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ARTICLE

ASSOCIATION OF *ZINGIBER AROMATICUM* VAL. WITH ZERUMBONE AND ITS BIOLOGICAL ACTIVITY: A LITERATURE REVIEW

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ABSTRACT

The main objective of this article is to explore the available classified information on *Zingiber aromaticum* Val. Rhizome and its active compound, Zerumbone. Throughout history, this plant has been utilized to treat various ailments such as abdominal disorders, cough, anemia, malaria, jaundice, arthritis, and infections. Recently, Zerumbone, a sesquiterpene compound found in the rhizomes, has gained attention for its biological activity. This article reviews the current research on the pharmacological activities of *Z. aromaticum* Val. Rhizome, with a specific focus on its active component, Zerumbone. This review found that the antioxidant and antiinflammatory effects of Zerumbone play a role in the pharmacological effects exhibited by *Z. aromaticum*, such as antidiabetic, antiparasitic, anti-hyperlipidemia, antianxiety, and antiaging effects. Additionally, the correlation between the biological activity of Zerumbone and the pharmacological activity of Z. aromaticum extract is discussed. This review provides a valuable reference for developing and further researching *Zingiber aromaticum* Val. and Zerumbone in medical treatments.

Keywords: Zerumbone; *Zingiber aromaticum*; *Zingiber aromaticum* Rhizome

АБСТРАКТ

Основной целью данной статьи является изучение доступной классифицированной информации о Zingiber aromaticum Val. Rhizome и его активном соединении Zerumbone. На протяжении всей истории человечества это растение использовалось для лечения различных заболеваний, таких как абдоминальные расстройства, кашель, анемия, малярия, желтуха, артрит и инфекции. Недавно Zerumbone, сесквитерпеновое соединение, найденное в корневищах, привлекло внимание своей биологической активностью. В данной статье рассматриваются современные исследования фармакологической активности Z. aromaticum Val. Rhizome, с особым акцентом на его активный компонент - зерумбон. Обзор показал, что антиоксидантное и противовоспалительное действие зерумбона играет определенную роль в фармакологических эффектах Z. aromaticum, таких как антидиабетический, антипаразитарный, антигиперлипидемический, противотревожный и антивозрастной эффекты. Кроме того, обсуждается корреляция между биологической активностью зерумбона и фармакологической активностью экстракта Z. aromaticum. Данный обзор представляет собой ценное пособие для разработки и дальнейшего изучения Zingiber aromaticum Val. и Zerumbone в медицине.

Ключевые слова: Zerumbone; Zingiber aromaticum; Zingiber aromaticum Rhizome

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INTRODUCTION

The Zingiberaceae family, which includes the Zingiber genus, is widely found in Asia, tropical regions, and South America. Among the plants in this family, *Zingiber aromaticum* Val., commonly known as fragrant ginger, also called Lempuyang wangi, stands out for its distinct aroma and is often employed for medicinal purposes.

Indigenous to the forests of Indonesia, this aromatic herb has a long history of traditional use in treating various conditions. Some of the ailments traditionally treated with *Z. aromaticum* Val. include jaundice, cholecystopathy, cold, whooping cough, , anorexia, cholera, arthritis, malaria, colitis, anemia, abdominal pain, and rheumatism [1,2]. Additionally, in Malaysia, aromatic lempuyang is utilized to address worm infections and abdominal ailments [3].

Zerumbon (2,6,9-humulatriene-8-one) is one of the main active compounds in *Z. aromaticum*. This compound is also found *in Curcuma heneyana* [4], *Zingiber zerumbet*, *Zingiber montanum*, *Zingiber amaricans*, *Zingiber otensii*, *Curcuma rubbescens*, *Cheilocostus speciosus*, *Alpinia galanga*, *Boesenbergia quangngaiensis*, *Amomum gagnepainii*, and *Cyperus rotundus* [5].

Some research studies have focused on exploring the phytochemical and pharmacological activities of *Z. aromaticum* Val., particularly its root. Meanwhile, Zerumbone has been extensively studied for its pharmacological activities. Some literature reviews have also discussed its anticancer activity. However, a review specifically elucidating the correlation between the pharmacological activities of *Z. aromaticum* and Zerumbone has yet to be established. This review explores the relationship between the pharmacological effects of *Z. aromaticum* and the biological activities exhibited by its active compound, Zerumbone.

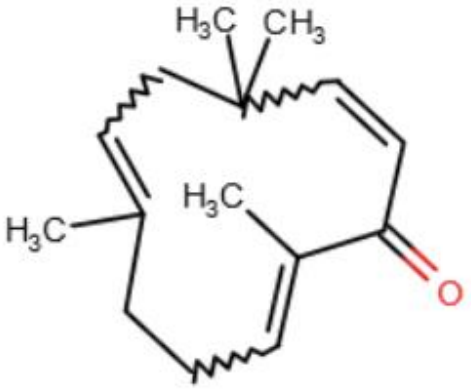

Figure 1. Chemical structure of Zerumbone

MATERIAL AND METHODS

This literature review comprehensively searched Zingiber aromaticum and Zerumbone research within the past ten years (2013-2023), utilizing databases such as PubMed, Scopus, ScienceDirect, and Google Scholar. The keywords used in the search were "*Zingiber aromaticum*,"; and "Zingiber aromaticum Rhizome" and "Zerumbone". The data were then identified, analyzed, and selected based on their relevance to the topic. The inclusion criteria for the journals included the pharmacological activity of *Zingiber aromaticum* and Zerumbone.

(A) **(B)**

Figure 2. *Zingiber aromaticum* plant (A) and its rhizome (B)

RESULT

Phytochemical compounds of *Z. aromaticum* rhizome

The phytochemical content of *Z. aromaticu*m in various extraction solvents and extraction methods is presented in the table below.

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Table 1. The phytochemical compound isolated from *Zingiber aromaticum.*

Sample	Extraction Methods	Phytochemical Compounds	Ref.
Methanol extract	N/A	50 chemical compound components, including: zerumbone (main compound, 36–49%), acetic acid, alpha humulene, humulene oxide, beta-eudesmol, beta-selinene, linalool, 12-oxabicyclo, caryophilene oxide, 3-octadecyne, hexadecanoic acid, dan 3-octyne 5-methyl	2
Methanol fraction of water extract	Column chromatography combined with TLC preparative	(2R,3R, 5R)-2,3-epoxy-6,9-humuladien-5-ol-8-one); (2R,3S,5R)-2,3-epoxy-6,9-humuladien-5-ol-8-one; zerumbone ; zerumbone epoxide; (5R)-2,6,9-humulatrien-5-ol-8-one; kaempferol-3-O-(2, 4-di-O-acetyl-a-L-rhamnopyranoside); kaempferol-3- O-(3,4-di-O-acetyl-a-L-rhamnopyranoside); kaempferol-3-O-(2-O-acetyl-a-L-rhamnopyranoside); kaempferol-3-O-(3-O-acetyl-a-L-rhamnopyranoside); kaempferol-3-O-(4-O-acetyl-a-L-rhamnopyranoside); kaempferol-3-O-(2,3-di-O-acetyla-L-rhamnopyranoside); kaempferol-3-O-(2,3,4-triO-acetyl-a-L-rhamnopyranoside); kaempferol-3-O-a-L-rhamnopyranoside); kaempferol-3-O-methyl ether; kaempferol-3,40 -di-O-methyl ether; trans-6-shogaol; (S)-6-gingerol	6
Ethanol extract	Maceration	Flavonoid, saponin dan tanin	7
Essential oil	Ultrasonic assisted extraction (30 min, room temperature)	α-Tricyclene; α-Pinene; α-Phellandrene; α-Fenchene; Camphene; β-Pinene; β-Phellandrene; 3-Carene; (+)-3-Carene; D-Limonene; β-Myrcene; trans β-Ocimene γ-Terpinene; β-Ocimene; Linalool; Bornyl acetate; Isobornyl acetate; α-Terpineol; Eucalyptol; o-Cymene; Terpinen-4-ol; endo-Borneol; (+)-4-Carene; β-Elemene; Caryophyllene; Humulene; α-Campholenal; (+)-2-Bornanone	8
Essential oil	Steam distillation	Linaool L; Camphor; 3-Terpinen-4-ol; Trans-Caryopyllene; α-Humulene; 4-Isoprophenyl-4,7-dimethyl-1- oxa-spiro-(2.5) octane; Dihydronopol; Cyclohexane; (-)-Caryophyllene oxide; β-Selinene; Isogeraniol; Cyclohexene; Methyl chavicol; β-Eudesmol; Zerumbone	9

The ethanol extract of *Z.aromaticum* showed inhibitory activity against α-glucosidase, an enzyme that breaks down carbohydrates into sugars and is involved in developing type 2 diabetes. The activity of the α-glucosidase inhibitor was measured using a spectrophotometer UV-Vis by observing the release of yellow p-nitrophenol at 400 nm. The IC_{50} of the ethanol extract of *Z. aromaticum* was 182.3 µg/mL [7].

Another study by Tunnisa F. et al. (2022) showed that 80 % methanol extract of Z. *aromaticum* has the highest inhibitory activity of α-glucosidase (82.0 ± 3.1%) from 11 species from Zingiberaceae. Ten compounds had α-glucosidase inhibitory activity in *Z. aromaticum*, according to the study's data analysis results using orthogonal projection to the least square analysis, including eucalyptol, α-phellandrene, α-pinene, camphene, humulene, D-limonene, linalool, o-cymene, terpinen-4-ol, and Fenchone [8].

In a study conducted by Saifudin et al., it was demonstrated that the methanol extract of Z. *aromaticum* exhibited antidiabetic activity by inhibiting protein tyrosine phosphatase 1B (PTB1B). Notably, (5R)-2,6,9-humulatrien-5-ol-8-one displayed strong inhibitory activity, with 86.0% inhibition observed at a 10 µg/mL concentration. In contrast, zerumbone only exhibited a 15.9% inhibition rate [6].

Antimicrobial

The disc-diffusion assay was utilized to examine the antimicrobial activity of the

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methanol extract from the rhizome and in vitro plantlets of *Z. aromaticum*. The methanol extract from the mother plant and in vitro plantlets displayed minimum inhibitory concentration values of 625 µg/mL and 1250 µg/mL against E. coli and P. aeruginosa, respectively. The in vitro plantlets also exhibited a minimum inhibitory concentration of 625 µg/mL against both bacteria. Analysis of the compounds using GC/MS showed the presence of 2-methoxy-4-vinylphenol, 1,3-propanediol, α-Humulene, and limonene dioxide in the in vitro plantlets of *Z. aromaticum* [10].

The antimicrobial properties of the diethyl ether extract from Z. aromaticum Val. were assessed using the TLC bioautographic method. The liquid dilution method was employed, and the minimum inhibitory value was determined. The findings indicated that the extract's minimum lethal concentration was 0.2% for *Bacillus subtilis* and *Salmonella typhi*, and 0.4% for *Staphylococcus epidermidis* and *Vibrio sp*. [11].

Antimalaria

In vitro studies on the antimalarial activity against *Plasmodium falciparum* parasites were conducted using methanol extract of *Z. aromaticum* and its isolated compound, Zerumbone. The study results revealed IC50 values of 74.13 µg/mL and 97.39 µg/mL, indicating the potency of the extracts and compound in inhibiting the growth of the malaria parasite [12].

Antihyperlipidemia

The test on the 96% ethanol extract of *Z. aromaticum* showed inhibitory activity against HMG-CoA reductase with an IC50 value of 88.1 ± 2.2 ppm, compared to Simvastatin with an IC50 value of 6.8 ± 0.1 ppm [13]. Although the IC50 value is higher than that of Simvastatin, it does not rule out the possibility that the pure active compound from the Extract has more significant activity in inhibiting the activity of the HMG-CoA reductase enzyme.

Antiaging

Apriliani, A. et al. conducted a study to test the inhibitory effect of tyrosinase, an enzyme involved in the pigmentation process, on 20 plants from the Zingiberaceae family. The inhibition of this enzyme is expected to decrease hyperpigmentation related to aging. The study utilized alpha-arbutin as a positive control in the *in vitro* tyrosinase inhibition test and the Extract was acquired by maceration with 96% ethanol, fractionation with n-hexane, and ethyl acetate. The results showed that the *Z. aromaticum* rhizome extract in 96% ethanol had a tyrosinase inhibitory activity of 14.68 ± 1.23% [14].

Antioxidant

According to Tunnisa et al. (2022), the Zingiberaceae family, which includes *Z.aromaticum* Val, has been found to exhibit antioxidant activity. Three different assays were conducted to determine the antioxidant activity: DPPH radical scavenging activity, FRAP assay, and CUPRAC assay. Among the 12 species examined, *Z. aromaticum* Val. had the highest total flavonoid content (80.1 7.1 mg QE/g) and a high total phenolic content (38.3 ± 0.1 mg GAE/g). Additionally, it demonstrated significant antioxidant activity with FRAP, CUPRAC, and DPPH values of 21.7 0.6 mol TE/g, 170.0 9.4 mol TE/g, and 341.3 1.8 mol TE/g, respectively [8].

A similar study was performed by Manuhara, Y.S.W., et al. (2022). Using the DPPH method, the antioxidant study was evaluated, and the total phenolic and flavonoid contents were also determined from the 10 plant Zingiberaceae family. The methanol extract of *Z. aromaticum* Val. showed IC50 315,00 µg/mL, TPC 563.67 ± 68.35 mg GAE/g) and TFC 97.67 ± 7.39 QE/g [4].

Antianxiety

The anxiolytic activity test of 96% ethanol extract of *Z. aromaticum* extract showed significant differences ($p<0.05$) in antianxiety activity compared to the negative control at a medium dose (425 mg/KgBW) and high dose

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(850 mg/KgBW) in the Hole board test, as evidenced by an increase in the number of head tips. In the open field test, the results did not show any differences with the negative control. In the elevated plus maze test, there was an increase in the average time spent in the center area, which was significantly different from the control group in the high-dose group (850 mg/KgBW)[15].

Pharmacological Activities of Zerumbone

The latest research on the pharmacological activity of zerumbone is presented in the table below.

Table 2. Pharmacology Activity of Zerumbone

Pharmacology Activity	*In vitro/in vivo*	Animal model/ cell Line/ Methods	Result	Ref.
Antidiabetic	*In vivo*	Streptozotocin-induced diabetic retinopathy rat	Decrease plasma glucose Reduce dilated and retinal vessel leakage Reduce retinal leukostasis Decrease retinal TNF-α, IL-1β, COX-2 and iNOS Decrease retinal VCAM-1 and ICAM-1 Decrease VEGF and PKC-β expression Decrease retinal p38 MAP and NF-κB activation	16
	In vivo	Streptozotocin-induced diabetic nephropathy rat	Decrease plasma glucose Decrease urine protein, Scr, and BUN Improve mesangial glomerulus expansion Reduce renal ICAM-1, MCP-1, IL-1β, IL-6, TNF-α, TGF-β1 and fibronectin expression Decrease renal p38	17
Antimicrobial	*In vivo*	ETBF colonized mice	Activate *Bacteroides fragilis to* become a part of the normal flora	18
	In vitro	MRSA (NCTC 13277) cell	Disrupt membrane cell via depolarization Improve membrane permeability	19
	In vitro	Disc agar diffusion assay	Inhibit grow , *B. subtilis, S. aureus, P. vulgaris* and *E. coli*	20
	In vitro	*H. pylori* Urease Activity Test	Dimerize, trimerize or tetramerize urease A and urease B	21
Antiprotozoa	*In vitro*	*Leishmania donovani* AG83	Increase ROS and lipid peroxides	22
Antihyperlipidemia	*In vivo*	New Zealand rabbit	Reduce aorta plaque size Improve profil lipid profile Decrease MDA level and increase SOD	23
Antiinflammatory	*In vitro*	LPS-induced inflammatory-J774A.1 cells	Decrease PGE 2, NO, IL-1β, IL-6, Reduce COX-2 and iNOS expression and ERK phosphorylation Inhibit NF-κB adn NLRP3 activity	21
Wound healing	*In vivo*	Diabetic wound rat	Reduce IL-6, IL-1β, TNF-α, hydroxyproline Reduce CAT and SOD	24

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Gastroprotective	*In vivo*	Sprague-Dawley male rat	Increase NP-SH and GSH Decrease MDA level Increase mucus secretion	25
	In vivo	Sprague-Dawley male rat	Relieve red, swelling, and erosion of gastric mucosal Upregulate HO-1 and Nrf-2 expression Increase SOD, CAT, and GSH level Decrease MDA level	26
Hepatoprotective	*In vivo*	CCl4-induced acute liver injury mice	Increase SOD, GSH-Px, GSH Decrease MDA Decrease IL-6, TNF-α TLR4, NF-κB p-p65, and COX-2	27
	In vivo	Paracetamol-induced acute hepatotoxicity rat	Decrease ALT, AST, and total hepatic protein Decrease neutrophil count	28
Antiphotoaging and dermatoprotective	*In vitro*	Human skin fibroblast cell	Reduce ROS Inhibit MMP-1 expression and Collagen-III degradation Inhibition c-Fos and c-Jun Phosphorylations Increase Nrf2 expression	29
Antianxiety	In vivo	Open field test (OFT) Elevated plus maze test (EPM) Morris water maze test (MWM)	Increased total activity, stereotype, and total distance traveled (OFT) Reduce the number of entry, percentage of time spent, and percentage of entry to the open arms (EPM) Increased escape latency time, reduced number of entry and percentage of time spent in the target quadrant (MWM)	14

ALT= alanine aminotransferase ; AST = aspartate aminotransferase ; COX-2= cyclooxygenase-2; CAT = catalase; LPS = lipopolysaccharide; MRSA= *Methicillin-Resistant Staphylococcus aureus*; H. Pylori= *Helicobacter pylori*; ETBF = *Enterotoxigenic Bacteroides fragilis*; GSH= glutathione; SOD =superoxide dismutase; HO-1= heme oxygenase-1 ; GSH-Px = glutathione peroxidase ; ICAM-1 = Intercellular Adhesion Molecule-1; VCAM-1 = Vascular Cell Adhesion Molecule-1 ; IL-6= interleukin-6 ; IL-1β = interleukin-1β ; i-NOS= inducible Nitric Oxide Synthase; MDA= malondialdehyde; NF-κB = nuclear factor-kappa B ; NP-SH= non-protein sulfhydryl; Nrf-2= nuclear factor E2-related factor 2; TNF-α = Tumor necrosis factor-alpha ; TLR4= Toll-like receptor 4;

Antimicrobial.

According to Lallo et al, Zerumbon has been found to exhibit growth inhibition activity against *Mycobacterium tuberculosis* when grown on Lowenstein Jensen slant agar medium, with significant inhibitory percentages of 90%, 88%, 86%, and 85% at concentrations of 0.5%, 0.1%, 0.05%, and 0.01%, respectively [30].

DISCUSSION

The chemical content of *Z. aromaticum* rhizome is highly dependent on the extraction process, including the extraction method and solvent used, as seen in **Table 1**.

The study results showed that *Z aromaticum* rhizome contains flavonoids, tannins, saponins, and essential oil, with the main component being zerumbone, α-humulene, and kaempferol.

Zerumbone ($C_{15}H_{23}O$), depicted in **Figure 1.**, is a monocyclic sesquiterpene composed of three isoprene units, totaling 15 carbon atoms. It is volatile and non-polar. Due to its characteristics, steam distillation is commonly used to extract essential oils containing zerumbone from *Z. aromaticum* rhizome. In addition, extraction using organic solvents such as methanol and ethanol is also viable.

The study's findings suggest that the Extract derived from Z. *aromaticum* rhizome possesses various pharmacological properties, such as antidiabetic, antimicrobial, antimalaria, antihyperlipidemic, antioxidant,

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and antiaging. Meanwhile, zerumbone has several biological activities such as antidiabetic, antimicrobial, antiparasite, antioxidant, antiinflammatory, renoprotective, retinoprotective, hepatoprotective, dermatoprotective and wound healing.

The mechanism of inhibition against enzymes involved in insulin regulation, such as alpha-glucosidase and PTB1B, represents two mechanisms of antidiabetic effects demonstrated by the *Z. aromaticum* extract. Meanwhile, zerumbone decreased blood glucose levels in streptozocin-induced diabetes rats by inhibiting p38 MAPK phosphorylation and NF-κB activation [16]. Those studies support the development of *Z. aromaticum* extract and zerumbone for type 2 diabetes therapy.

The antimicrobial study indicated that *Z. aromaticum* extract can inhibit the growth of gram-negative bacteria (*E. coli, S. typhi, Vibrio sp, P. aeruginosa*) and gram-positive bacteria (*B. subtilis*, *S. epidermidi*s, and *MRSA*) [10,11]. Similarly, zerumbone demonstrates antibacterial activity against gram-negative bacteria (*E. coli*, *P. vulgaris*, *Bacteroides fragilis*) and gram-positive bacteria (*S. aureus, B. subtilis*, *MRSA*, *H. pylori*). The antibacterial mechanism of zerumbone on MRSA is reported to occur through the disruption of the cell membrane via membrane depolarization and increased membrane permeability [19].

The empirical use of *Z. aromaticum* in antimalarial therapy has been scientifically proven through its methanol extract, but studies on Zerumbone have yet to be conducted. Studies on Zerumbone as an antiparasitic agent have been performed on *L. donovani*, demonstrating its mechanism of action through apoptosis induction via oxidative stress and lipid peroxidation [22].

The ethanolic Extract of *Z. aromaticum* exhibits antihyperlipidemia activity through the inhibition of the HMGCoA reductase. On the other hand, the hypolipidemic effect of zerumbone is attributed to its antioxidant properties. A study on rabbits induced with atherosclerosis through a high-cholesterol diet showed that zerumbone could prevent the formation of atherosclerotic plaques, as indicated by the reduction of oxidative stress biomarkers and increased SOD activity, as well as a decrease in MAD levels. Additionally, there was an improvement observed in the blood lipid profile [23].

The antiinflammatory effect of zerumbone is closely related to its pharmacological activities, such as renoprotective, retinoprotective, hepatoprotective, dermatoprotective and wound healing. In conditions of hyperglycemia, p38 MAPK activation contributes to the development of diabetic nephropathy and retinopathy. Excessive activation of p38 MAPK can increase the expression of ICAM-1 and MCP-1, leading to increased infiltration of monocytes and macrophages into the local tissue, such as the retina and kidney. The activation of macrophages enhances the expression of inflammatory cytokines such as IL-1, IL-6, and TNF-α. A study on streptozotocin-induced diabetic nephropathy in rats also indicated that zerumbone has renoprotective effects, as demonstrated by improvements in renal function parameters (serum creatinine, BUN) and reduction of the inflammatory response through inhibition of the p38 pathway [17]. In another study using the streptozotocin-induced diabetic retinopathy rat model, zerumbone exhibited prevention of diabetic retinal vascular diseases by inhibiting inflammation in the P38 and NF-κB pathways [16]. In CCl_4-induced acute liver damage rats, zerumbone reduces IL-6 and TNF- in blood and hepatocytes and enhances the inflammatory response in vitro and in vivo via the TLR4/NF-B/COX-2 signaling pathway[27]. The antiinflammatory and antioxidant properties of Zerumbone have a significant impact on the healing of wounds in diabetic rats. The decrease in pro-inflammatory cytokines (IL-6, IL-1, and TNF-) and rise in antioxidant enzymes (CAT and SOD) confirm this.[24].

Oxidative stress can trigger the emergence of various diseases, such as gastric ulcers,

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atherosclerosis, and aging. Phenolic compounds, including flavonoids, contribute to the antioxidant activity of plants. Studies on several plants from the Zingiberaceae family showed a correlation between TPC and TFC levels and antioxidant activity[4]. The gastroprotective ability of zerumbone is closely associated with its antioxidant activity, which is demonstrated by reducing lipid peroxidation as indicated by decreased MDA levels and increased endogenous antioxidants (GSH) in rats [25,26]. Similarly, in a study conducted by Hemn et al. on rabbits, zerumbone increased SOD levels [23]. In addition to enhancing endogenous antioxidant levels, zerumbone can also regulate transcription factors such as Nrf2 and HO-1, which play a role in oxidative processes at the cellular level. The Extract of *Z. aromaticum* as a tyrosinase inhibitor supports its activity as an antiaging agent [14]. At the same time, Zerumbone plays a role in exhibiting dermo protective activity by inhibiting Nrf2 activation. This was demonstrated through testing using Ultraviolet A (UVA) irradiation in human skin fibroblast cells [29].

In addition to the positive results on anxiety tests with *Z. aromaticum* extract[15], an in vivo study on rats using three different methods by Jafarian et al. revealed that administering of Zerumbone at the dosage of 1 mg/kg BW and 10 mg/kg BW improved anxiousness behavior in scopolamine-induced anxiety in rats. The mechanism of action is believed to be associated with $GABA_A$ receptor activity [31].

Although Zerumbone has excellent potential for development as a new drug, it faces limitations such as limited water solubility, inadequate absorption, or low bioavailability. As a result, several further studies have started to develop drug delivery systems to improve Zerumbone bioavailability, such as inclusion complexes, encapsulation, and nano-technology-based drug delivery systems[5, 32].

CONCLUSION

Based on existing studies, there is a correlation between the biological activity of Zerumbone and the pharmacological activity of *Z. aromaticum* extract, particularly in the antioxidant and antiinflammatory effects exhibited by Zerumbone. Both can potentially be developed for treating diseases such as diabetes, infectious diseases, hyperlipidemia, atherosclerosis, anxiety, and aging. However, considering the current study, further studies are necessary to ensure its safety and efficacy. Furthermore, exploring different formulations to transform them into potential new drug candidates is essential.

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DECLARATIONS

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