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Review

Several aspects of *Zingiber zerumbet*: a review

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ABSTRACT

Zingiber zerumbet (L.) Roscoe ex Sm., Zingiberaceae, is a perennial, aromatic and tuberose plant that grows in humid locations. Also known as bitter ginger, *Z. zerumbet* is traditionally found throughout Asia, where it is widely used in foods, beverages and for ornamental purposes. The viscous juice present in the inflorescence of the plant is rich in surfactants and is also known as "ginger shampoo". The rhizome can be macerated in ethanol and used as a tonic and a stimulant. In Brazil *Z. zerumbet* is found in the Amazon region, in Taruma-mirim and Puraquequara (rural areas of Manaus, Amazon, Brazil). The main chemical compounds found in *Z. zerumbet* are terpenes and polyphenols. Zerumbone, a sesquiterpene, is the principal bioactive compound of *Z. zerumbet* and it is widely studied for its medicinal properties. The extracts and isolated metabolites of *Z. zerumbet* have exhibited the following properties: anti-inflammatory, antioxidant, antidiabetic, anticancer, antimicrobial, analgesic and antiviral. The National Institute of Amazon Research in Brazil is currently conducting studies using extracts from this plant to obtain compounds active in tumor models. The aim of this review is to provide a overview about the main aspects related with pharmacognosy and pharmacology of *Z. zerumbet* published in the literature over the last decade.

Introduction

Zingiberaceae includes approximately 53 genera and more than 1200 species, which are distributed across south and southeast Asia (Kress et al., 2002; Khatun et al., 2003). The members of this family, such as *Zingiber officinale* (ginger), *Curcuma longa* (turmeric), *Zingiber zerumbet* (bitter ginger) and *Elettaria cardamomum* (cardamom), are used in folk medicine, agriculture, as food condiments, and for ornamental purposes (Filho et al., 2000; Jamal et al., 2006; Andreo and Jorge, 2011).

The genus *Zingiber* contains approximately 85 species (Chaveerach et al., 2007). The main species of ginger consumed in Brazil is *Z. officinale* Roscoe, whose bioactive compounds gingerol, shogaol and other gingerones confer its characteristic flavor, aroma and anti-inflammatory properties. For these reasons it is mainly used in medicines and for culinary purposes (Elpo and Negrelle, 2004; Andreo and Jorge, 2011). The city of Morretes in the state of Paraná is the largest producer of ginger in Brazil (Elpo et al., 2008).

Z. zerumbet (L.) Roscoe ex Sm. is widely cultivated in tropical and subtropical regions around the world (Baby et al., 2009; Al-Zubairi et al., 2010; Eid et al., 2011). This species is traditionally known as Asian ginger or bitter ginger. In Brazil, it is mainly found in the regions of Taruamã-Mirim and Puraquequara, which are rural areas of Manaus in the state of Amazonas.

The studies on chemical profiles of *Z. officinale* and *Z. zerumbet* has provided some differences between the two species. Limonene occurs exclusively in *Z. zerumbet*, while citronellal is present only in *Z. officinale* (Jiang et al., 2006).

Interest in the therapeutic potential of *Z. zerumbet* has resulted in several studies regarding its chemical composition. Research has shown that bitter ginger yields a complex mixture of terpenes, with a predominance of sesquiterpenes (Yu et al., 2008a).

From a commercial point of view, *Z. zerumbet* is a medicinal plant with great potential for cultivation that does not require high costs. In Brazil, the National Institute of Amazonian Research, in partnership with Biozer company, has developed products using bitter ginger such as yogurt with a property that enhances the functions of the gastrointestinal tract (Pinheiro and Castro, 2005).

Traditional uses

It is widely recognized that popular knowledge about the use of medicinal plants in the treatment of several diseases needs to be confirmed. The traditional use of medicinal plants contributes to the spread of this knowledge and serves as a basis for scientific research seeking evidence of such pharmacological activities (Deb et al., 2011).

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In *Z. zerumbet* the rhizome is the part that is most used for medicinal purposes (Norulaini et al., 2009). These folk medicines are generally prepared by maceration and infusion of fresh rhizome, but tinctures, poultices and even the plant *in natura* are other therapeutic uses (Tushar et al., 2010). *Z. zerumbet* has a wide spectrum of traditional uses, as well as biological and pharmacological properties. The cone-shaped flowers are long-lasting and are employed in craft arrangements for ornamental purposes (Devi et al., 2014). The rhizome is used as a tonic and as a stimulant (Sakinah et al., 2007). The rhizome serves as a seasoning in foods, while the floral buds are consumed as vegetables (Sirirugsa, 1999).

The rhizome of ginger has been extensively used with remarkable therapeutic effects for the treatment of inflammation, diarrhea, stomach cramps, bacterial infections, fever, flatulence, allergies and poisoning (Tewtrakul and Subhadhirasakul, 2007; Okamoto et al., 2011; Prakash et al., 2011b; Sidahmed et al., 2015). Powdered rhizome is used to treat ear infections, toothache and, in the form of tea, to treat stomach disease (Ghosh et al., 2011). The leaves are also used in therapies for joint pain. The juice of cooked rhizome was reported to be effective in combating worms in children (Somchit and Shukriyah, 2003; Ibrahim et al., 2007). The creamy substance present in the mature inflorescence, is rich in surfactants and serves as a natural shampoo (Yu et al., 2008b).

Botanical description

Z. zerumbet is a perennial tuberous plant that can be found naturally as scattered plants in damp and shady parts of lowlands or mountain slopes. It is often found near rivers, waterfalls and other water sources (Nalawade et al., 2003; Tzeng et al., 2013). This species reproduces asexually by multiplying rhizome fragments (Kavitha and Thomas, 2008).

This plant is characterized by the presence of stems approximately 1–2 m tall, which are erect, oblique, round and covered by sheaths of flat leaves. The leaves and inflorescences grow from a thick rhizome or underground stem. The sheets are thin and are approximately 25–35 cm long, with a central raised midrib which strongly raised on the lower surface. The sheets are arranged alternately along the stem (Yob et al., 2011). The inflorescence, which is green when young, becomes red when old and reaches 6–12 cm in height. It is supported on a separate pseudostem from the leaves by a narrow overlap that forms an open pouch, from which the flowers arise. An important botanical feature of *Z. zerumbet* is that the yarn is connected to a long curved beak. The fruit is white, glabrous, thin-walled and is approximately 1.5 cm long. The seeds are ellipsoids and black. The rhizome is perennial, thick, aromatic and yellow (Yob et al., 2011).

Chemical composition

Z. zerumbet is a rich source of different classes of compounds that belong to a wide variety of chemical metabolites, such as polyphenols, alkaloids and terpenes (Matthes et al., 1980; Jang et al., 2004; Jang and Seo, 2005; Chung et al., 2007; Chang et al., 2012c).

Terpenes

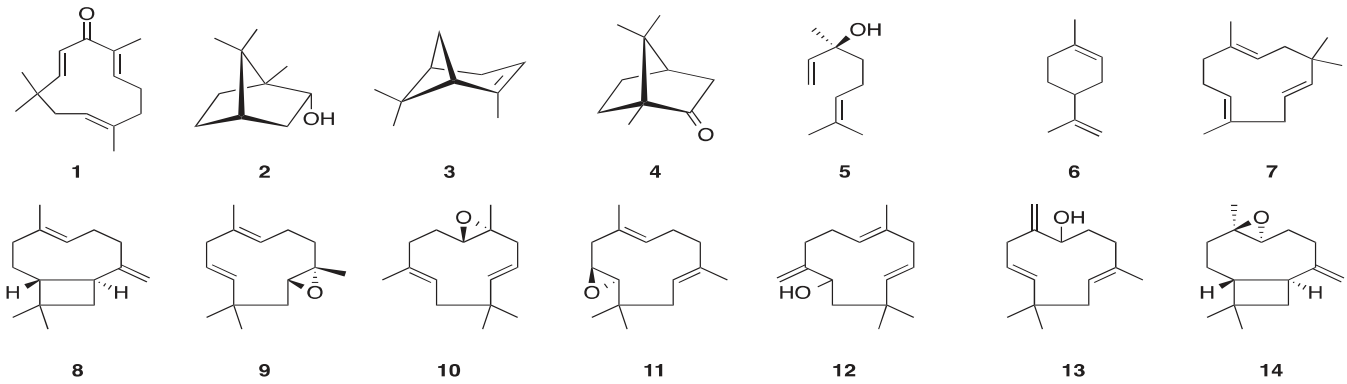
Dev (1960) isolated zerumbone (**1**) from essential oil of *Z. zerumbet* and determined its structure, while Ramaswami and Bhattacharyya (1962) identified humulene monoxide and humulene dioxide. Nigam and Levi (1963) studied the compounds present in eight essential oil fractions and obtained borneol (**2**), α-pinene (**3**), camphor (**4**), linalool (**5**), zerumbone (**1**), limonene (**6**), α-humulene (**7**) and β-caryophyllene (**8**).

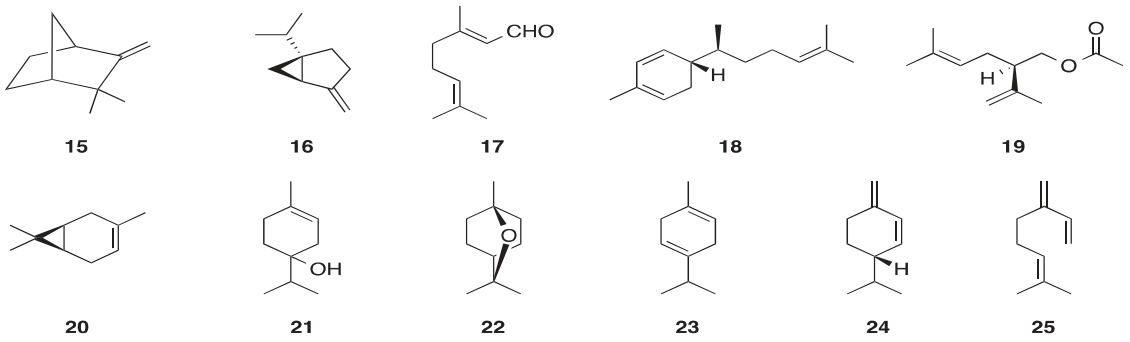
Damodaran and Dev (1968a,b,c) characterized the following sesquiterpenes: humulene epoxide I (**9**), II (**10**) and III (**11**), humulenol I (**12**) and II (**13**) and caryophyllene oxide (**14**).

Dai et al. (2013) identified the presence of 46 compounds in the essential oil extracted from the rhizome of *Z. zerumbet*. The most abundant components were monoterpenes (76.1%): camphene (**15**) (16.3%), sabinene (**16**) (14.6%), citral (**17**) (26.1%), zingiberene (**18**) (7.2%) and lavandulyl acetate (**19**) (6.7%). In the aforementioned study, the essential oil showed a low zerumbone content (1.2%). Zerumbone (**1**) is a monocyclic sesquiterpene with three double bonds, two of which are coupled with carbonyl grouping and the other is isolated (Songsiang et al., 2010; Kitayama, 2011; Kumar et al., 2013). Rout et al. (2009) performed a quantitative analysis of zerumbone in different parts of *Z. zerumbet*. The highest values were found in the rhizome, followed by the roots. Bhuiyan et al. (2009) evaluated the essential oil of *Z. zerumbet* using GC-MS and identified the terpenes α-pinene (**3**), camphor (**4**), linalool (**5**), zerumbone (**1**), limonene (**6**), camphene (**15**), α-caryophyllene, 3-carene (**20**), 4-terpineol (**21**) and eucalyptol (**22**).

Sulaiman et al. (2010) isolated and also quantified the compounds present in the essential oil. The sesquiterpenes were the major components, followed by monoterpenes. Zerumbone (**1**) (36.12%) was the most abundant compound, followed by humulene (10.03%). The following monoterpenes were identified and quantified using GC–MS: borneol (**2**) (4.78%), α-pinene (**3**) (3.71%), camphor (**4**) (4.18%), linalool (**5**) (1.06%), camphene (**15**) (14.29%), eucalyptol (**22**) (3.85%), γ-terpinene (**23**) (2.00%) and β-phellandrene (**24**) (1.63%).

Yu et al. (2008a) found that 85.81% of the compounds in the essential oil were sesquiterpenes, confirming the aforementioned study. The oil was characterized by the presence of zerumbone (**1**) (48.13%) and α-humulene (**7**) (17.23%). Other sesquiterpenoids were also isolated but in lower concentrations. Batubara et al.





15 16 17 18 19

20 21 22 23 24 25

(2013) studied the components of the essential oil from *Z. zerumbet*, and obtained a yield of 0.12% of essential oil with characteristic flavor and color. The essential oil consisted of monoterpenes and sesquiterpenes. The authors found that the essential oil is rich in zerumbone (**1**) (11.05%), sabinene (**16**) (32.96%) and β-myrcene (**25**) (13.27%).

Polyphenols

Chien et al. (2008) isolated the following flavonoids from the rhizome of *Z. zerumbet*: 3-methyl kaempferol, kaempferol-3-*O*-(2,4-di-*O*-acetyl-α-L-rhamnopyranoside) (**26**) and kaempferol-3-*O*-(3,4-di-*O*-acetyl-α-L-rhamnopyranoside) (**27**). The phenolic compounds were extracted using ethyl acetate and identified by HPLC-DAD.

Ruslay et al. (2007) analyzed the composition of *Z. zerumbet* extract and also isolated and identified some flavonoids. The compounds were kaempferol-3-*O*-rhamnoside (**28**), kaempferol-3-*O*-(2″-*O*-acetyl)rhamnoside, kaempferol-3-*O*-(3″-*O*-acetyl)rhamnoside, kaempferol-3-*O*-(4″-acetyl)rhamnoside (**29**), kaempferol-3-*O*-(3″,4″-diacetyl)rhamnoside (**27**) and kaempferol-3-*O*-(2″,4″-diacetyl)rhamnoside (**26**).

Similarly, Jang et al. (2004) studied the aromatic compounds and flavonoids present in *Z. zerumbet*. The compounds that were isolated included: kaempferol-3,4′-*O*-dimethylether (**30**), kaempferol-3-*O*-methylether (**31**), kaempferol-3,4′,7-*O*-trimethylether (**32**), 4″-*O*-acetylafzelin (**33**), 2″,4″-*O*-diacetylafzelin (**34**), 3″,4″-*O*-diacetylafzelin (**35**), kaempferol-3-*O*-(4-*O*-acetyl-α-L-rhamnoside), kaempferol-3-*O*-(3,4-*O*-diacetyl-α-L-rhamnopyranoside), kaempferol-3-*O*-(2,4-*O*-diacetyl-α-L-rhamnopyranoside).

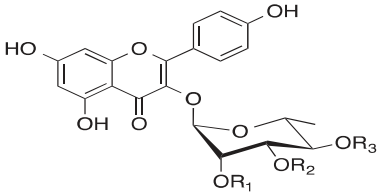
The principal compounds found in *Z. zerumbet* are presented in Box 1. According to Bhuiyan et al. (2009), the components present in *Z. zerumbet* can vary according to the region where it is cultivated, which results in different percentages.

Pharmacological activities

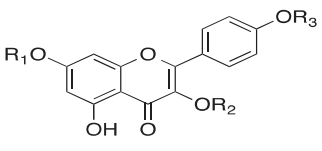
The therapeutic properties of the active compounds extracted from the rhizome have been used for treating stomach problems (Prakash et al., 2011a), and have been reported as having anti-inflammatory (Murakami et al., 2002; Jalil et al., 2015), antitumoral (Rashid and Pihie, 2005; Takada et al., 2005; Abdelwahab et al., 2010), antioxidant (Ruslay et al., 2007; Rout et al., 2011), antibacterial (Kumar et al., 2013), antiviral (Epstein–Barr virus) (Murakami et al., 1999) and analgesic (Somchit et al., 2005) properties. The health benefits of *Z. zerumbet* have been described by many authors. Pharmacological actions that highlight the properties of pure zerumbone and rhizome extracts with different solvents are presented in Box 2.

Z. zerumbet inhibits the activity of the enzyme cyclooxygenase (COX) both in peripheral and central nervous system and the synthesis of inflammatory mediators (Zakaria et al., 2010). Chien et al. (2008) reported on the anti-inflammatory activity of isolated compounds of *Z. zerumbet* in two different models: paw edema in mice, and cell cultures (macrophages). The treatment of macrophages RAW 264.7 with zerumbone compounds and 3-*O*-methyl-kaempferol presented the greatest suppression of the production of inflammatory mediators (PGE2 and NO). Regarding the animal experiments, zerumbone showed a lower increase in paw volume when compared with indomethacin (positive control) (38.8 ± 16.7 and 51.0 ± 16.7%, respectively).

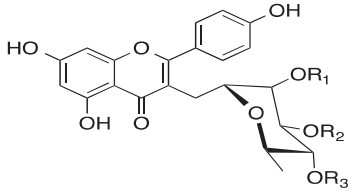
Chaung et al. (2008) analyzed the aqueous extract of the rhizome of *Z. zerumbet* to assess its anti-inflammatory activity *in vitro* and *in vivo*. Intraperitoneal macrophages were obtained from BALB/c mice and used to evaluate the production of TNF-α (tumor necrosis factor) and IL-4 interleukins. The cells were stimulated with lipopolysaccharide (LPS from *Escherichia coli* 0127: B8) and phorbol 12-myristate 13-acetate (PMA). Female specific-pathogen-free ICR mice were used for *in vivo* assay. Anti-inflammatory activity was evaluated after oral administration of extract at a dosage of 100 mg/kg per day for 28 days. Lung tissue was taken and levels of IL-1α were determined by ELISA kit. Hepatotoxicity was evaluated at the concentrations of 0, 10, 100 and 1000 mg/kg per day for 60 days. Treatment with 50–500 μg/ml of the extract inhibited the release of TNF-α in peritoneal macrophages of 38 and 55%, respectively. The lowest dose required to inhibit the production of interleukin was 500 μg/ml. The lung tissue of animals treated with extract showed significantly lower amounts of LTC_4 than control mice (429 ± 69 *versus* 261 ± 23 pg/lung). No differences in hepatic



26 R_1=R_3=Ac; R_2=H
27 R_1=H; R_2=R_3=Ac
28 R_1=R_2=R_3=H
29 R_1=R_2=H; R_3=Ac



30 R_1=H; R_2=R_3=CH_3
31 R_1=R_3=H; R_2=CH_3
32 R_1=R_2=R_3=CH_3



33 R_1=R_2=H; R_3=Ac
34 R_1=R_3=Ac; R_2=H
35 R_1=H; R_2=R_3=Ac

Box 1
Reported principal compounds found in *Zingiber zerumbet*.

Class	Sub-class	Compounds	References
Terpene	Sesquiterpenes	Zerumbone (**1**), humulene (**7**), caryophyllene, zingiberene (**18**)	Nakamura et al. (2004), Abdul et al. (2008), Chung et al. (2008), Fakurazi et al. (2008), Rout et al. (2009), Keong et al. (2010), Chang et al. (2012a) and Rahman et al. (2013)
	Monoterpenes	Borneol (**2**), α-pinene (**3**), linalool (**5**), limonene (**6**), camphene (**15**), sabinene (**16**), citral (**17**), γ-terpinene (**23**), eucalyptol (**22**), β-mircene	Hashemi et al. (2008), Rana et al. (2008) and Dai et al. (2013)
Polyphenol	Flavonoids	Kaempferol, kaempferol-3-*O*-methyl; Kaempferol-3-*O*-(2,4-di-*O*-acetyl-α-L-rhamnopyranoside) (**26**), Kaempferol-3-*O*-(3,4-di-*O*-acetyl-α-L-rhamnopyranoside) (**27**), Kaempferol-3-*O*-(4-acetyl)rhamnoside (**29**), Kaempferol-3,4′,7-*O*-trimethylether	Masuda et al. (1991), Nakatani et al. (1991) and Chang et al. (2012c,d)

Box 2
Some pharmacological activities of *Zingiber zerumbet*.

Source	Extract/active compound	Biological activity	Reference
Rhizome	Methanol	Anti-inflammatory and antinociceptive effects	Zakaria et al. (2010)
Rhizome	Chloroform	Antimicrobial activity	Phongpaichit et al. (2006)
Rhizome	Chloroform	Antimicrobial activity against methicillin-resistant *S. aureus*	Voravuthikunchai et al. (2006)
Rhizome	Ethanol	Antimalarial activity	Sriphana et al. (2013)
Rhizome	Chloroform	Activity against Epstein–Barr virus early antigen	Vimala et al. (1999)
Commercial	Zerumbone	Antiproliferative and anti-inflammatory Effects	Takada et al. (2005)
Rhizome	Zerumbone	Anti-inflammatory and anticarcinogenic activity	Murakami et al. (2002)
Rhizome	Zerumbone	Activity against liver cancer	Taha et al. (2010)
Rhizome	Zerumbone	Activity against ovarian and cervical cancer	Abdelwahab et al. (2012)
Rhizome	Diethyl ether	Antitumor effects	Huang et al. (2005)
Commercial	Zerumbone	Activity against breast cancer cells	Sung et al. (2008)
Rhizome	Ethyl acetate	Nephroprotective effects	Abdul Hamid et al. (2012)
Rhizome	Ethanol	Analgesic and anti-pyretic activities	Somchit et al. (2005)
Rhizome	Zerumbone	Systemic antinociception	Perimal et al. (2010)
Rhizome	Water	Aqueous extract are not acute toxic in concentrations of the test	Hashemi et al. (2008)
Rhizome	Zerumbone	Gastroprotective effect	Sidahmed et al. (2015)
Rhizome	Zerumbone	Alzheimer's disease treatment	Bustamam et al. (2008)
Commercial	Zerumbone	Inhibition of angiogenesis	Park et al. (2015)

enzymes AST (aspartate transaminase) and ALT (alanine transaminase) were observed between negative control, parallel control and aqueous extract groups.

Zakaria et al. (2011) reported on the anti-inflammatory activities of the essential oil of *Z. zerumbet* administered intraperitoneally in male Sprague-Dawley rats. The paw edema test induced by carrageenan was used as a model of acute inflammation and the cotton pellet-induced granuloma test was used for the chronic inflammation model. The inflammatory response induced by carrageenan paw edema is considered COX-dependent, while the cotton pellet model showed antiproliferative activity against antitransudative and granulomatous edema.

Nag et al. (2013) evaluated the determination of total phenolics (Folin Ciocalteu method), the flavonoid content (complexation with aluminum chloride) and antioxidant activity (DPPH and hydroxyl free radicals) of the ethanol extract of bitter ginger rhizome. The results showed polyphenols of 33.64 ± 3.22 mg (gallic acid/g extract), flavonoids of 26.79 ± 0.68 mg (quercetin/g extract) and kaempferol 11.63 ± 0.09 mg/g extract. The antioxidant activity showed IC_{50} values of 417.14 (ascorbic acid: 2.71 μg/ml) and 13.24 mg/ml (quercetin: 2.46 μg/ml) in tests with DPPH and hydroxyl, respectively. *Z. zerumbet* demonstrated inhibition of DPPH in various concentrations; however, there are no other studies in the literature using this radical in the evaluation of the antioxidant activity of this kind.

Hasham-hisam et al. (2011) screened samples of fresh ginger which were boiled for one hour and baked for 15 min. The extraction of oleoresin was performed using a Soxhlet extractor with different solvents and different extraction times. For the determination of antioxidant activity, the β-carotene-linoleic acid assay was used. The antioxidant activity of the extracts was compared to that of butylated hydroxytoluene (BHT – positive control). The combination of fresh sample with a polar solvent (acetone) with 12 h of extraction resulted in higher antioxidant activity.

Kader et al. (2011) studied the inhibition potential of extracts from dried rhizomes. These extracts were used to determine antimicrobial activity by being tested with five gram positive (*Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *Staphylococcus aureus*, *Sarcina lutea*), eight gram negative (*Escherichia coli*, *Salmonella paratyphi*, *Salmonella typhi*, *Vibrio parahemolyticus*, *Vibrio mimicus*, *Shigella dysenteriae*, *Shigella boydii*, *Pseudomonas aeruginosa*) and three pathogenic fungi (*Candida albicans*, *Aspergillus niger*, *Saccharomyces cerevisiae*). The ether and chloroform fractions showed moderate activity against the bacteria and fungi that were tested. The ethanol extract (400 mg/disk) showed the best antimicrobial activity against *Vibrio parahaemolyticus* (inhibition zone: 10 mm), and all the tested fungi. The data showed the antimicrobial and antifungal potential of the compounds present in *Z. zerumbet* extracts.

Antitumor agents are known to interact with specific biological molecules or pathways of cancer cells (Weijl et al., 1997). More than sixty types of chemotherapeutic drugs used in cancer treatment are molecules obtained from medicinal plants (Nadzri et al., 2013). Recent studies have shown a significant protective activity of zerumbone in colon cancer (Yodkeeree et al., 2009); pancreas cancer (Shamoto et al., 2014); liver cancer (Alwi et al., 2007; Sakinah et al., 2007; Taha et al., 2010); and leukemia (Xian et al., 2007; Rahman et al., 2014).

Studies have demonstrated that zerumbone has little or no cytotoxic effect on normal human endothelial cells, dermal fibroblasts

but induces apoptosis in many cancer cell lines. Zerumbone may modulate a variety of molecular targets, both for the prevention of and for the treatment of cancer (Murakami et al., 2002; Xian et al., 2007; Prasannan et al., 2012).

Kim et al. (2009), isolated and purified the zerumbone compound of the chloroform extract. In order to evaluate anticancer activity, ICR mice have been used (rectal colon cancer assessment) and A/J (chemoprevention of lung cancer). The administration of zerumbone significantly decreased mucosal inflammation in the colon compared with the untreated group. Treatment with zerumbone also affected the incidence of hyperplasia and adenoma in the lungs, reducing the multiplicity of both.

The benefit of *Z. zerumbet* regarding insulin sensitivity in fructose-fed rats was studied by Chang et al. (2012c). Extraction was carried out by maceration using hydroethanolic solution (95%, v/v) for seven days. Wistar rats were divided into two experimental groups. The first was chosen at random and received a diet to induce insulin resistance. The control group received a standard diet. A group of animals fed with fructose was treated by oral gavage with pioglitazone hydrochloride (hypoglycemic). Similarly to pioglitazone, *Z. zerumbet* inhibits the glycation of hemoglobin and promotes normoglycemia. These results show that the extract of bitter ginger can reverse the effects of hyperglycemia. The ability to reverse insulin resistance may be attributed to the presence of bioactive compounds such as quercetin, curcumin and kaempferol.

Tzeng et al. (2013) conducted a study of the mechanism of action of the ethanolic extract of *Z. zerumbet* in its ability to attenuate streptozotocin-induced diabetic nephropathy. Bitter ginger can promote glucose homeostasis and, therefore, it can be used as a therapeutic to control diabetic complications. The ethanolic extract (95%) was prepared by the maceration method. Male Wistar rats were used in the experiments and diabetes was induced by injecting streptozotocin (plasma glucose equal or higher than 350 mg/dl). The urine of the animals was used to determine the concentrations of albumin and creatinine. A reduction in body weight was observed during the experimental period. The other parameters, such as glycated hemoglobin fasting glucose, were reduced during the eight weeks of treatment with *Z. zerumbet* when compared with the control group. The improved renal function during treatment, and the volume of urine and excretion of proteins, was lower than the group treated with vehicle only. The ginger extract and metformin caused significant improvements in the relative weight of the kidneys, suggesting that both can reverse hypertrophy in diabetic animals.

Analgesic activity can be associated with different mechanisms of action, involving the release of inflammatory mediators, with central and peripheral action. Sulaiman et al. (2010) evaluated the analgesic activity of essential oil from *Z. zerumbet* in three different models: acetic acid-induced abdominal writhing, formalin and the hot-plate tests. The acetic-acid writhing test was used to study the peripheral nociception, while hot plate test to assess the central analgesia and formalin test evaluated both pathways. The essential oil administered intraperitoneally caused a dose-dependent inhibition induced by acetic acid when compared to the control with 80.2% of inhibition for the dose of 300 mg/kg. This effect was also observed in the animals treated with acetylsalicylic acid. The results of hot plate and formalin tests indicated that the anti-inflammatory action of essential oil of *Z. zerumbet* is mediated both centrally and peripherally.

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

Chang et al. (2012b) evaluated the acute and chronic toxicity of the ethanol extract of *Z. zerumbet*. The rhizome remained macerated for seven days in ethanol. The phytochemical analysis showed the presence of alkaloids, saponins, flavonoids, lipids, polyphenols and terpenoids. *In vivo* experiments using male rats were used and aqueous solution was administered orally for fourteen days in the acute toxicity test.

In the chronic toxicity test the concentrations used were 1000, 2000 and 3000 mg/kg extract administered by gavage, while the control group received vehicle only for four weeks. The following analyses were performed: hematological (red cells, white cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count and volume of platelets); biochemical (glucose, urea, creatinine, ALT, AST, total cholesterol, triacylglyceride, HDL, LDL, gamma-GT, direct and indirect bilirubin); and histopathological after the end of treatment. There was no evidence of toxicity and no changes in the hematological parameters were observed. There were also no changes in weight and in the histological analysis of the tissue. Hematological analysis is important for assessing the risk in humans. The data obtained indicated that both the acute care and chronic care produced no clinical signs of change, death or toxicity in relation to the doses used. This information can be useful for future studies of the pharmacological potential of bitter ginger.

Discussion

Populations around the world use medicinal plants to treat numerous diseases and ethnopharmacological information serves as a starting point for developing new drugs.

Originating in India, *Z. zerumbet* has aroused the interest of researchers due to its various applications. Currently, researchers in the north of Brazil are studying the pharmacological activities attributed to the bioactive compounds present in the rhizome. In Brazil the National Institute of Amazonian Research has developed important research regarding the biological activities of *Z. zerumbet* to help to develop new drugs.

The evidence of the therapeutic properties of zerumbone from bitter ginger, which are mainly secondary metabolites, is important information that can help in the search to discover new drugs. From a commercial point of view, a positive aspect is that ginger is easy to cultivate and it has a lot of pharmacological properties.

The analysis of the literature presented in this study has great relevance because several recent studies have demonstrated the pharmacological activities of *Z. zerumbet*. The outcome of these studies provides a view of the current state of research on the chemical nature of the bioactive compounds and biological activities of *Z. zerumbet* and will arouse the interest of many other researchers to conduct further studies.

Based on numerous scientific references, *Z. zerumbet* is a plant with high therapeutic potential. Further studies are required in order to target the benefits of its use as a medicinal plant and to determine whether it can be a source of molecules that can serve as a model for the discovery new drugs.

Final considerations

Studies of *Z. zerumbet* have shown the immense potential of this medicinal plant in the treatment of various diseases. Its phytochemical composition reveals that sesquiterpenes, monoterpenes and phenolic compounds are the major compounds, and many of

its proven pharmacological properties are attributed to the main sesquiterpene, zerumbone. In Brazil, bitter ginger has been cultivated in the Amazon and is spreading throughout the country. Due to its numerous health benefits, this ginger deserves special attention and greater diffusion of its culture as much as *Z. officinale* Roscoe.

Authors' contributions

AVP supervised and helped article writing, FLB was responsible for review of article, and AYK (MSc student) was responsible for bibliographic search.

Conflicts of interest

The authors declare no conflicts of interest.

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