Major Bioactive Compounds in Essential Oils Extracted From the Rhizomes of *Zingiber zerumbet* (L) Smith: A Mini-Review on the Anti-allergic and Immunomodulatory Properties

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**INTRODUCTION**

*Zingiberaceae* is the largest families of the plant kingdom. Its plants tend to be high in medicinal values and provide many useful products for food, spices, medicines, dyes, perfume and esthetics (Jantan et al., 2003; Koga et al., 2016). *Zingiber* is a genus of *Zingiberaceae* with approximately 141 species (Sirirugsa, 1995). *Zingiber zerumbet* (L) Smith is a wild ginger belonging to the *Zingiber*
genus and is well-known among local cultures as “Lempoyang,” “Ghitarian,” “Yaimu,” “Jangli adha,” “Awapuhi,” “Zurunbah,” “Hong Qu Jiar,” and “Hiao Dam.” This particular type of wild ginger grows naturally in damp, shaded parts of the low land and is believed to be native to India and the Malaysian Peninsula (Yob et al., 2011). The traditional uses of ginger are broad, including but not limited to the treatment of nausea, hangovers, migraine headache, morning and motion sickness, worm infestation in children, as well as cuts and bruises skin (Nik Norulaini et al., 2009; Butt and Sultan, 2011; Sahebkar, 2011). Various local groups have been using ginger to provide remedy against allergic diseases including asthma and sinusitis for centuries (Butt and Sultan, 2011; Sahebkar, 2011). As one type of wild ginger, the crude extract as well as the active compounds extracted from the rhizome and leaves of Z. zerumbet have been reported to possess various pharmacological properties including anti-inflammatory (Murakami et al., 2002; Jalil et al., 2015), antitumor (Rashid and Pihie, 2005; Takada et al., 2005; Abdelwahab et al., 2010), antioxidan (Ruslay et al., 2007; Rout et al., 2011), antibacterial (Kumar et al., 2013), antiviral (Epstein-Barr virus) (Murakami et al., 1999), analgesic (Somchit et al., 2005), anti-allergic (Tewtrakul and Subhadhirasakul, 2007) characteristics and usefulness for treating stomach problems (Prakash et al., 2011).

THE ANTI-ALLERGIC AND IMMUNE MODULATION ACTIVITIES OF Z. zerumbet

Although there have been quite a number of studies conducted to study the effectiveness of Z. zerumbet in a broad range of biological activities related to human health, there has been very few reported studies of Z. zerumbet as well as its bioactive compounds focusing on anti-allergy. Increasing levels of allergic diseases, such as allergic rhinitis (AR), atopic dermatitis, asthma and food allergies in many of the developed countries (Carlsen, 2003) are causing significant health problems, especially in children. Therefore, various research has been carried out extensively to combat these diseases (Pawankar et al., 2013).

In one of the studies, the ethanolic and aqueous extraction of Z. zerumbet were subjected to an in vitro investigation for its anti-allergic activities (Tewtrakul and Subhadhirasakul, 2007). This study has shown that the ethanolic and aqueous extracts of Z. zerumbet (10–100 μg/mL) inhibited the release of β-hexosaminidase from RBL-2H3 cells as much as 8.4–53.7% (IC50 = 91 μg/mL) and 10.9–59.1% (IC50 = 68.2 μg/mL), respectively. Several patents were filed due to the exceptional anti-allergic activities shown by Z. zerumbet. Among which, a patent by Chaung et al. (2009) provides a method of preparing polar solvent extraction from the root of Z. zerumbet as well as the use of this formulation to prevent or to treat an allergic disorder. Another patent by Lin et al. (2013) provides a method of preparing solvent extraction by using ethanol, water, or a mixture of both from the root of Z. zerumbet for treating AR or allergic eczema.

The essential oils from rhizomes of Z. zerumbet have also been shown to contain several beneficial effects such as analgesic activity (Sulaiman et al., 2010), anti-nociceptive activity (Khalid et al., 2011), and anti-microbial activity (Kader et al., 2010). However, anti-allergic activities involving the essential oils extracted from the rhizomes of Z. zerumbet are still yet to be well-reported. Hence, this mini-review focuses on the major bioactive compounds found in the essential oils extracted from the rhizomes of Z. zerumbet which have been reported to possess anti-allergic and immunomodulatory properties in order to improve the understanding on the use of Z. zerumbet and its bioactive compounds in the treatment of allergy and allergic-related diseases.

THE ANTI-ALLERGIC AND IMMUNOMODULATORY ACTIVITIES OF THE MAJOR BIOACTIVE COMPOUNDS IN THE ESSENTIAL OILS EXTRACTED FROM THE RHIZOMES OF Z. zerumbet

Currently, there are only a few zinger genus that have been reported to contain anti-allergic properties, including Z. officinale, Z. cassumunar, Z. zerumbet, and Z. mioga (Tewtrakul and Subhadhirasakul, 2007; Shin et al., 2015). The major bioactive compounds which can be found in the essential oil of Z. officinale are α-zingiberene (17.4–32.2%), β-sesquiphellandrene (6.6–27.16%), and geraniol (25.9%); for Z. cassumunar is sabinene (36.71–53.50%); for Z. zerumbet are zerumbone (35.5–84.8%) and pinene (10.3% to 31.4%); for Z. mioga is β-phellandrene (26.60%) (Kurobayashi et al., 1991; Sharifi-Rad et al., 2017). Interestingly, zerumbone was found to be exclusively and abundantly present (>80%) in the essential oil extracted from the rhizomes of Z. zerumbet, in comparison to other major bioactive compounds extracted from Z. officinale, Z. cassumunar and Z. mioga. According to Shieh et al. (2015), the anti-allergic effects of Z. zerumbet may be due to zerumbone as this compound has been shown to effectively inhibit asthma in mice. Apart from zerumbone (35.5–84.8%), the other major compounds that can be found in the essential oils extracted from the rhizomes of Z. zerumbet are pinene (10.3–31.4%), humulene (10.03–17.23%), linalool (7.7–17.1%), Caryophyllene (6.9–10.2%), bornol (4.78%), and limonene (0.8–1.3%) (Figure 1). Among which, it is interesting to note that limonene can only be found in Z. zerumbet but not the other Zingerber genus (Sun, 2007; Bhuiyan et al., 2008).

The biomedical applications of some of these major bioactive compounds found in Z. zerumbet have been previously summarized in several review papers (Calderón-Montaño et al., 2011; Singh et al., 2012; Kalantari et al., 2017). However, the anti-allergic properties of these major bioactive compounds were not included. In this review, the major bioactive compounds found in the essential oils extracted from the rhizomes of Z. zerumbet, such as zerumbone, limonene, borneol, pinene, linalool, humulene, and caryophyllene, and their reported anti-allergic and immune modulation activities are summarized in Table 1.
Zerumbone
Zerumbone is a sesquiterpene compound abundantly present (35.5–84.8%) in essential oils extracted from the rhizomes of *Z. zerumbet* (Tewtrakul and Subhadhirasakul, 2007; Sharifi-Rad et al., 2017). A study done by Shieh et al. (2015) showed that zerumbone isolated from *Z. zerumbet* decreased the severity of airway hyperresponsiveness and the accumulation of eosinophils in bronchoalveolar lavage fluid (BALF) collected from OVA-challenge female BALB/c mice. The oral administration of zerumbone (0.1, 1, and 10 mg/kg) also significantly reduced serum anti-OVA IgE levels in mice (Shieh et al., 2015), which further resulted in the reduction of OVA-induced cytokine secretions (IL-4, IL-5, IL-10, and IL-13) in the BALF collected (Shieh et al., 2015). Thus, the authors speculated that zerumbone may have an anti-allergic effect on allergic asthma by suppressing Th2-related cytokines (IL-4, IL-5, IL-10, and IL-13) secretion and consequently reducing IgE production by B cells (Shieh et al., 2015). The data reported in this study was the first known report to provide a rationale for extensive preclinical studies on zerumbone in IgE-mediated allergic asthma.

Pinene
Pinene is a monoterpene compound that can be isolated from *Z. zerumbet* (Koga et al., 2016) in relatively higher quantities (10.3–31.4%) than other plants from the same genus. The percentages of pinene found in *Z. corallinum* and *Z. cassumunar* were only 2.16–3.23% and 5.2–7.25%, respectively (Koga et al., 2016). In addition, pinene has been reported to attenuate OVA-induced AR in female BALB/c mice by decreasing the infiltration of eosinophils and mast cells in AR nasal mucosa tissue, as well as reducing the level of TNF-α and number of nose rubs in mice orally pre-treated with α-pinene (0.1, 1, or 10 mg/kg) (Nam et al., 2014). The authors even demonstrated that post-treatment of α-pinene in the OVA-induced mice significantly decreased nasal mucosa IgE level and the number of nose rubs (Nam et al., 2014). The in vitro study also reported that α-pinene (0.1, 1, or 10 μg/mL) inhibits the production and mRNA expression of TNF-α in PMACI-induced activation of HMC-1 cells (Nam et al., 2014). In term of regulatory mechanism of α-pinene on allergic inflammation, this compound inhibits PMACI-induced activation of NF-κB and IKK-β in HMC-1 cells (Nam et al., 2014). In conclusion, that study suggested that α-pinene was able to exert its anti-allergic effects by interfering the NF-κB/IκB signaling pathway as this pathway is closely related with the inhibition of allergic inflammation in human mast cells (Singh et al., 2011).

Humulene
Similar to zerumbone, humulene is a sesquiterpene compound that can be found abundantly (10.03–17.23%) in *Z. zerumbet* (Baby et al., 2009). Its key enzyme, α-humulene synthase, has been shown to play a part in the synthesis of zerumbone (Baby et al., 2009). However, other *Zingiber* species such as *Z. nimmonii* and *Z. cassumunar* have been shown to contain higher levels of humulene (19.6–27.7% and 23.92%, respectively), in comparison to *Z. zerumbet*. Rogerio et al. (2009) reported on the inhibitory effect of α-humulene on OVA-induced airway allergic inflammation in female BALB/c mice. They showed that therapeutic treatment with α-humulene (50 mg/kg) may be able to decrease leukocyte recruitment (neutrophils, eosinophils and mononuclear) as well as allergic associated mediators including leukotriene (LT)B4 and IL-5 levels in the BALF (Rogerio et al., 2009). The immunohistochemistry staining in this study also revealed the inhibitory effects of α-humulene on the phosphorylation of p65 NF-κB and c-Jun AP-1 subunits, which are the two important modulators for the control production of the Th2 cytokine, IL-5 and the recruitment of leukocytes (Rogerio et al., 2009). These results suggest the potential of α-humulene as a candidate for the treatment of asthma and other allergic diseases.

Linalool
Linalool is a monoterpene in *Z. zerumbet* that contributes to the aromatic scent of this plant (7.7–17.1%) (Baby et al., 2009). In one study, linalool and other 20 types of natural compounds were shown to inhibit β-hexosaminidase release at the concentration of 100 μg/mL in RBL-2H3 cells induced with calcium ionophore, A23187 (Mitoshi et al., 2014). The study also demonstrated the protective effects of orally administered linalool (100 mg/kg)
| Compound | Experimental model | Anti-allergic or immune modulation activities | Concentrations/ Doses of compound used | Mode of application | End-point assessment | Extraction method | Relative quantities in the essential oil extracted from the rhizome of *Z. zerumbet* |
|----------|------------------|---------------------------------------------|-------------------------------------|-------------------|-------------------|------------------|-------------------------------------------|
| Zerumbone | *In vivo* Fournial et al., 2013; Shieh et al., 2015 | Exhibited anti-asthmatic activities in BALB/c mice by decreasing the severity of airway hyperresponsiveness, cytokine secretions and inflammatory cells infiltration. New topical use for the treatment of cutaneous rednesses. | 0.1 – 10 mg/kg, Oral route | Co-treatment (zerumbone administration: day 23–39) (OVA challenge: day 28, 35–36, 37–39) | Day 40 | Solvent extraction (ethanol, dichloromethane), Supercritical CO$_2$, Hydro-distillation | 35.5–84.8% |
| Pinene | *In vivo* Nam et al., 2014 | Exhibited anti-allergic activities by reducing infiltration of inflammatory cells, IgE level and release of allergic mediators in allergic rhinitis (AR)-induced BALB/c mice. | 0.1 – 10 mg/kg, Oral route | Pre-treatment (1 h before OVA challenge from day 15–24) Post-treatment (1 h after OVA challenge from day 15–24) | Day 24 | Solvent extraction (petroleum ether, pentene and benzene), Hydro-distillation | 10.3–31.4% |
| Pinene | *In vitro* Nam et al., 2014 | Inhibited activation of NF-$\kappa$B translocation and mRNA expression of protein mediators in PMACI-induced activation of HMC-1 cells. | 0.1 – 10 µg/mL, Oral route | Pre-treatment (1 h before PMACI challenge) | 8 h after challenge |  |  |
| Humulene | *In vivo* Rogerio et al., 2009 | Exhibited anti-asthmatic activities by reducing eosinophil recruitment into the airways of BALB/c mice induced with allergic inflammation. | 50 mg/kg, Oral route | Pre-treatment (1 h before OVA challenge from day 18–22) | Day 22 | Solvent extraction (petroleum ether, pentene and benzene) | 10.03–17.23% |
| Linanol | *In vivo* Mitsushi et al., 2014 | Demonstrated protective effects against DNP-human serum albumin-induced passive cutaneous anaphylaxis reaction in ICR mice. | 100 mg/kg, Oral route | Pre-treatment (2 h before DNP-HSA challenge) | 30 min after challenge | Solvent extraction (petroleum ether, pentene and benzene), Hydro-distillation | 7.7–17.1% |
| Citral | *In vitro* Mitsushi et al., 2014 | Exhibited anti-allergic properties in RBL-2H3 cells by reducing levels of mediators’ release. | 100 µg/mL, Oral route | Co-treatment (30 min with calcium ionophore challenge) | 30 min after challenge |  |  |
| Caryophyllene | *In vivo* Passos et al., 2007; Jin et al., 2011 | Exhibited anti-allergic activities in OVA-evoked allergic pleurisy in Wistar rats by reducing eosinophil migration, cyclooxygenase (COX) activity and levels of mediators’ release. Exhibited anti-allergic activities in picryl chloride-induced delayed hypersensitivity in ICR mice. | 600 mg/kg, Oral route 50 - 300 mg/kg, Oral route | Pre-treatment (1 h before bee venom challenge) Post-treatment (24 h after picryl chloride or acetone challenge) | 6 h after challenge 25 h after challenge | Solvent extraction (petroleum ether, pentene and benzene), Hydro-distillation | 6.9–10.2% |
| Caryophyllene | *In vitro* Jin et al., 2011 | Exhibited anti-allergic properties in rat basophilic leukemia (RBL)-1 cells by reducing 5-lipoxygenase (LOX) inhibitory activity as well as levels of mediators’ release. | 30 – 300 µg/mL | Pre-treatment (10 min before calcium ionophore challenge) | 10 min after challenge |  |  |

(Continued)
TABLE 1

| Compound       | Experimental model | Anti-allergic or immune modulation activities                                                                 |
|----------------|--------------------|-------------------------------------------------------------------------------------------------------------|
| Borneol        | In vivo            | Exerted inhibitory effects on histamine release from abdominal mast cells induced by ovalbumin (OVA).       |
|                |                    | End-point assessment: No data                                                                               |
| Limonene       | Ex vivo            | Reduced Dermatophagoides farinae-induced airway remodeling and airway hyperresponsiveness (AHR) in mice.   |
|                |                    | End-point assessment: Pre-treatment (1 h before OVA challenge from day 27–29)                               |

Caryophyllene

Caryophyllene, one of the natural bicyclic sesquiterpenes in Z. zerumbet, contributes to the spiciness taste of this plant (Baby et al., 2009). In comparison to Z. nimmonii and Z. officinale which have been reported to possess 26.9–42.2% and 15.29% of caryophyllene, respectively, Z. zerumbet has a relative lower quantity of caryophyllene (6.9–10.2%). Studies have shown that the oral administration of caryophyllene significantly inhibited the oedemagenic response caused by Apis mellifera venom in the OVA-sensitized male Wistar rat paws (Passos et al., 2007). Furthermore, the administration of caryophyllene significantly reduced the eosinophil migration at the site of venom induction, leading to reduced levels of tumor necrosis factor alpha (TNF-α), prostaglandin E2 (PGE2) and COX activity (Passos et al., 2007). These results strongly suggest the potential of caryophyllene in the treatment of allergic conditions.

Another study conducted by Jin et al. (2011) demonstrated that preinucubation of caryophyllene (100 µM) with rat basophilic leukemia-1 (RBL-1) was able to significantly reduce 5-LOX inhibitory activity as well as the release of cysteinyl LTs (LTC4/LT/D/E4), and the effect was more prominent in comparison to the other two bioactive compounds of Z. zerumbet - limonene and pinene (Jin et al., 2011). Caryophyllene also significantly attenuated the antigen-induced degranulation of β-hexosaminidase and phosphorylation of Lyn molecules in RBL-2H3 cell culture (Jin et al., 2011). Furthermore, the in vivo immune modulatory effects of caryophyllene were also demonstrated. Caryophyllene was able to significantly inhibit the picryl chloride-induced delayed type hypersensitivity (DTH) response in mice, when given orally (100–300 mg/kg), as evidenced by decreased measurements in the ear thickness of mice (Jin et al., 2011). These findings concluded that caryophyllene exerts anti-allergic activity against mast cell degranulation and offers immune modulatory effects against DTH.

Limonene

Limonene is the only major bioactive compound found exclusively in Z. zerumbet in the Zingiberaceae family (Koga et al., 2016). Limonene has shown a potent reduction in the airway inflammatory reactions with improving asthma symptoms in Dermatophagoides farinae-induced allergic airway inflammation of male BALB/c mice (Hirota et al., 2012). One study demonstrated a lowered level of serum total IgE, allergen specific IgG1 and allergic associated mediators (IL-5 and IL-13) in mice after inhalation of limonene (1 mg/kg) (Hirota et al., 2012). Additionally, limonene was able to decrease AHR in mice against DNP-HSA induced passive cutaneous anaphylaxis (PCA) reaction in mice whereby linalool significantly reduced the amount of Evans blue dye present in the exudates collected from ear samples (Mitoshi et al., 2014). In the discussion it was hypothesized that the anti-allergic effects of linalool may be at least in part dependent on the inhibition of NF-κB activation (Mitoshi et al., 2014). However, further investigation should be carried out, as its underlying molecular mechanism remains unelucidated.
by suppressing the number of eosinophils found in the collected BALF (Hirota et al., 2012). It also significantly reversed allergen-induced lung histopathological changes in mice by lowering perivascular and peribronchial infiltration of eosinophils, goblet cells hyperplasia, airway fibrosis and smooth muscle thickness (Hirota et al., 2012). These findings have shown that limonene may be beneficial as a prophylactic and therapeutic agent for asthma in the future.

DISCUSSION

Most major bioactive compounds found in the essential oils extracted from the rhizome of Z. zerumbet are terpene compounds with long hydrocarbon tails, generally resulting in low polarity (Jiang et al., 2016). As such, a few preferred ways of extracting terpene compounds from Z. zerumbet are hydrodistillation and solvent extraction using organic solvents such as ethanol and methanol; or non-polar solvents such as petroleum ether, pentene, hexane, and benzene (Kalantari et al., 2017). A previous study by Tewtrakul and Subhadhirasakul (2007) showed that an ethanolic extract of Z. zerumbet containing both polar and non-polar compounds exhibited exceptional anti-allergic effects by inhibiting the release of β-hexosaminidase from RBL-2H3 cells. However, not much attention has been given to the anti-allergic effects of other extracts from Z. zerumbet and particularly essential oil, in which the main constituent is zerumbone. Although it has once been reported that the essential oil of Z. zerumbet failed to inhibit β-hexosaminidase, the reported yield of essential oil from the whole plant of Z. zerumbet in that study was only 3.0%, in comparison to other studies reporting yields ranging from 5 to 13% (Rashid and Pihie, 2005; da Silva et al., 2017). It is also important to note that the essential oils used in that particular study were extracted from the whole plant but not the rhizomes of Z. zerumbet alone (Tewtrakul and Subhadhirasakul, 2007). Low levels of bioactive compounds present in the yield in particular terpene compounds may be too low to significantly exhibit an anti-allergic response. Further studies should be carried out with the yield of extracted essential oil from the rhizomes of Z. zerumbet. Distilled hexane can be added during the hydro-distillation process to increase the yield of oil extracted from Z. zerumbet (Nik Norulaini et al., 2009). It would be interesting to study whether the essential oils extracted from the rhizomes of Z. zerumbet exhibit anti-allergic response as the extracted oil particularly from the rhizomes of Z. zerumbet has been proven to have many beneficial properties such as analgesic activity (Sulaiman et al., 2010), anti-nociceptive activity (Khalid et al., 2011) and anti-microbial activity (Kader et al., 2010).

Due to the presence of various bioactive compounds in a plant extract, it is difficult to confirm which bioactive compound contributes to the intended beneficial effects in a disease model (Sasidharan et al., 2011; Katiyar et al., 2012). Therefore, it would be much preferable to identify and isolate the major bioactive compounds present in a plant extract and study them individually. Since many major bioactive compounds found in the essential oil extracted from the rhizomes of Z. zerumbet have been shown to be effective in treating allergic responses, it would be important to know whether the doses used in these studies are practical to be translated into clinical studies. The highest oral doses of Z. zerumbet extract used in rats and mice were 600 and 300 mg/kg, respectively, equivalent to 97 and 24 mg/kg in humans, according to the human equivalent dose equation (Reagan-Shaw et al., 2016). In terms of bioactive compounds, the highest oral dose of purified zerumbone compound isolated from Z. zerumbet used in mice was 10 mg/kg, which is equivalent to 0.81 mg/kg when translated for human consumption. When the translated doses of these bioactive compounds are compared with cromolyn sodium, which is a well-known standard mast cell stabilizer used in many clinical studies to treat various allergic diseases (Burgher et al., 1971; Businco et al., 1983; Burks and Sampson, 1988), the doses used ranging from 8 to 40 mg/kg. Although all of the bioactive compounds found in the essential oil extracted from the rhizomes of Z. zerumbet reported in this mini-review are yet to enter clinical trials, this mini-review provides an insight of the recommended doses to be used in any future studies involving these bioactive compounds. Comparisons of the doses used in animal and human studies also indicate the potential of these bioactive compounds to be developed as therapies for the treatment of allergy and allergic-related diseases in future.

CONCLUSION

This mini-review summarizes the anti-allergic and immunomodulatory properties of the major bioactive compounds found in the essential oil extracted from the rhizomes of Z. zerumbet in order to demonstrate the importance of Z. zerumbet in the treatment of allergy and allergic-related diseases, in addition to the other biomedical applications which have been widely reported and extensively studied. Future studies should focus in-depth on exploring the potential therapeutic applications of the major bioactive compounds found in the essential oil extracted from the rhizomes of Z. zerumbet toward various allergy-related diseases. It is also important to dissect the mechanism of action of these major bioactive compounds in order to determine how they exert their anti-allergic properties.

AUTHOR CONTRIBUTIONS

JT and CT prepared the manuscript. DI reviewed the drafts and provided important information for the completion of this manuscript. CT conceived the idea, reviewed the drafts, and provided important information for the completion of this manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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