zerumbone against Paracetamol-Induced Acute Hepatotoxicity in Rats. *Malays J Med Sci*.

He, L., He, T., Farrar, S., Ji, L., Liu, T., & Ma, X. (2017). Antioxidants Maintain Cellular Redox Homeostasis by Elimination of Reactive Oxygen Species. *Cellular Physiology and Biochemistry*, *44*(2), 532–553. https://doi.org/10.1159/000485089

Hemn, H. O., Noordin, M. M., Rahman, H. S., Hazilawati, H., Zuki, A., & Chartrand, M. S. (2015). Antihypercholesterolemic and antioxidant efficacies of zerumbone on the formation, development, and establishment of atherosclerosis in cholesterol-fed rabbits. *Drug Design, Development and Therapy*, *9*, 4173. https://doi.org/10.2147/DDDT.S76225

Heneka, M. T., Carson, M. J., Khoury, J. El, Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's Disease. *The Lancet. Neurology*, *14*(4), 388. https://doi.org/10.1016/S1474-4422(15)70016-5

Hensley, K. (2010). Neuroinflammation in Alzheimer's disease: Mechanisms, pathologic consequences, and potential for therapeutic manipulation. *Journal of Alzheimer's Disease*, *21*(1), 1–14. https://doi.org/10.3233/JAD-2010-1414

Hinson, J. A., Roberts, D. W., & James, L. P. (2010). Mechanisms of Acetaminophen-Induced Liver Necrosis. *Handbook of Experimental Pharmacology*, *196*(196), 369. https://doi.org/10.1007/978-3-642-00663-0_12

Ho, Y. C., Lee, S. S., Yang, M. L., Huang-Liu, R., Lee, C. Y., Li, Y. C., & Kuan, Y. H. (2017). Zerumbone reduced the inflammatory response of acute lung injury in endotoxin-treated mice via Akt-NFκB pathway. *Chemico-Biological Interactions*, *271*, 9–14. https://doi.org/10.1016/j.cbi.2017.04.017

Hseu, Y. C., Huang, Y. C., Korivi, M., Wu, J. J., Way, T. Der, Ou, T. T., Chiu, L. W., Lee, C. C., Lin, M. L., & Yang, H. L. (2015). Zerumbone attenuates TGF-β1-mediated epithelial–mesenchymal transition via upregulated E-cadherin expression and downregulated Smad2 signalling pathways in non-small cell lung cancer (A549) cells. *Journal of Functional Foods*, *18*, 58–72. https://doi.org/10.1016/J.JFF.2015.06.058

Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C. B., & Rahu, N. (2016). Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? *Oxidative Medicine and Cellular Longevity*, *2016*. https://doi.org/10.1155/2016/7432797

Hwang, J., Youn, K., Ji, Y., Lee, S., Lim, G., Lee, J., Ho, C.-T., Leem, S.-H., & Jun, M. (2020). Biological and Computational Studies for Dual Cholinesterases Inhibitory Effect of Zerumbone. *Nutrients*, *12*(5). https://doi.org/10.3390/NU12051215

Hwang, S., Jo, M., Hong, J. E., Park, C. O., Lee, C. G., Yun, M., & Rhee, K.-J. (2019). Zerumbone Suppresses Enterotoxigenic Bacteroides fragilis Infection-Induced Colonic Inflammation through Inhibition of NF-κB. *International Journal of Molecular Sciences*, *20*(18). https://doi.org/10.3390/IJMS20184560

Ilari, S., Giancotti, L. A., Lauro, F., Dagostino, C., Gliozzi, M., Malafoglia, V., Sansone, L., Palma, E., Tafani, M., Russo, M. A., Tomino, C., Fini, M., Salvemini, D., Mollace, V., & Muscoli, C. (2020). Antioxidant modulation of sirtuin 3 during acute inflammatory pain: The ROS control. *Pharmacological Research*, *157*(May). https://doi.org/10.1016/j.phrs.2020.104851

Ilari, S., Giancotti, L. A., Lauro, F., Gliozzi, M., Malafoglia, V., Palma, E., Tafani, M., Russo, M. A., Tomino, C., Fini, M., Salvemini, D., Mollace, V., & Muscoli, C. (2020). Natural antioxidant control of neuropathic pain—exploring the role of mitochondrial sirt3 pathway. *Antioxidants*, *9*(11), 1–19. https://doi.org/10.3390/antiox9111103

Jaeschke, H., & Bajt, M. L. (2006). Intracellular signaling mechanisms of acetaminophen-induced liver cell death. *Toxicological Sciences*, *89*(1), 31–41. https://doi.org/10.1093/toxsci/kfi336

Jafariana, S., Ling, K.-H., Hassan, Z., Perimal-Lewis, L., Sulaiman, M. R., & Perimala, E. K. (2019). Effect of zerumbone on scopolamine-induced memory impairment

and anxiety-like behaviours in rats. *Alzheimer's & Dementia (New York, N. Y.)*, *5*, 637–643. https://doi.org/10.1016/J.TRCI.2019.09.009

Jalili-Nik, M., Sadeghi, M. M., Mohtashami, E., Mollazadeh, H., Afshari, A. R., & Sahebkar, A. (2020). Zerumbone Promotes Cytotoxicity in Human Malignant Glioblastoma Cells through Reactive Oxygen Species (ROS) Generation. *Oxidative Medicine and Cellular Longevity*, *2020*. https://doi.org/10.1155/2020/3237983

Jantan, I., Haque, M. A., Ilangkovan, M., & Arshad, L. (2019). Zerumbone from Zingiber zerumbet inhibits innate and adaptive immune responses in Balb/C mice. *International Immunopharmacology*, *73*, 552–559. https://doi.org/10.1016/J.INTIMP.2019.05.035

Jeon, M., Han, J., Nam, S. J., Lee, J. E., & Kim, S. (2016). Elevated IL-1β expression induces invasiveness of triple negative breast cancer cells and is suppressed by zerumbone. *Chemico-Biological Interactions*, *258*, 126–133. https://doi.org/10.1016/J.CBI.2016.08.021

Jiang, D., Rasul, A., Batool, R., Sarfraz, I., Hussain, G., Mateen Tahir, M., Qin, T., Selamoglu, Z., Ali, M., Li, J., & Li, X. (2019). Potential Anticancer Properties and Mechanisms of Action of Formononetin. *BioMed Research International*, *2019*. https://doi.org/10.1155/2019/5854315

Jorvig, J. E., & Chakraborty, A. (2015). Zerumbone inhibits growth of hormone refractory prostate cancer cells by inhibiting JAK2/STAT3 pathway and increases paclitaxel sensitivity. *Anti-Cancer Drugs*, *26*(2), 160–166. https://doi.org/10.1097/CAD.0000000000000171

June Yowtak, K., Kim, H. Y., Jigong Wang, H. K., Chung, K., & Chung, J. M. (2011). Reactive oxygen species contribute to neuropathic pain by reducing spinal GABA release. *Pain*.

Kabeer, F. A., Rajalekshmi, D. S., Nair, M. S., & Prathapan, R. (2017). Molecular mechanisms of anticancer activity of deoxyelephantopin in cancer cells. *Integrative Medicine Research*, *6*(2), 190. https://doi.org/10.1016/J.IMR.2017.03.004

Kalantari, K., Moniri, M., Moghaddam, A. B., Rahim, R. A., Ariff, A. Bin, Izadiyan, Z., & Mohamad, R. (2017). A Review of the Biomedical Applications of Zerumbone and the Techniques for Its Extraction from Ginger Rhizomes. *Molecules 2017, Vol. 22, Page 1645*, *22*(10), 1645. https://doi.org/10.3390/MOLECULES22101645

Kim, S., Lee, J., Jeon, M., Lee, J. E., & Nam, S. J. (2016). Zerumbone suppresses the motility and tumorigenecity of triple negative breast cancer cells via the inhibition of TGF-β1 signaling pathway. *Oncotarget*, *7*(2), 1544. https://doi.org/10.18632/ONCOTARGET.6441

Klein, W. L., Stine, W. B., & Teplow, D. B. (2004). Small assemblies of unmodified amyloid β-protein are the proximate neurotoxin in Alzheimer's disease. *Neurobiology of Aging*, *25*(5), 569–580. https://doi.org/10.1016/j.neurobiolaging.2004.02.010

Leung, W. S., Yang, M. L., Lee, S. S., Kuo, C. W., Ho, Y. C., Huang-Liu, R., Lin, H. W., & Kuan, Y. H. (2017). Protective effect of zerumbone reduces lipopolysaccharide-induced acute lung injury via antioxidative enzymes and Nrf2/HO-1 pathway. *International Immunopharmacology*, *46*, 194–200. https://doi.org/10.1016/J.INTIMP.2017.03.008

Li, Lei, Wu, X.-H., Zhao, X.-J., Xu, L., Pan, C.-L., & Zhang, Z.-Y. (2020). Zerumbone ameliorates behavioral impairments and neuropathology in transgenic APP/PS1 mice by suppressing MAPK signaling. *Journal of Neuroinflammation*, *17*(1). https://doi.org/10.1186/S12974-020-01744-1

Li, Liqing, Kong, L., & Song, H. (2017). The therapeutic effect of zerumbone on chronic gastritis via antioxidant mechanisms. *Experimental and Therapeutic Medicine*, *14*(3), 2505–2510. https://doi.org/10.3892/etm.2017.4795

Lingappan, K. (2017). NF-κB in Oxidative Stress. *Curr Opin Toxicol.*, *7*, 81–86. https://doi.org/10.1016/j.cotox.2017.11.002. NF-

Liu, W. Y., Tzeng, T. F., & Liu, I. M. (2016). Zerumbone, a bioactive sesquiterpene, ameliorates diabetes-induced retinal microvascular damage through inhibition of phospho-p38 mitogen-activated protein kinase and nuclear factor-κB pathways. *Molecules*, *21*(12). https://doi.org/10.3390/molecules21121708

Long, J. M., & Holtzman, D. M. (2019). Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell*, *179*(2), 312. https://doi.org/10.1016/J.CELL.2019.09.001

Lv, T., Zhang, W., & Han, X. (2018). Zerumbone suppresses the potential of growth and metastasis in hepatoma HepG2 cells via the MAPK signaling pathway. *Oncology Letters*, *15*(5), 7603. https://doi.org/10.3892/OL.2018.8335

Ma, S., Lei, Y., Zhang, L., & Wang, J. (2018). Effects of zerumbone on proliferation and apoptosis of esophageal cancer cells and on P53 and Bcl-2 expression levels. *Oncology Letters*, *16*(4), 4379. https://doi.org/10.3892/OL.2018.9184

Mittal, M., Siddiqui, M. R., Tran, K., Reddy, S. P., & Malik, A. B. (2014). Reactive Oxygen Species in Inflammation and Tissue Injury. *Antioxidants & Redox Signaling*, *20*(7), 1126. https://doi.org/10.1089/ARS.2012.5149

Nakamura, H., & Takada, K. (2021). Reactive oxygen species in cancer: Current findings and future directions. *Cancer Science*, 3945–3952.

Oladele, J. O., Oladiji, A. T., Oladele, O. T., & Oyeleke, O. M. (2021). Reactive Oxygen Species in Neurodegenerative Diseases: Implications in Pathogenesis and Treatment Strategies. In R. Ahmad, *Reactive Oxygen Species.* IntechOpen.

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., & Bitto, A. (2017). Oxidative Stress: Harms and Benefits for Human Health. *Oxidative Medicine and Cellular Longevity*, *2017*. https://doi.org/10.1155/2017/8416763

Rahman, H. S., Rasedee, A., How, C. W., Zeenathul, N. A., Chartrand, M. S., Yeap, S. K., Abdul, A. B., Tan, S. W., Othman, H. H., Ajdari, Z., Namvar, F., Arulselvan, P., Fakurazi, S., Mehrbod, P., Daneshvar, N., & Begum, H. (2015). Antileukemic effect of zerumbone-loaded nanostructured lipid carrier in WEHI-3B cell-induced murine leukemia model. *International Journal of Nanomedicine*, *10*, 1649. https://doi.org/10.2147/IJN.S67113

Rahman, H. S., Rasedee, A., Yeap, S. K., Othman, H. H., Chartrand, M. S., Namvar, F., Abdul, A. B., & How, C. W. (2014). Biomedical properties of a natural dietary plant metabolite, Zerumbone, in cancer therapy and chemoprevention trials. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/920742

Reid, G. A., Chilukuri, N., & Darvesh, S. (2013). Butyrylcholinesterase and the cholinergic system. *Neuroscience*, *234*, 53–68. https://doi.org/10.1016/J.NEUROSCIENCE.2012.12.054

Reyes-Gordillo, K., Shah, R., & Muriel, P. (2017). Oxidative Stress and Inflammation in Hepatic Diseases: Current and Future Therapy. *Oxidative Medicine and Cellular Longevity*, *2017*(ii). https://doi.org/10.1155/2017/3140673

Safakhah, H. A., Kor, N. M., Bazargani, A., Bandegi, A. R., Pourbadie, H. G., Khoshkholgh-Sima, B., & Ghanbari, A. (2017). Forced exercise attenuates neuropathic pain in chronic constriction injury of male rat: An investigation of oxidative stress and inflammation. *Journal of Pain Research*, *10*, 1457–1466. https://doi.org/10.2147/JPR.S135081

Salehi, B., Ata, A., Kumar, N. V. A., Sharopov, F., Ramírez-Alarcón, K., Ruiz-Ortega, A., Ayatollahi, S. A., Fokou, P. V. T., Kobarfard, F., Zakaria, Z. A., Iriti, M., Taheri, Y., Martorell, M., Sureda, A., Setzer, W. N., Durazzo, A., Lucarini, M., Santini, A., Capasso, R., … Sharifi-Rad, J. (2019). Antidiabetic Potential of Medicinal Plants and Their Active Components. *Biomolecules*, *9*(10). https://doi.org/10.3390/BIOM9100551

Samad, N. A., Abdul, A. B., Rahman, H. S., Rasedee, A., Ibrahim, T. A. T., & Keon, Y. S. (2017). Zerumbone Suppresses Angiogenesis in HepG2 Cells through Inhibition of Matrix Metalloproteinase-9, Vascular Endothelial Growth Factor, and Vascular Endothelial Growth Factor Receptor Expressions. *Pharmacognosy Magazine*, *13 (Suppl*(62), 179–188. https://doi.org/10.4103/pm.pm

Sehrawat, A., Arlotti, J. A., Murakami, A., & Singh, S. V. (2012). Zerumbone causes Bax and Bak-mediated apoptosis in human breast cancer cells and inhibits orthotopic xenograft growth in vivo. *Breast Cancer Research and Treatment*, *136*(2), 429. https://doi.org/10.1007/S10549-012-2280-5

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *1*(1). https://doi.org/10.1101/cshperspect.a006189

Shamoto, T., Matsuo, Y., Shibata, T., Tsuboi, K., Nagasaki, T., Takahashi, H., Funahashi, H., Okada, Y., & Takeyama, H. (2014). Zerumbone inhibits angiogenesis by blocking NF-κB activity in pancreatic cancer. *Pancreas*, *43*(3), 396–404. https://doi.org/10.1097/MPA.000000000000

0039

Shams, S. G. E., & Eissa, R. G. (2022). Amelioration of ethanol-induced gastric ulcer in rats by quercetin: implication of Nrf2/HO1 and HMGB1/TLR4/NF-κB pathways. *Heliyon*, *8*(10), e11159. https://doi.org/10.1016/j.heliyon.2022.e11159

Shoaib, M., Shah, I., Ali, N., Adhikari, A., Tahir, M. N., Shah, S. W. A., Ishtiaq, S., Khan, J., Khan, S., & Umer, M. N. (2017). Sesquiterpene lactone! a promising antioxidant, anticancer and moderate antinociceptive agent from Artemisia macrocephala jacquem. *BMC Complementary and Alternative Medicine*, *17*(1), 1–11. https://doi.org/10.1186/s12906-016-1517-y

Shyanti, R. K., Sehrawat, A., Singh, S. V., Mishra, J. P. N., & Singh, R. P. (2017). Zerumbone modulates CD1d expression and lipid antigen presentation pathway in breast cancer cells. *Toxicology in Vitro*, *44*, 74–84. https://doi.org/10.1016/J.TIV.2017.06.016

Sidahmed, H. M. A., Hashim, N. M., Abdulla, M. A., Ali, H. M., Mohan, S., Abdelwahab, S. I., Taha, M. M. E., Fai, L. M., & Vadivelu, J. (2015). Antisecretory, Gastroprotective, Antioxidant and Anti-Helicobcter Pylori Activity of Zerumbone from Zingiber Zerumbet (L.) Smith. *PLoS ONE*, *10*(3). https://doi.org/10.1371/JOURNAL.PONE.0121060

Su, C. C., Wang, S. C., Chen, I. C., Chiu, F. Y., Liu, P. L., Huang, C. H., Huang, K. H., Fang, S. H., Cheng, W. C., Huang, S. P., Yeh, H. C., Liu, C. C., Lee, P. Y., Huang, M. Y., & Li, C. Y. (2021). Zerumbone Suppresses the LPS-Induced Inflammatory Response and Represses Activation of the NLRP3 Inflammasome in Macrophages. *Frontiers in Pharmacology*, *12*(May), 1–12. https://doi.org/10.3389/fphar.2021.652860

Sulaiman, M. R., Perimal, E. K., Akhtar, M. N., Mohamad, A. S., Khalid, M. H., Tasrip, N. A., Mokhtar, F., Zakaria, Z. A., Lajis, N. H., & Israf, D. A. (2010). Anti-inflammatory effect of zerumbone on acute and chronic inflammation models in mice. *Fitoterapia*, *81*(7), 855–858. https://doi.org/10.1016/j.fitote.2010.05.009

Suzuki, H., Nishizawa, T., Tsugawa, H., Mogami, S., & Hibi, T. (2012). Oxidative Stress in Stomach Disorders. *J. Clin. Biochem. Nutr.*, *50*(1), 35–39. https://doi.org/10.1016/B978-0-12-819547-5.00005-5

Tavassolifar, M. j., Vodjgani, M., Salehi, Z., & Izad, M. (2020). The Influence of Reactive Oxygen Species in the Immune System and Pathogenesis of Multiple Sclerosis. *Autoimmune Desease*.

Truong, V. Van, Duy, T., Ngoc, T., Thi, N., & Minh, P. (2015). Synthesis and Anti-proliferative Activity of Novel Azazerumbone Conjugates with Chalcones Bioorganic & Medicinal Chemistry Letters Synthesis and anti-proliferative activity of novel azazerumbone conjugates with chalcones. *Bioorganic & Medicinal Chemistry Letters*, *25*(22), 5182–5185. https://doi.org/10.1016/j.bmcl.2015.09.069

Tsuboi, K., Matsuo, Y., Shamoto, T., Shibata, T., Koide, S., Morimoto, M., Guha, S., Sung, B., Aggarwal, B. B., Takahashi, H., & Takeyama, H. (2014). Zerumbone inhibits tumor angiogenesis via NF-κB in gastric cancer. *Oncology Reports*, *31*(1), 57–64. https://doi.org/10.3892/OR.2013.2842

Tzeng, T.-F., Liou, S.-S., Chang, C. J., & Liu, I.-M. (2013a). Zerumbone, a Natural Cyclic Sesquiterpene of Zingiber zerumbet Smith, Attenuates Nonalcoholic Fatty Liver Disease in Hamsters Fed on High-Fat Diet. *Evidence-Based Complementary and Alternative Medicine : ECAM*, *2013*. https://doi.org/10.1155/2013/303061

Tzeng, T.-F., Liou, S.-S., Chang, C. J., & Liu, I.-M. (2013b). Zerumbone, a tropical ginger sesquiterpene, ameliorates streptozotocin-induced diabetic nephropathy in rats by reducing the hyperglycemia-induced inflammatory response. *Nutrition & Metabolism*, *10*(1), 64. https://doi.org/10.1186/1743-7075-10-64

Tzeng, T.-F., Liou, S.-S., Tzeng, Y.-C., & Liu, I.-M. (2016). Zerumbone, a Phytochemical of Subtropical Ginger, Protects against Hyperglycemia-Induced Retinal Damage in Experimental Diabetic Rats. *Nutrients*, *8*(8). https://doi.org/10.3390/NU8080449

Vigneron, A., & Vousden, K. H. (2010). p53, ROS and senescence in the control of aging. *Aging (Albany NY)*, *2*(8), 471. https://doi.org/10.18632/AGING.100189

Wang, C., Zou, S., Cui, Z., Guo, P., Meng, Q., Shi, X., Gao, Y., Yang, G., & Han, Z. (2015). Zerumbone protects INS-1 rat pancreatic beta cells from high glucose-induced apoptosis through generation of reactive oxygen species. *Biochemical and Biophysical Research Communications*, *460*(2), 205–209. https://doi.org/10.1016/j.bbrc.2015.03.009

Wang, D., Li, Y., Cui, P., Zhao, Q., Tan, B. bo, Zhang, Z. dong, Liu, Y., & Jia, N. (2016). Zerumbone induces gastric cancer cells apoptosis: Involving cyclophilin A. *Biomedicine & Pharmacotherapy*, *83*, 740–745. https://doi.org/10.1016/J.BIOPHA.2016.07.034

Wang, M., Niu, J., Gao, L., Gao, Y., & Gao, S. (2019). Zerumbone inhibits migration in ESCC via promoting Rac1 ubiquitination. *Biomedicine & Pharmacotherapy*, *109*, 2447–2455. https://doi.org/10.1016/J.BIOPHA.2018.11.134

Wang, M., Niu, J., Ou, L., Deng, B., Wang, Y., & Li, S. (2019). Zerumbone Protects against Carbon Tetrachloride (CCl4)-Induced Acute Liver Injury in Mice via Inhibiting Oxidative Stress and the Inflammatory Response: Involving the TLR4/NF-κB/COX-2 Pathway. *Molecules*, *24*(10). https://doi.org/10.3390/MOLECULES24101964

Weng, H. Y., Hsu, M. J., Wang, C. C., Chen, B. C., Hong, C. Y., Chen, M. C., Chiu, W. T., & Lin, C. H. (2012). Zerumbone suppresses IKKα, Akt, and FOXO1 activation, resulting in apoptosis of GBM 8401 cells. *Journal of Biomedical Science*, *19*(1), 1–11. https://doi.org/10.1186/1423-0127-19-86

Wenhong, D., Jia, Y., Weixing, W., Xiaoyan, C., Chen, C., Sheng, X., & Hao, J. (2012). Zerumbone Attenuates the Severity of Acute Necrotizing Pancreatitis and Pancreatitis-Induced Hepatic Injury. *Mediators of Inflammation*, *2012*, 12. https://doi.org/10.1155/2012/156507

Xu, D.-P., Li, Y., Meng, X., Zhou, T., Zhou, Y., Zheng, J., Zhang, J. J., & Li, H. Bin. (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International Journal of Molecular Sciences*, *18*(1), 20–31. https://doi.org/10.3390/ijms18010096

Xu, M., Rui, D., Yan, Y., Xu, S., Niu, Q., Feng, G., Wang, Y., Li, S., & Jing, M. (2017). Oxidative Damage Induced by Arsenic in Mice or Rats: A Systematic Review and Meta-Analysis. *Biological Trace Element Research*, *176*(1), 154–175. https://doi.org/10.1007/S12011-016-0810-4

Yan, H., Ren, M. Y., Wang, Z. X., Feng, S. J., Li, S. I., Cheng, Y. I., Hu, C. X., Gao, S. Q., & Zhang, G. Q. (2017). Zerumbone inhibits melanoma cell proliferation and migration by altering mitochondrial functions. *Oncology Letters*, *13*(4), 2397–2402. https://doi.org/10.3892/ol.2017.5742

Zainal, N. S., Gan, C. P., Lau, B. F., Yee, P. S., Tiong, K. H., Abdul Rahman, Z. A., Patel, V., & Cheong, S. C. (2018). Zerumbone targets the CXCR4-RhoA and PI3K-mTOR signaling axis to reduce motility and proliferation of oral cancer cells. *Phytomedicine*, *39*, 33–41. https://doi.org/10.1016/J.PHYMED.2017.12.011

Zhang, S., Liu, Q., Liu, Y., Qiao, H., & Liu, Y. (2012a). Zerumbone, a Southeast Asian ginger sesquiterpene, induced apoptosis of pancreatic carcinoma cells through p53 signaling pathway. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 12–15. https://doi.org/10.1155/2012/936030