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Review

Bioactive Compounds from *Zingiber montanum* and Their Pharmacological Activities with Focus on Zerumbone

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Abstract: The genus *Zingiber* consists of about 85 species and many of these species are used as food, spices, and medicines. One of the species, *Zingiber montanum* (J. Koenig) Link ex A. Dietr. is native to Southeast Asia and has been extensively used as traditional medicines and food. The aim of this review was to collect and critically analyze the scientific information about the bioactive compounds and pharmacological activities of *Z. montanum* with focus on one of the main components, zerumbone (ZER). Various studies have reported the analysis of volatile constituents of the essential oils from *Z. montanum*. Similarly, many phenylbutanoids, flavonoids and terpenes were also isolated from rhizomes. These essential oils, extracts and compounds showed potent antimicrobial, anti-inflammatory and antioxidant activities among others. Zerumbone has been studied widely for its anticancer, anti-inflammatory, and other pharmacological activities. Future studies should focus on the exploration of various pharmacological activities of other compounds including phenylbutanoids and flavonoids. Bioassay guided isolation may result in the separation of other active components from the extracts. *Z. montanum* could be a promising source for the development of pharmaceutical products and functional foods.

Keywords: *Zingiber montanum*; *Zingiber cassumunar*; zerumbone; anticancer; anti-inflammatory

1. Introduction

The Zingiberaceae family consists of about 50 genera and more than 1500 species which are distributed all over the world and most of them are found in Asia, Central

America, and Africa. Plants belonging to various genera of Zingiberaceae family are used as food, spice and medicines in many parts of the world [1]. One of the must studied genera of this family, *Zingiber* consists of about 85 species [2] and *Zingiber officinale* Roscoe. is the most commonly cultivated and used species. There are many other important species of *Zingiber* which are widely used as spices, food supplements and as crude drug in traditional medicines such as *Zingiber montanum* (J. Koenig) Link ex A. Dietr.

Zingiber montanum (Figure 1, Syns: *Amomum cassumunar* (Roxb.) Donn, *Amomum montanum* J. König, *Amomum xanthorhiza* Roxb. ex Steud., *Cassumunar roxburghii* Colla, *Jaegera montana* (J. König) Giseke, *Zingiber anthorrhiza* Horan., *Zingiber cassumunar* Roxb., *Zingiber cassumunar* var. *palamauense* Haines, *Zingiber cassumunar* var. *subglabrum* Thwaites, *Zingiber cliffordiae* Andrews, *Zingiber luridum* Salisb., *Zingiber montanum* (J. König ex Retz.) Theilade, *Zingiber purpureum* Roscoe, *Zingiber purpureum* var. *palamauense* (Haines) K.K. Khanna, *Zingiber xantorrhizon* Steud.) [3] is commonly known as "Banada" in Bangladesh, "Phlai" in Thailand, "Jangliadrak" in India, and "Bangle" in Malaysia. It is reported to be native to Southeast Asia and has been extensively planted in Thailand, Malaysia, and Indonesia [4]. The rhizomes of this plant are used in traditional medicines for the treatment of constipation, dyspepsia, gastritis, stomach bloating and stomach-ache. Various parts of *Z. montanum* are used in Thailand as daily diet [5], while the rhizome is used in the as vermifuge in Malaysia, and applied for abscesses, colic, diarrhea, fever and intestinal disorders. In Northeast India, the rhizome paste was reported to be used in the treatment of dyspepsia and stomach bloating [6,7].

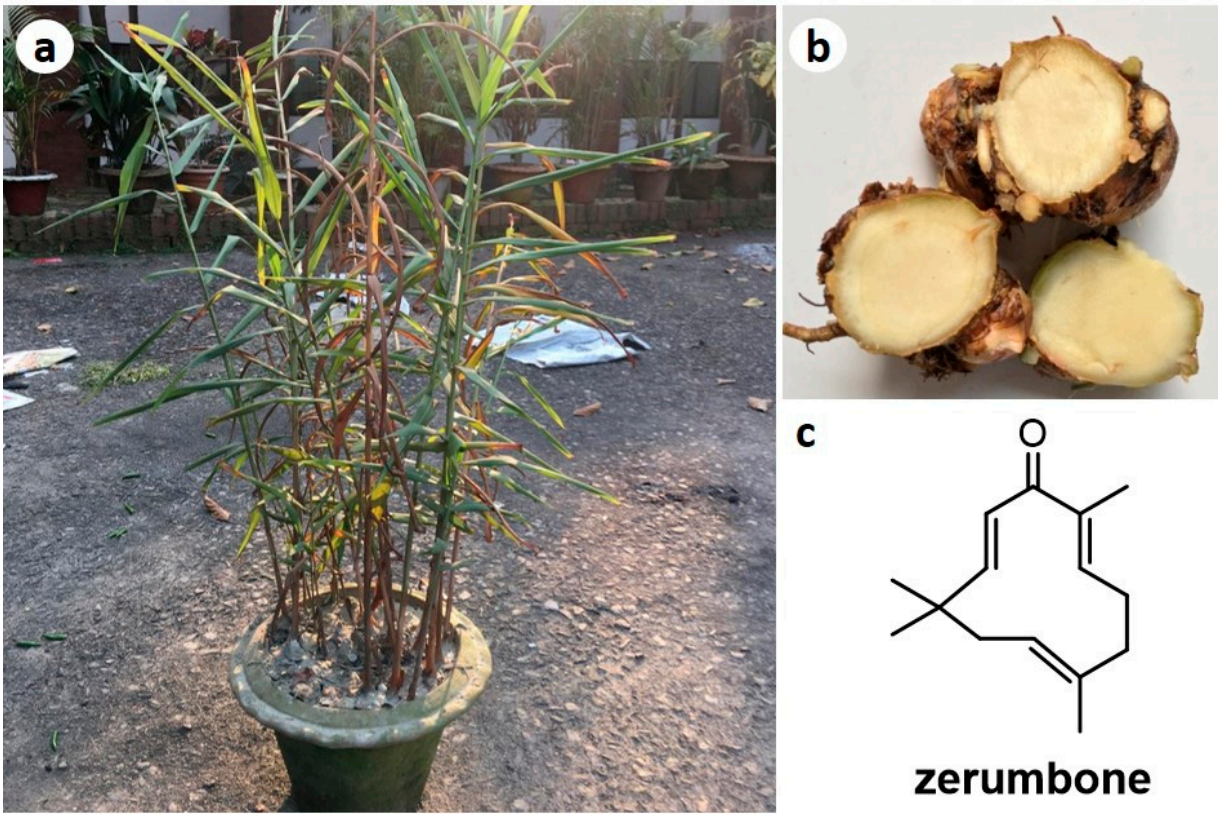

Figure 1. Photographs of *Zingiber montanum* plant (**a**) and rhizomes (**b**), and chemical structure of zerumbone (ZER) (**c**).

Zerumbone (ZER) (Figure 1c), a sesquiterpenoid, is one of the major compounds in the essential oils and rhizomes of *Z. montanum* [4]. In recent years, it has received much attention among researchers as a potent antitumor and anti-inflammatory compound [8–15]. *Z. montanum* being extensively used in traditional medicine but very few investigations were found for their bioactive constituents and mechanism based pharmacological actions. Thus, the main aim of this review is to scientifically analyze the available scientific information about the chemical constituents and pharmacological activities of extracts and compounds isolated form *Zingiber montanum* along with the various activities of ZER.

2. Traditional Uses of *Zingiber montanum*

Zingiber montanum rhizomes are traditionally used for the treatment of asthma, cough, colic, constipation, dyspepsia, diarrhea, inflammation, sprains, stomach bloating and wounds [4,16–31]. It is also used as a tonic and appetizer. It is given along with black pepper in the treatment of cholera and also used as a vermifuge [32]. The rhizome is also used to prepare cleansing solution for skin diseases [33]. The rhizome oil is applied in the treatment of swelling [25]. Rhizomes are also used as anti-inflammatory, antifungal, and antibacterial agent [19,34].

3. Bioactive Compounds

Phytochemical investigation of rhizomes of *Z. montanum* revealed the presence of numerous bioactive chemical constituents such as alkaloids, saponins, tannins, flavonoids, terpenoids, phenolic compounds, phlobatannins, steroids, and glycosides [35,36]. The gas chromatography-mass spectrometry (GC-MS) analysis of essential-oil constituents of fresh rhizomes of *Z. montanum* reported the presence of various compounds such as α-thujene, α-pinene, β-mycrene, α-terpinene, *p*-cymene, β-phellandrene, γ-terpinene, sabinene, sabinene hydrate, terpinolene, terpinen-4-ol, terpinyl acetate, β-sesquiphellandrene, and 4-(3,4-dimethoxyphenyl)but-1,3-diene (DMPBD) which were identified on the basis of retention time and comparison with standard compounds [37]. In another study, GC-MS analysis of essential oils of *Z. montanum* revealed the presence of sixty four constituents in leaf oil and thirty two constituents in the rhizome oil [38]. The major active chemical constituents of the rhizome oil were sabinene (27–34%), γ-terpinene (6–8%), α-terpinene (4–5%), terpinen-4-ol (30–5%), DMPBD (12–19%), triquinacene 1,4-bis (methoxy) (26.5%), (Z)-ocimene (22.0%), and β-phellandrene (1.0–4.4%) [35,37–39]. Whereas, the major constituents in leaf oil were sabinene (15.0%), β-pinene (14.3%), caryophyllene oxide (13.9%) and caryophyllene (9.5%) [38]. Kantoyos and Paisooksantivatana analyzed the chemical constituents in the essential oils obtained from ten *Zingiber* species in Thailand including *Z. montanum*. Among the studied plant species, the oil obtained from *Z. montanum* rhizomes had highest yield ($0.89 \pm 0.14\%$, v/w) and also showed highest total curcuminoid content (2.633% w/w) and terpinen-4-ol content ($14.5 \pm 2.59\%$) [37]. Structures of some of the main compounds in essential oils are given in Figure 2.

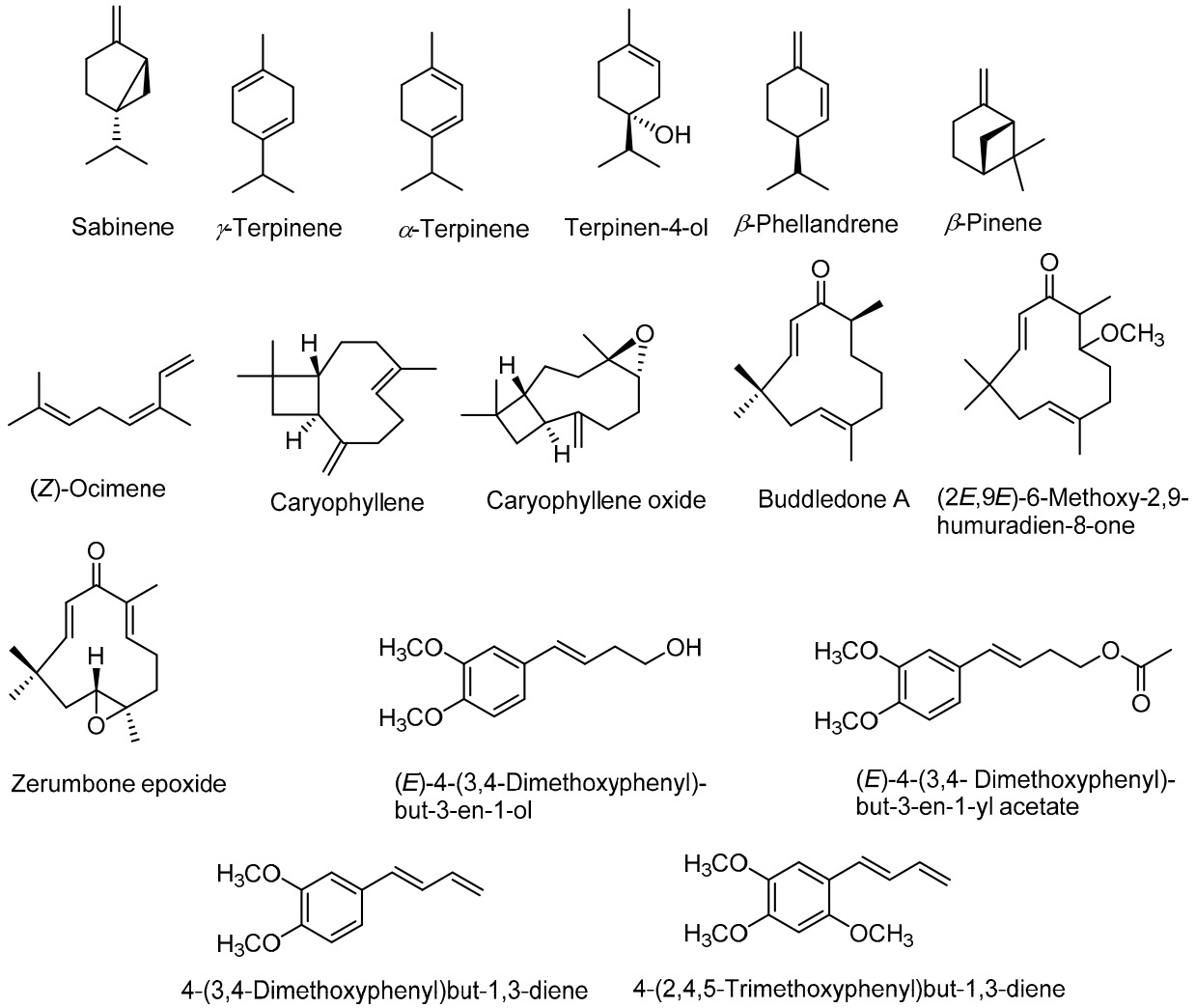

Figure 2. Structures of major constituents of leaf and rhizome essential oils.

There are also various reports on the compounds isolated from the extracts including non-volatile compounds from the rhizomes. They include mainly phenylbutanoids (Figure 3), flavonoids (Figure 4), terpenes and many other compounds. A list of some of these compounds is provided in Table 1.

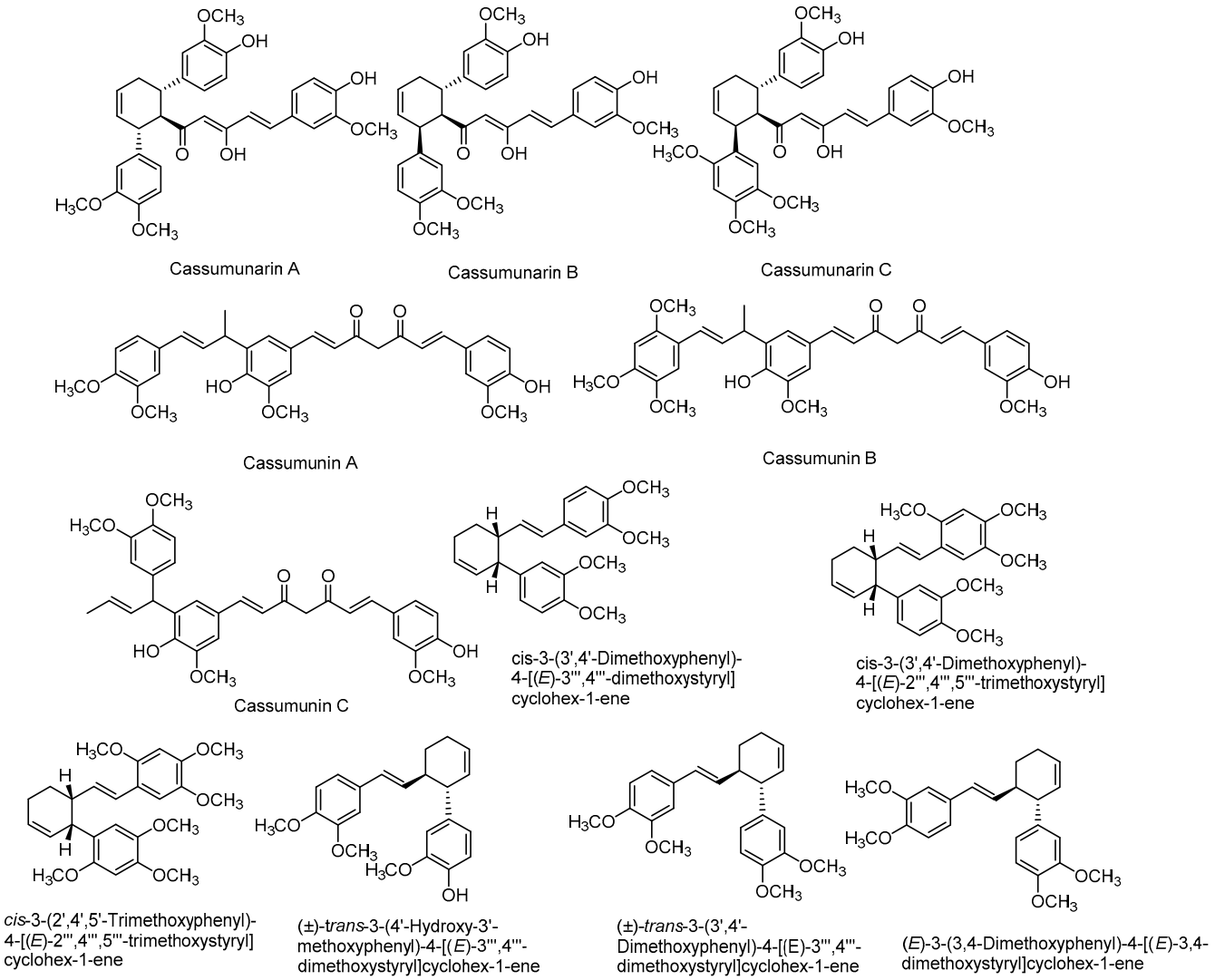

Figure 3. Structures of some major compounds isolated from the extracts of rhizomes of *Z. montanum*.

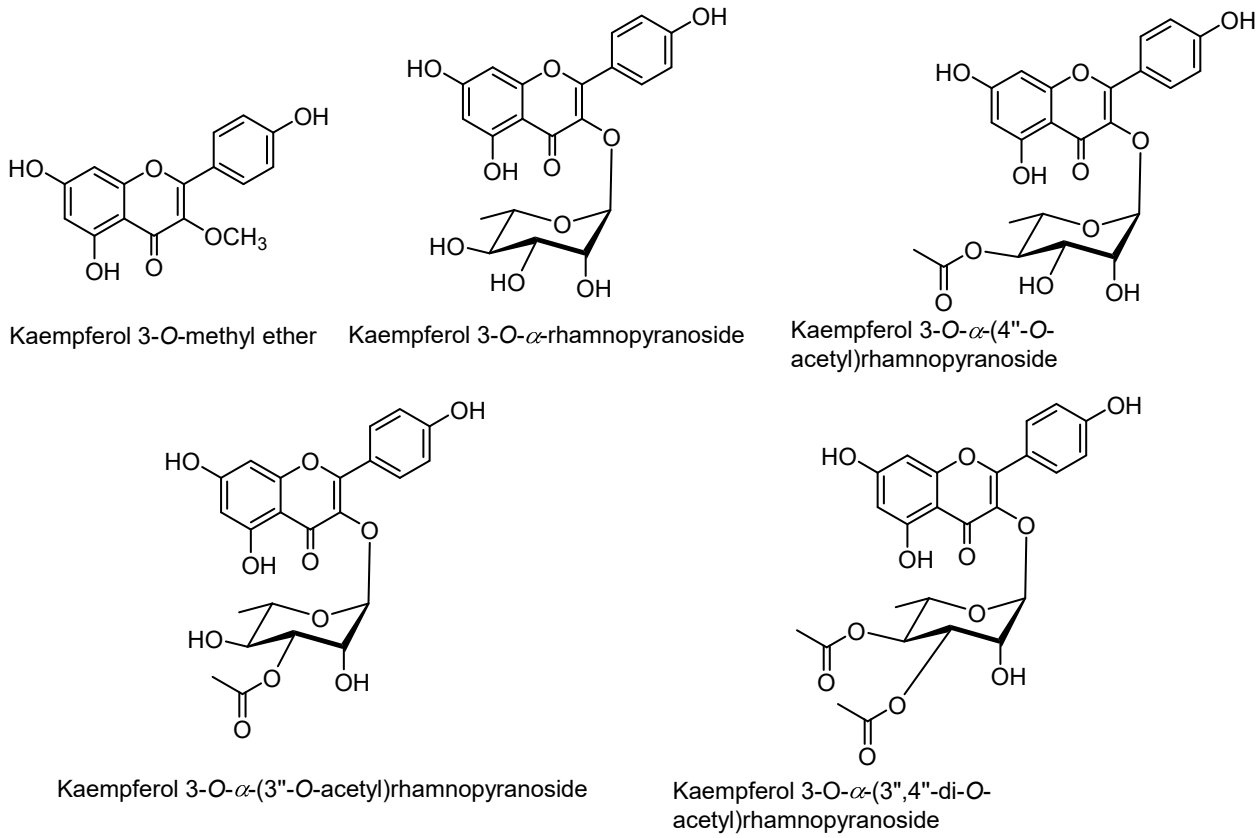

Figure 4. Structures of kaempferol derivatives isolated from the extracts of rhizomes of *Z. montanum.*

Table 1. List of compounds isolated from the rhizomes of *Z. montanum.*

Extraction Solvent	Compounds	References
Hexane extract	(*E*)-4-(3,4-dimethoxyphenyl)-but-3-en-1-ol (*E*)-4-(3,4-Dimethoxyphenyl)-but-3-en-1-yl acetate (*E*)-3-(3,4-Dimethoxyphenyl)-4-[(*E*)-3,4-dimethoxystyryl]cyclohex-1-ene	[40]
Hexane extract	4-(3′,4′-Dimethoxyphenyl)but-3-ene 4-(3′,4′-Dimethoxyphenyl)but-1,3-diene 4-(2′,4′,5′-Trimethoxyphenyl)but-3-ene 4-(2′,4′,5′-Trimethoxyphenyl)but-1,3-diene (*E*)-4-(3′,4′-Dimethoxy)but-3-en-1-yl palmitate (*E*)-4-(3′,4′-Dimethoxyphenyl)but-3-en-l-y1 palmitate 3,4-Dimethoxybenzaldehyde 2,4,5-trimethoxybenzaldehyde	[41]
Chloroform extract	*cis*-3-(2′,4′,5′-Trimethoxyphenyl)-4-[(*E*)-2‴,4‴,5‴-trimethoxystyryl] cyclohex-1-ene *cis*-3-(3′,4′-Dimethoxyphenyl)-4-[(*E*)-3‴,4‴-dimethoxystyryl]cyclohex-l-ene *cis*-3-(3′,4′-Dimethoxyphenyl)-4-[(*E*)-2‴,4‴,5‴-trimethoxystyryl]cyclohex-1-ene *cis*-3-(2′,4′,5′-Trimethoxyphenyl)-4-[(*E*)-3‴,4‴-dimethoxystyryl]cyclohex-1-ene (*E*)-4-(3′,4′-Dimethoxypheny1)but-3-en-1-o1 (*E*)-4-(3′,4′-Dimethoxypheny1) but-3-en-1-yl acetate 8-(3′,4′-Dimethoxypheny1)-2-methoxynaphtho-1,4-quinone	[27,42]

Table 1. *Cont.*

Extraction Solvent	Compounds	References
Chloroform extract	*cis*-4[(*E*)-3,4-Dimethoxylstyryl]-3-(2,4,5-trimethoxyphenyl)cyclohex-1-ene *trans*-3-(3,4-Dimethoxyphenyl)-4[(*E*)-3,4-dimethoxystyryl]-cyclohex-1-ene *trans*-3-(3,4-Dimethoxyphenyl)-4-[(*E*)-2,4,5-trimenthoxystyryl] cyclohex-1-ene (*E*)-4-(3,4-Dimethoxyphenyl) but-3-en-1-yl palmitate (*E*)-1-(3,4-Dimethoxyphenyl) but-1-ene (*E*)-1-(3,4-Dimethoxyphenyl) butadiene 2-Methoxy-8(2,4,5-trimethoxyphenyl)-naphtho-1,4-quionone Curcumin Vanillic acid Vanillin Veratric acid Terpinen-4-ol	[42]
Toluene extract	Cassumunaquinone 1 Cassumunaquinone 2 Alflabene Cassumunene 2-(3,4-Dimethoxystyryl) ethanol	[43,44]
Methanol extract	(*E*)-1-(3,4-Dimethoxyphenyl)but-1-ene (*E*)-1-(3,4-Dimethoxyphenyl)butadiene Zerumbone	[45]
Acetone extract	Cassumunin A Cassumunin B Cassumunin C	[46]
Acetone extract	Cassumunarin A Cassumunarin B Cassumunarin C	[47]
Acetone extract	(±)-*trans*-3-(2,4,5-Trimethoxyphenyl)-4-[(*E*)-3,4-dimethoxystyryl]-cyclohexene (±)-*cis*-1,2-Bis[(*E*)-3,4-dimethoxystyryl]-cyclobutane (±)-*cis*-3-(3,4-Dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl]-cyclohexene (±)-*trans*-3(3,4-Dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl]-cyclohexene	[48]
Acetone extract	(*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-1-yl acetate (*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-2-en-1-ol (*E*)-2-Hydroxy-4-(3,4-dimethoxyphenyl)but-3-en-1-ol (*E*)-2-Methoxy-4-(3,4-dimethoxyphenyl)but-3-en-1-ol (*E*)-4-(3,4-Dimethoxyphenyl)but-3-en-1-ol (*E*)-4-(3,4-Dimethoxyphenyl)but-3-en-1-yl acetate (*E*)-3-Hydroxy-1-(3,4-dimethoxyphenyl)but-1-ene	[49]
Hexane extract	(*E*)-4-(3′,4′ Dimethoxyphenyl)but-3-enyl acetate *cis*-3-(3′,4′-Dimethoxyphenyl)-4-[(*E*)-3,‴,4‴-dimethoxystyryl]cyclohex-l-ene *cis*-3-(3′,4′-Dimethoxyphenyl)-4-[(*E*)-2‴,4‴,5‴-trimethoxystyryl]cyclohex-1-ene *cis*-3-(2′,4′,5′-Trimethoxyphenyl)-4-[(*E*)-2‴,4‴,5‴-trimethoxystyryl]cyclohex-l-ene (*E*)-4-(3′-4′-dime-thoxyphenyl)but-3-en-l-ol	[50]

Table 1. *Cont.*

Extraction Solvent	Compounds	References
Ethanol extract	(*E*)-4-(3′,4′-dimethoxyphenyl)but-3-enyl acetate (*E*)-4-(3′,4′-dimethoxyphenyl)but-1,3-diene	[51]
Methanol extract	Phlain I Phlain II Phlain III Phlain IV Phlain V Phlain VI 3,4-Dimethoxybenzaldehyde 2,4,5-Trimethoxybenzaldehyde (*E*)-1-(3,4-Dimethoxyphenyl)buta-1,3-diene (*E*)-1-(2,4,5-Trimethoxyphenyl)buta-1,3-diene (*E*)-4-(3,4-Dimethoxyphenyl)but-3-en-1-ol (*E*)-4-(3,4-Dimethoxyphenyl)but-3-enyl acetate (*E*)-1-(3,4-Dimethoxyphenyl)but-1-ene (*E*)-1-(2,4,5-Trimethoxyphenyl)but-1-ene (±)-*cis*-3-(3,4-Dimethoxyphenyl)-4-[(*E*)-3,4-dimethoxystyryl]cyclohex1-ene (±)-cis-3-(2,4,5-Trimethoxyphenyl)-4-[(*E*)-2,4,5-trimethoxystyryl]cyclohex-1-ene Cassumunaquinone 1 Cassumunaquinone 2 (-)-*β*-Sesquiphellandrene Curcumin Vanillic acid *β*-Sitosterol	[52]
Methanol extract	Cassumunol A Cassumunol B Cassumunol C Cassumunol D Cassumunol E Cassumunol F Cassumunol G Cassumunol H	[53]
Methanol extract	(±)-*trans*-3-(4′-Hydroxy-3′-methoxyphenyl)-4-[(*E*)-3‴,4‴-dimethoxystyryl]cyclohex-1-ene (±)-*trans*-3-(3,4-Dimethoxyphenyl)-4-[(*E*)-3,4-dimethoxystyryl]cyclohex-1-ene 4-(3,4-Dimethoxyphenyl)but-1,3-diene 4-(2,4,5-Trimethoxyphenyl)but-1,3-diene	[54]
Chloroform extract	(*E*)-4-(3,4-Dimethoxy-phenyl)but-3-en-1-*O*-*β*-D-glucopyranoside (±)-*trans*-3-(3,4-Dimethoxyphenyl)-4-[(*E*)-3,4-dimethoxystyryl]cyclohex-1-ene (±)-*trans*-3-(4-Hydroxy-3-methoxyphenyl)-4-[(*E*)-3,4-dimethoxystyryl]cyclohex-1-ene 4-(2,4,5-Trimethoxyphenyl)-but-1,3-diene, 4-(3,4-Dimethoxyphenyl)but-1,3-diene (*E*)-4-(3,4-Dimethoxyphenyl)but-3-en-1-ol (*E*)-4-(3,4-Dimethoxyphenyl)but-3-en-1-yl acetate	[55]

Table 1. *Cont.*

Extraction Solvent	Compounds	References
Hexane extract	Zerumbone Zerumbol Buddledone A Furanodienone Germacrone Borneol Camphor	[20]
Chloroform extract	(*E*)-8(17),12-labdadiene-15,16-dial Camphor	[20]
Methanol extract	Zerumbone Kaempferol 3-*O*-methyl ether Kaempferol 3-*O*-*α*-rhamnopyranoside Kaempferol 3-*O*-*α*-(4″-*O*-acetyl)rhamnopyranoside Kaempferol 3-*O*-*α*-(3″-*O*-acetyl)rhamnopyranoside Kaempferol 3-*O*-*α*-(3″,4″-di-*O*-acetyl)rhamnopyranoside	[4]

4. Pharmacological Activities of *Z. montanum* Extracts and Compounds

Various pharmacological activities such as antimicrobial, anti-inflammatory, antioxidant, antihistaminic, smooth muscle relaxant, insecticidal activities are reported for the essential oils, extracts and some isolated compounds of *Z. montanum*. Some of these activities are discussed in detail in following sections.

4.1. Anti-Inflammatory Activity

The hexane extract of *Z. montanum* showed remarkable inhibitory effect on carrageenan-induced rat paw edema, acetic acid-inducing writhing reaction in mice and yeast-triggered hyperthermia in rats [56]. Moreover, phenylbutanoids have been reported as active constituents for anti-inflammatory activities [45]. Sabinene and terpinene-4-ol from essential oil of *Z. montanum* significantly reduced nuclear factor-kappa B (NF-κB) protein expression in human leukemic monocyte lymphoma cells and interleukin-6 (IL-6) secretion in lipopolysaccharide (LPS) stimulated mice macrophage (RAW264.7) [57]. Methyl t-butyl ether (MTBE) and methanol extracts of *Zingiber* were effective to inhibit LPS induced in vitro production of prostaglandin E_2 (PGE_2) and TNF-α in human promonocytic U937 cells [58]. The methanol extract and phenylbutanoids of *Z. montanum* rhizome showed inhibitory effects on the production of NO from LPS induced peritoneal macrophages from mouse [52]. Methanol extract and its fractions (petroleum ether, hexane and aqueous) of *Z. montanum* showed anti-inflammatory activity in carrageenan-induced edema in rats, and acetic acid-induced vascular permeability and writhing test in mice [45].

4.2. Antifungal Activity

Jantan et al. reported that the *Z. montanum* rhizome oil at a dose of 0.75 mg/disc showed significant fungicidal activity against five dermatophytes fungi (*Trichophyton mentagrophytes*, *T. rubrum*, *Microsporum canis*, *M. nanum* and *Epidermophyton floccosum)* and three filamentous fungi (*Aspergillus niger*, *A. fumigatus* and *Mucor* sp.) [59]. Another study reported that the essential oil of the rhizome showed antifungal activity against *Thanetophorus cucumeris* [60]. *Z. montanum* exhibited high activity against the yeasts namely *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, *Candida albicans*, *C. tropicalis*, *C. glabrata* [59]. Tripathi et al. reported the essential oils of *Z. montanum* at 500 mg/L showed 100% growth inhibition of fruit fungus *Botrytis cinerea* [61].

4.3. Antioxidant Activity

Many studies have demonstrated the antioxidant properties of *Z. montanum*. Extract from *Z. montanum* exhibited potent antioxidant activity hydroxyl radical (OH) scavenging assay [62]. Anastasia et al. reported the antioxidant activities of different fractions of *Z. montanum* by using 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydrogen peroxide (H_2O_2), β-carotene bleaching assays. Among different fractions, chloroform fraction showed highest antioxidant activities in DPPH radical scavenging assay, hexane fraction showed highest activity in H_2O_2 assays and ethyl acetate fraction in β-carotene bleaching assay [63]. Masuda et al. studied the antioxidant activity of cassumunins A, B and C isolated from *Z. montanum* rhizomes acetone extract using a thiocyanate method which demonstrated that all cassumunins at a dose of 2.7 μM inhibited accumulation of linoleic acid hyperoxide [64]. Bua-in and Paisooksantivatana reported the antioxidant activity of the extracts obtained from the rhizomes of *Z. montanum* collected from various localities in Thailand [65].

4.4. Antibacterial Activity

Z. montanum essential oil showed potent antibacterial activity against a number of Gram-positive and Gram-negative bacteria. Compared to methanolic extract, chloroform extract showed significant antimicrobial activity against a wide range of pathogens [66]. The rhizomes of *Z. montanum* are reported to be rich in essential oil effective against a range of pathogenic bacteria including *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella paratyphi*, *S. typhi* and *Shigella flexneri* [27]. *Z. montanum* oil showed potent antimicrobial activity against seventy-four microbial strains with most potent activity against bacteria as such *Bacillus subtilis*, *E. coli*, and *Salmonella typhi* evaluated by disc-diffusion broth dilution method [19]. Boonyanugomol et al. reported significant antimicrobial activity of the essential oil of *Z. montanum* against Gram-negative *Acinetobacter baumannii* strains by agar disc-diffusion tests [67]. Sesquiterpenes, monoterpenes and diterpenes from *Z. montanum* showed various degrees of antimicrobial action against *B. cereus*, *Staphylococcus aureus*, *E. coli*, and *Pseudomonas aeruginosa* [68].

4.5. Analgesic and Antipyretic Activity

Plai cream, a water in oil emulsion prepared from the essential oil of rhizomes of *Z. montanum*, was reported to reduce the delayed onset of muscle soreness in healthy volunteers [30,69]. Strong antipyretic action of *Z. montanum* hexane extract was observed in yeast induced hyperthermia rats and analgesic activity was observed on acetic acid-induced writhing response in mice [56]. In another study, strong analgesic activity was observed in hot plate method compared to the standard pentazocine in case of chloroform and dichloromethane extract of *Z. montanum* [70].

4.6. Antiulcer Activity

Al-Amin et al. evaluated the antiulcer activity of methanol extract of *Z. montanum* in mice and it showed 62.0% and 83.1% inhibition of stomach lesions induced by 1N hydrochloric acid (HCl) at doses of 200 mg/kg and 400 mg/kg, respectively. The major compound isolated from the extract i.e., zerumbone also showed potent antiulcer activity in ethanol and indomethacin induced gastric lesions in mice [16]. Another study reported that different concentration of rhizome extracts of *Z. montanum* showed significant antiulcer activity in comparison with control group in aspirin-induced rat model [71].

4.7. Anti-Allergic Activity

Ethanolic and aqueous extracts of *Z. montanum* exhibited the most potent anti-allergic activity in antigen induced beta hexosaminidase release in RBL-2H3 cell lines [72]. Capsules prepared from *Z. montanum* inhibited wheal and flare responses (Type 1 allergic reaction) induced by the mite skin prick test in allergic rhinitis patients [73].

4.8. Cytotoxicity Activity

Zulkhairi et al. reported the cytotoxicity activity of different extracts and compounds from rhizomes in human T-acute lymphoblastic leukemia cancer cells (CEMss) and human cervical cancer cells (HeLa) [74]. Crude methanolic extract of *Z. montanum* rhizomes showed significant cytotoxic activity in NIH 3T3 fibroblast cell line [65].

4.9. Other Activities

Dulpinijthmma et al. reported that *Z. montanum* capsule had remarkable role in the treatment of asthma by reducing the bronchial hyperresponsiveness [75]. Crude ethanolic *Z. montanum* extracts showed potent inhibitory effect on phorbol 12-myristate 13-acetate (PMA) induced mucous producing gene (MUC2, MUC5AC) as well as its protein expression in epithelial cell via inhibition of extracellular signal-regulated kinase pathway [76]. Dichloromethane extract from the rhizome of *Z. montanum* showed significant mosquito larvicidal activity [77]. Kato et al. reported the neutrophilic activity of phenylbutanoid constituents [17]. Okonogi et al. reported that essential oil showed moderate butyrylcholinesterase inhibitory [78].

5. Biological Activities of Zerumbone (ZER)

Zerumbone was initially isolated in 1960 from *Z. zerumbet* [79] and structurally characterized in 1965 [80]. Other than *Z. zerumbet* [81–84], it has been reported as one of the main constituents from *Z. montanum* [4,16,20,85]. It is also reported from many other species such as *Z. aromaticum* [84], *Z. spectabile* [86]. Zerumbone is widely studied for its various pharmacological activities such as such as anticancer, anti-inflammatory, antioxidant, antimicrobial, anti-ulcer, hepatoprotective activities among others [8,87–90]. These activities are explained in detail in following sections.

5.1. Anticancer Activity

Cancer is one of the leading causes of death worldwide [91]. Various studies have evaluated the anticancer potential of zerumbone. It was assessed against HeLa cell line and interestingly it showed a selective inhibition of HeLa cells proliferation (IC_{50} of 14.2 ± 0.5 µmol/L) via enhancement of cellular uptake compared to the normal cell line L929 [92]. Moreover, Rosa and co-workers revealed the anticancer mechanism of ZER on three cell lines including HeLa, B16F10 and undifferentiated Caco-2 cell lines. It was shown that ZER altered the total lipid and fatty acid profile in cancer cells, inducing marked changes in the phospholipid/cholesterol ratio [93]. In addition, the anticancer activity was assessed on Jurkat cells, human T cell leukemia, and it was found that ZER-pendant derivatives showed antiproliferative effects (IC_{50} values as low as 1–10 µM for most derivatives) [94]. A recent study reported that ZER inhibited cell migration of human esophageal squamous cancer by suppressing Rac1 expression, which is achieved through promoting Rac1 ubiquitination and degradation [95]. Wide number of studies had reported the in vivo, in vitro and in silico anticancer activities of ZER. Herein, an in vivo study showed that ZER significantly controls the growth of tumor and metastasis in BALB/c female mice injected with 4T1 (6-thioguanine resistant cell line) to spontaneously produce highly metastatic tumor [96]. Sithara et al. reported the anticancer activity of ZER against colorectal cancer cells, where they showed that ZER activates caspase 3, caspase 8, and caspase 9. ZER resulted in cell cycle arrest at the G2/M phase [97]. Similarly, other study reported induction of apoptosis in hepatoma HepG2 cells by ZER [98]. Eid and co-workers attempted to explore the underlying mechanism of ZER against breast cancer using in silico study. Since estrogen mediates several pathophysiological signaling pathways associated with cancer progression, the author had selected estrogen as a target for breast cancer and found that the promising molecular interaction, binding interaction, and stability of ZER and estrogen receptor-β (ERβ) suggests ZER as lead compound for breast cancer [99]. More details of these activities are given in Table 2.

Table 2. Anticancer activities of zerumbone (ZER).

Experimental Models	Results and Possible Mechanisms	Reference
HeLa cells	ZER selectively inhibited the proliferation of HeLa cells and also enhanced the anti-proliferative activity of anticancer agents vinblastine and paclitaxel.	[92]
HeLa cells	ZER stimulated the apoptosis.	[100]
Non-small cell lung cancer (NSCLC) A549 cells	ZER showed suppression of OPN induced cell invasion through inhibition of FAK/AKT/ROCK pathway.	[101]
NSCLC cells	ZER induceed mitochondrial apoptosis and enhanced the susceptibility to cisplatin.	[102]
DU145 prostate cancer cells	ZER exerted anticancer effects against hormone refractory DU145 prostate cancer cells mediated through the inhibition of aberrant signaling axis of IL-6/JAK2/STAT3.	[103]
Triple negative breast cancer (TNBC) cells	ZER supressed IL-1β induced cell invasion.	[104]
HCT-116 and SW48 cells	ZER exerted antimetastatic effects through inhibition of FAk/PI3k/NF-κB-uPA signaling pathway.	[105]
P-338D1 and HL-60 cells and Splenocytes from CDF1 mice	ZER inhibited the growth of P-338D1 and HL-60 cells and prolonged the life of P-338D1-bearing CDF1 mice.	[106]
PANC-1 cells	ZER induced apoptosis through p53 signal pathway.	[107]
Breast cancer (MCF-7) cells	Cytotoxicity of ZER against estrogen receptor positive breast cancer (MCF-7) cells was significantly increased through co administration with TP5-iRGD peptide.	[108]
CEM-ss cells	ZER showed apoptotic activity on T-acute lymphoblastic leukemia.	[109]
PC-3 and DU-145, two human hormonerefractory prostate cancer (HRPC) cell lines	ZER inhibited tubulin assembly and induced a crosstalk between ER stress and mitochondrial insult, leading to apoptosis and autophagy in HRPCs.	[110]
HCT-116 and SW-48 cells	ZER reduces the risk of CRC progression by suppressing the β-catenin pathway via miR-200.	[111]
Jurkat cells	ZER conjugated with salicylic acid and benzoic acid derivates inhibited the growth of human T-cell lymphoid Jurkat cells.	[94]
Esophageal squamous cell carcinomas (ESCC)	ZER inhibited cell migration of human esophageal squamous cancer by suppressing Rac1 expression through promoting Rac1 ubiquitination and degradation.	[95]
EC-109 cells	ZER inhibited the proliferation and induced apoptosis of esophageal cancer EC-109 cells by upregulating the mRNA expression of P53 and downregulating the mRNA expression of Bcl-2.	[112]
Canine mammary gland tumor (CMT) adenocarcinoma primary cell line.	ZER loaded into nanostructured lipid carrier (NLC) exerted CMT cell death via regulation of Bcl-2 and Bax gene expressions and caspase activation.	[9]
Colorectal cancer cells (SW480)	ZER activated caspase 3, caspase 8, and caspase 9 and resulted in cell cycle arrest at the G2/M phase	[97]
Human colonic adenocarcinoma cell lines (LS174T, LS180, COLO205, and COLO320DM)	ZER inhibited the proliferation of LS174T, LS180, COLO205, and COLO320DM cell lines.	[113]
SKBR3 breast cancer cells	ZER supressed EGF-induced phosphorylation of STAT3.	[114]
HCC1806 cells	ZER suppressed TGF-β1-induced FN, MMP-2, and MMP-9 expression.	[115]
HepG2 cells	ZER induced apoptosis in hepatoma HepG2 cells.	[98]
HepG2 cells	ZER inhibited the proliferation, and invasion and migration of hepatoma cells.	[116]
Laryngeal carcinoma cells (Hep-2)	ZER arrested Hep-2 proliferation at S and G2/M phases and induced cell death.	[117]

Table 2. *Cont.*

Experimental Models	Results and Possible Mechanisms	Reference
BALB/c female mice	ZER controled the growth of tumor and metastasis via delayed progression of cancer cell cycle and apoptosis.	[96]
Male ICR mice	ZER effectively suppressed mouse colon and lung carcinogenesis through multiple modulatory mechanisms of growth, apoptosis, inflammation and expression of NFκB and HO-1.	[118]
Female Balb/c mice	ZER induced apoptosis in cervical tissues from female Balb/c mice treated prenatally with diethylstilboestrol.	[119]
Caov-3 and HeLa cells	ZER inhibited cancer cell growth through the induction of apoptosis and arrested cell cycle at G2/M phase.	[120]
Female BALB/c Mice	Combination of ZER and cisplatin modulated the serum level of interleukin 6 in mice with cervical intraepithelial neoplasia.	[121]
HeLa cells	ZER caused prominent growth retardation of HeLa cells.	[122,123]
HepG2 cells	ZER increased apoptosis in HepG2 cells by up-regulating pro-apoptotic Bax protein and suppressing anti-apoptotic Bcl-2 protein expression.	[124]
MCF-7 and MDAMB-231cells	ZER inhibited the viability of MCF-7 and MDA-MB-231 cells	[125]
HepG2 cells	Highly soluble inclusion complex of ZER-hydroxypropyl-β-cyclodextrin induced apoptosis of HepG2 via Caspase8/BH3 interacting-domain death agonist cleavage switch and modulating Bcl2/Bax ratio.	[12]
HepG2, human umbilical vein endothelial cells (HUVECs)	ZER inhited prolieration and migration of HepG2 cells and inhibited angiogenesis, and expression of matrix metalloproteinase-9, vascular endothelial growth factor (VEGF) and VEGF receptor proteins in HUVECs cell line.	[126]
MDA-MB-231, MCF-7, and MCF-10A cells	ZER induced G2/M phase cell cycle arrest and Bax/Bak mediated apoptosis in human breast cancer cells, and also retarded the growth of MDA-MB-231 xenografts in vivo.	[127]
MCF-7 and MDA-MB-231 cells	ZER treatment resulted in increased Notch2 cleavage accompained by Persenlin-1 protein expression.	[88]
Human PaCa cell lines BxPC-3 and MIA PaCa-2	ZER blocked the PaCa-associated angiogenesis through the inhibition of NF-κB and NF-κB dependent proangiogenic gene products.	[128]
Human renal cell carcinoma (RCC) cell line 786-O and Caki-1	ZER acted as a novel blocker of STAT3 signaling cascade.	[129]
Oral squamous cell carcinoma (OSCC) lines	ZER inhibited the activation of CXCR4-RhoA and PI3K-mTOR signaling pathways resulting into reduced cell viability of OSCC cells.	[130]
Mouse epidermal cell line, JB6 Cl41	ZER induced HO-1 expression mediated through activation of Nrf2 signaling.	[89]
MDA-MB-231, MDA-MB-468, MDA-MB-361, T-47D, MCF-7 and MCF-10A cells	ZER inhibited the growth of breast cancer call line by downregulating CD1d overexpression.	[131]
Murine leukemia induced with WEHI-3B cells	ZER-loaded nanostructured lipid carrier (ZER-NLC) induced mitochondrial-dependent apoptotic pathway in murine leukemia.	[132]
Human gastric cancer cell line SGC-7901	ZER induced human gastric cancer cells apoptosis.	[133]
Human malignant melanoma (MM) A375 cell line	ZER induced apoptosis of A375 cells by activating Caspase-3.	[15]
Human Rac1 were cloned from HEK293 T cells	ZER inhibits cell migration by suppressing Rac1 expression.	[95]

Table 2. *Cont.*

Experimental Models	Results and Possible Mechanisms	Reference
Huh-7 and MHCC-LM3 cells and NSG mice	ZER prevented liver tumorigenesis through regulating cell metabolism and inducing cell cycle arrest and apoptosis.	[134]
Human glioblastoma multiforme (GBM8401) cells	ZER induced apoptosis through inactivation of IKKα, followed by Akt and FOXO1 phosphorylation and caspase-3 activation.	[135]
Human skin melanoma cell line CHL-1	ZER showed chemotherapeutic effects on human melanoma cells by altering mitochondrial function.	[136]
K562 cells	ZER treatment in K562 cells induced apoptosis through mitochondrial mediated pathway linked to upregulation of total histone H2AX, increased calcium and ROS production.	[137]

FAK: focal adhesion kinase, AKT: protein kinase B, ROCK: Rho-associated protein kinase, OPN, IL-6: interleukin-6, JAK2: Janus kinases 2, STAT3: signal transducer and activtor of transcription proteins 3, IL-1β: interleukin-1β, PI3k: phosphatidylinositol-3-kinase, NF-κB: nuclear factor kappa B, uPA: urokinase plasminogen activator, MMP: matrix metalloproteinase, ER: endoplasmic reticulum, Rac1: Ras-related C3 botulinum toxin substrate, mRNA: messenger ribonucleic acid, Bcl-2: B-cell lymphoma 2, TGF-β1: transforming growth factor beta 1, Bax: Bcl-2-associated X protein, Hsp90/Cdc37: heat shock protein 90 co-chaperone Cdc37, RhoA: Ras homolog family member A, mTOR: mechanistic target of rapamycin, HO-1: heme oxygenase -1, Nrf2: nuclear factor-erythroid factor 2-related factor 2, IKKα inhibitory-kB kinase-α, FOXO1: forkhead box protein O1, H2AX: H2A histone family member X.

5.2. Anti-Inflammatory Activity

The anti-inflammatory property of ZER is also reported by many studies in vitro and in vivo studies using different models. Various cellular mechanisms of anti-inflammatory activities are also reported. The details of these activities are given in Table 3.

Table 3. Anti-inflammatory activity of ZER.

In Vitro/In Vivo	Models	Activity	References
In vitro	Macrophages differentiated from human monocyte (THP-1)	ZER inhibited the secretion of pro-inflammatory cytokines in lipopolysaccharide (LPS)-activated inflammation in THP-1 cell-derived macrophages.	[138]
In vivo	Mice (endotoxin-treated mice induce acute lung injury)	ZER reduced leukocytes infiltration into the alveolar space and inhibited lung edema in LPS-induced aculte lung injury.	[139]
In vivo	Rats using Paw edema model	ZER reduced both λ-carrageenan- and prostaglandin E_2-induced inflammation.	[140]
In vitro	RAW264.7 murine macrophages	ZER induced proteo-stress leading to activition of HSF1 resulting into anti-inflammatory activity.	[141]
In vivo	Wild-type C57BL/6 mice	ZER decreased ETBF-induced colitis through inhibition of NF-κB signaling pathway.	[142]
In vitro	U937 monocytes	ZER supressed the activation of inflammatory markers in the macrophages via MyD88-dependent NF-κB/MAPK/PI3K-Akt signaling pathways.	[143]
In vivo	Adult male pathogen-free ICR mice	ZER showed protective effect on acute lung injury induced by LPS via suppression of intracellular adhesion molecules-1, IL-1β, macrophage inflammatory protein -2, downregulation of Akt, p38 MAPK/JNK, and IκB/NF-κB pathways.	[144]
In vivo	Adult male pathogen-free ICR mice	ZER showed protective effect on acute lung injury induced by LPS- via upregulation of antioxidative enzymes and Nrf2/HO-1 pathway.	[145]
In vitro	RAW 264.7 cells	ZER inhibited proinflammatory gene inducible nitric oxide (iNOS) and COX2 expression by atteunating IkB degradation.	[146]
In vitro	RAW264.7 cells	ZER significantly accelerated spontaneous COX-2 mRNA decay.	[147]
In vitro	Murine macrophage RAW264.7 cells	ZER stimulated HO-1.	[148]

5.3. Antimicrobial Activity

Various studies have reported the potent antibacterial activity of zerumbone [87,149]. A recent study reported the inhibitory effect of ZER extract and its compounds against multi-drug resistant and methicillin resistant *Staphylococcus aureus* [20]. In addition, ZER has an anti-biofilm potential; where it is reported to significantly suppress the expression level of BmeB12 along with antibacterial activity against *Bacteroides fragilis* [150]. Moreover, a study reported the bactericidal action of ZER against the carcinogenic bacterium *Streptococcus mutans* (ATCC35668) [151]. Synthetic derivatives of zerumbone are also reported as potent antimicrobial compounds [152].

5.4. Other Pharmacological Activities

Various other pharmacological activities are also reported for ZER such as immunomodulatory activity, neuroprotective effect, antinociceptive, anti-platelet and anti-melanogenic activities (Table 4). Different studies reported the immunomodulatory properties of ZER. Keong et al. revealed ZER activates mice thymocytes, splenocytes and peripheral blood mononuclear cells (PBMC) at dose dependent pattern [153]. A similar study assessed a commercially obtained ZER on human peripheral blood, where it showed that ZER activates human lymphocytes and upregulates interleukin-12p70 cytokine [154]. For neuroprotective effect of ZER, Hamdi et al. reported that ZER oxide protects NG108-15 cells from H_2O_2 induced oxidative stress [155]. Apart from that, ZER has a gastroprotective effect, where ZER reduces submucosal edema and leukocyte infiltration. On the other hand, a recent in vivo study reported the antinociceptive activity of ZER on mouse, where ZER suppresses inflammatory mediators without any signs of sedation [156]. An in vivo assessment reported the anti-platelet action of ZER investigated from human blood [157]. For the anti-melanogenic activity, a recent study reported that ZER attenuates melanin accumulation in α-melanoma cells [158].

Table 4. Other pharmacological activities of ZER.

In Vitro/In Vivo	Model Cells/Animals	Activity	References
Hepatoprotective activity			
In vitro	C57BL/6 mice	In a chronic liver injury model induced by CCl_4, ZER treatment alleviated the hepatocellular toxicity and inhibitd activation of primary hepatic stellate cells.	[159]
In vivo	Mice	ZER restored the activities of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. It also reduces the release of pro-inflammatory cytokines such as IL-6 and TNF-α, and inactivated the TLR4/NF-κB/COX-2 pathway in acute liver injury induced by CCl_4 in mice.	[160]
In vivo	Rats	ZER possessed protective activity against paracetamol-induced acute hepatotoxicity.	[161]
Immunosuppressive and Immunomodulatory activities			
In vivo	Male wistar rats	ZER inhibited the migration of neutrophils, expressions of CD11b/CD18 integrin, phagocytic activity, and production of reactive oxygen species	[162]
In vitro	CD18 integrin expression and phagocytic engulfment	ZER showed strong inhibition on the phagocytosis of neutrophils.Z	[163]
In vitro	Asthmatic mouse model	ZER reduced ovalbumin (OVA)-specific immunoglobulin E (IgE) and induced IgG2a antibody production. It also reduced the production of eotaxin, keratinocyte-derived chemokine (KC), IL-4, IL-5, IL-10, and IL-13, and promoted Th1 cytokine interferon (IFN)-γ production.	[164]
In vitro	Zymogen and PMA based chemiluminescence assay	ZER significantly inhibited intracellular and extracellular reactive oxygen species (ROS) production.	[165]

Table 4. *Cont.*

In Vitro/In Vivo	Model Cells/Animals	Activity	References
Anti-hypercholesterolemic activity			
In vivo	Rabbit	ZER preventd the development of atherosclerotic lesions and supressed macrophage aggregation.	[166]
Anti-hyperlipidemic activity			
In vivo	high-fat diet (HFD)-induced hyperlipidemic hamsters	ZER improved dyslipidemia by modulating lipolytic and lipogenic pathways of lipids metabolism	[167]
Anti-obesity activity			
In vivo	C57BL/6N mice	ZER ameliorated diet-induced obesity and inhibited adipogenesis by restoring AMPK-regulated lipogenesis and the microRNA-146b/SIRT1-mediated adipogenesis.	[168]
In vivo	C57BL/6 mice	ZER decreased the levels of plasma triglycerides well as plasma insulin and leptin.	[169]
Anti-hyperglycemia and related activities			
In vitro	MDCK cells	ZER increased AMPK phosphorylation at Thr172 under normal/high glucose without affecting mitochondrial function.	[170]
In vivo	STZ-diabetic rats	ZER ameliorated diabetic nephropathy by inhibiting hyperglycemia-induced inflammation.	[171]
In vivo	STZ-diabetic rats	ZER protected from hyperglycemia-induced retinal damage.	[172]
In vitro	INS-1 rat pancreatic β cells	ZER protected against high glucose-induced apoptosis of INS-1 pancreatic β cells.	[173]
Wound healing activity			
In vivo		ZER treated wound sections showed greater tissue regeneration and more fibroblasts possibly through the inhanced expression of VEGF, TGF-β1 and collagen IV.	[174]
Antiallergic activity			
In vivo	Female BALB/c and C57BL/6 mice	ZER showed antiallergic effect via modulation of Th1/Th2 cytokines in an asthmatic mouse model	[164]

Although zerumbone shows promising biological activities, its low water solubility and poor bioavailability is one of the limiting factor for wider applications of various formulations containing zerumbone. Few studies have been reported aimed at improving the solubility and bioavailability of zerumbone such as formulation inclusion complexes with cyclodextrin [8,175], nanostructured lipid careers [9], etc.

6. Conclusions and Future Prospects

This review highlighted the traditional food and medicinal uses, bioactive chemical constituents, and pharmacological activities of *Z. montanum*. Various bioactive compounds have been isolated and identified form the different plant parts. The most widely used and studied part was rhizome. Studies have reported both volatile and non-volatile compounds from the rhizomes. Sesquiterpene lactone, ZER was one of the main components in the rhizomes. ZER has been studied widely for its anticancer, anti-inflammatory, and other pharmacological activities. Future studies should focus on the exploration of various pharmacological activities of other compounds including flavonoids and phenylbutanoids. Bioassay guided isolation may result in the isolation of other active components from the extracts. Future studies should also focus on in vivo studies dealing with pharmacological and pharmacokinetic evaluations. Moreover, clinical studies should be conducted to validate the promising biological activities of ZER. Based on these data, *Z. montanum* can be a potential source for the development of functional and health beneficial food products.

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