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Ethnobotany, Phytochemistry and Pharmacology of *Zingiber cassumunar* Roxb. (Zingiberaceae)

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Abstract
Zingiber cassumunar Roxb. Known as "Tekhao Yaikhu" in Manipur is often used as traditional medicine for inflammation, sprains, rheumatism, muscular pain, wounds and asthma. Phytochemical investigations by various eminent scientists have revealed that many components are bio-active due to the presence of broad range of secondary active metabolites such as terpenoids, flavonoids, alkaloids, steroids, and benzenoids. Sabinene and terpinen-4-ol have been reported as the main constituents of all the reported oils. *In vitro*, *in vivo* examinations or clinical evaluations have shown the major pharmacological activities that includes analgesic activity, antimicrobial activity, anti-inflammatory activity, anticancer and radical scavenging activity, anti-malarial activity and others activities. The information in this review is intended to serve as a reference tool to practitioners in the fields of ethnopharmacology, natural product chemistry and drug discovery research.

Keywords: Anti-cancer, DMPBD, Phenylbutenoid, Terpenes, *Zingiber cassumunar* Roxb.

1. Introduction
The family Zingiberaceae is a monocotyledonous angiosperm of plant kingdom belonging to the order Zingiberales with 50 genera and 1500 species found worldwide. The North-East region of India has the greatest concentration reporting 19 genera and about 88 species out of the total 22 genera and 170 species of Zingiberaceae [1]. Zingiberaceae family is an important natural resource providing many useful products for food, spices, medicines, dyes, perfume and aesthetics [2].
Zingiber cassumunar Roxb. (Family Zingiberaceae), locally known as "Tekhao Yaikhu" in Manipur, India. The root of this plant is perennial, tuberous, furnished with long, white fleshy fibres and jointed like ginger but much larger: when fresh, of a deep yellow: possessing a strong camphoraceous odour, warm spicy, bitterish taste (Roxburgh) [3]. Commonly known as Cassumnar ginger, this plant have varied names-Bengal root or Curry turmeric in English; Plai in Thailand; Kunyit bolai in Malaysia; Banada in Hindi; Agala Shunti in Kanada and Vanardraka in Sanskrit. The genus comprises about 100-150 species and is distributed in tropical and subtropical Asia [4].
This valuable plant, *Z. cassumunar* Roxb. have been used in folk medicine for the treatment of conditions such as inflammation, sprains, rheumatism, muscular pain, wounds and asthma, as a mosquito repellent, a carminative, a mild laxative, an antidysenteric agent, cough and used as a cleansing solution for skin diseases. A major part of the pale amber colour oil obtained from *Z. cassumunar* Roxb. Consists of monoterpenes with sabinene and terpinen-4-ol as main constituents. Sesquiterpenes accounted for a small part of the oil with sesquiphellandrene being the main constituent. In addition to these terpenes, the oil contains several Phenylbutenoid [5]. With the rising popularity of herbal products as drugs and cosmetic being reported, methanolic extract of Z. cassumnar have inhibited PGE production by in human promonocytic U937 cells (IC_{50} = 7.7 µg/mL [6] and significantly inhibiting CYP3A4 i human liver microsomes [7]. This review is aimed to summarize on ethnobotany, phytochemistry and pharmacology of this valuable herbs.

2. Material and Methods
2.1 Ethnobotany and traditional uses of *Z. cassumnar*
Ethnobotany is concerned with local people's interaction with plants and medicinal uses in treating human health problems, social and economic support systems and benefits in our day today life. From the variety of many medicinal plants, *Z. cassumnar* has traditionally, been widely used to beautify the skin, to ward off asthma, chronic, colds, nausea poultice, decoction, & medicinal massage treatment. *Z. cassumnar* is used in relieving abdomen pain,

headache, stomachache, anodyne, constipation, colic, cramps, constipation, fever, flatulence, gonorrhoea, jaundice, malaria, numbness, parturition, vermifuge. Moreover, it has also been used in joint and muscle inflammation and helps to reduce fever generation. It has antiviral, antiseptic, analgesic and antibacterial properties as well. It also contains cassumunarin that have especially antioxidant property. It has been reported that *Z. cassumnar* is used in the treatment of asthma in traditional Thai [8-13]. The traditional uses of *Z. cassumnar* in different countries are listed in the **table 1** below.

Table 1: The traditional uses of *Z. Cassumnar* rhizome in different countries.

S.No.	Country	Traditional uses
1.	India	Oral consumption of the paste treats dyspepsia and stomach bloating [13].
2.	Thailand	Oil relieves muscle pain, used as a rubbing or poultice, a decoction, analcoholic tincture, a massage or eaten fresh [14].
3.	Malaysia	Used for postpartum medication [13, 15]. Treat stomach-ache, constipation, diarrhoea, flatulence and as a vermifuge [16].
4.	Indonesia	Rubbed in the abdomen to relieve colic in children [16].
5.	Canada	Used for treating asthma, with either tarragon (*Artemisia dracunculus* L.) or Rosemary (*Rosmarinus officinalis* L.) and cypress (*Cupressus sempervirens* L.) [14].
6.	USA	Used as a post-operative blend on knee surgery [14].

2.2 Phytochemistry of *Z. cassumnar*

Phytochemical analysis revealed that carbohydrate, tannin, alkaloid, steroid, terpenoid, and flavonoid were present in the extracts of *Z. cassumnar* rhizome. The Chemical constituents isolated from the extract of the rhizome of *Z. cassumnar* were cassumunarin A, cassumunarin B, cassumunarin C, terpinen-4-ol, alpha and beta-pinene, sabinene, myrcene, terpinene, limonene, *p*-cymene, terpinolene, phenyl Butanoic dimers, (E)-4-(3',4'-dimethoxyphenyl)-but-3-en-l-ol On steam distillation, the content of essential oil of *Z. cassumnar* varies, 0.5% in dried rhizomes and 3.49% for fresh rhizomes. Almost compounds extracted from *Z. cassumnar* were monoterpenes which exhibits the least volatility among all constituents, containing many known major components, such as α-pinene, β-pinene, sabinene, α-terpinene and γ-terpinene **(fig.1)**. Sabinene and terpinen-4-ol have been reported as the main constituents of all the reported oils in the world. Of which terpinene-4-ol is a remarkable oxygenated compound present in the rhizome [17-22].

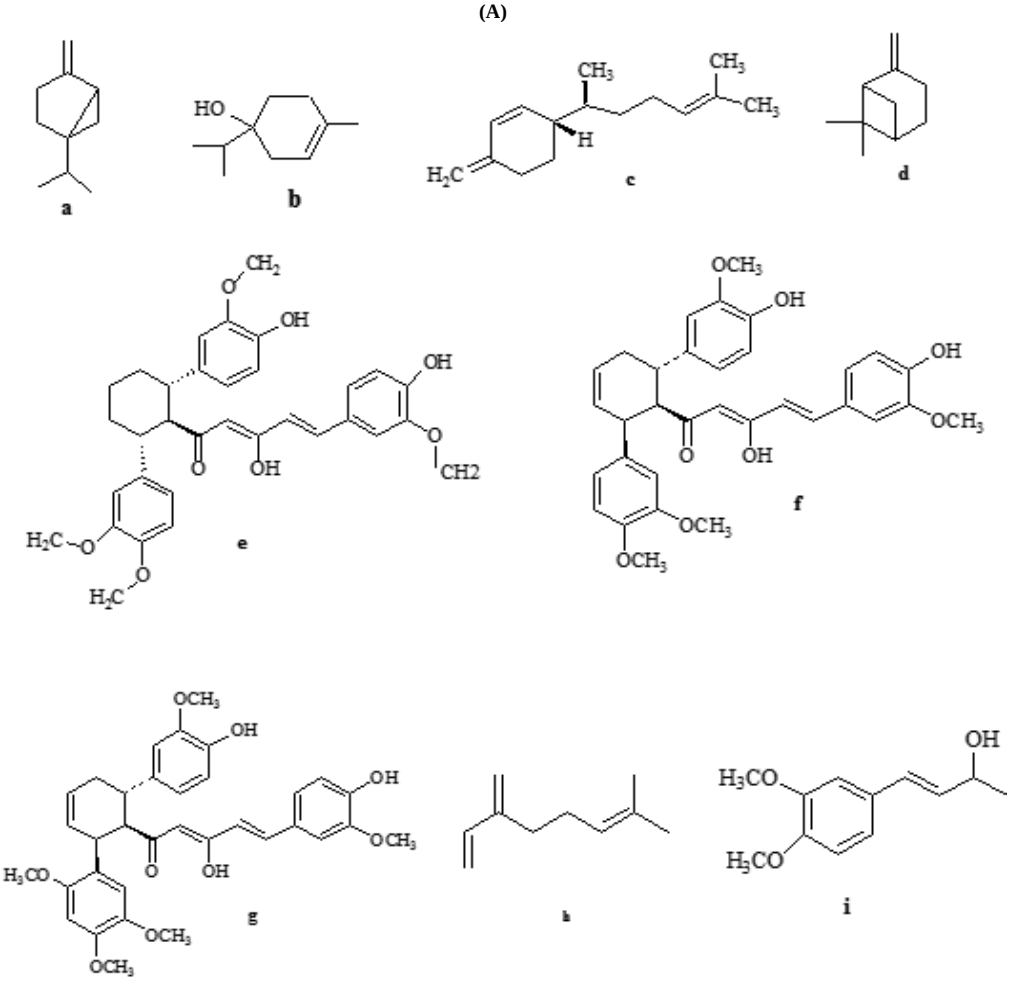

Fig 1 (A): Chemical structures reported from *Z. cassumnar* Roxb.-(a) sabinene; (b) terpineol 4-ol; (c) Sesquiphellandrene; (d) *β*-Pinene; (e) Cassumunarin A; (f) Cassumunarin B; (g) Cassumunarin C ; (h) myrcene; (i) (*E*)-4-(3′, 4′-dimethoxyphenyl)but-3-en-2-ol

(B)

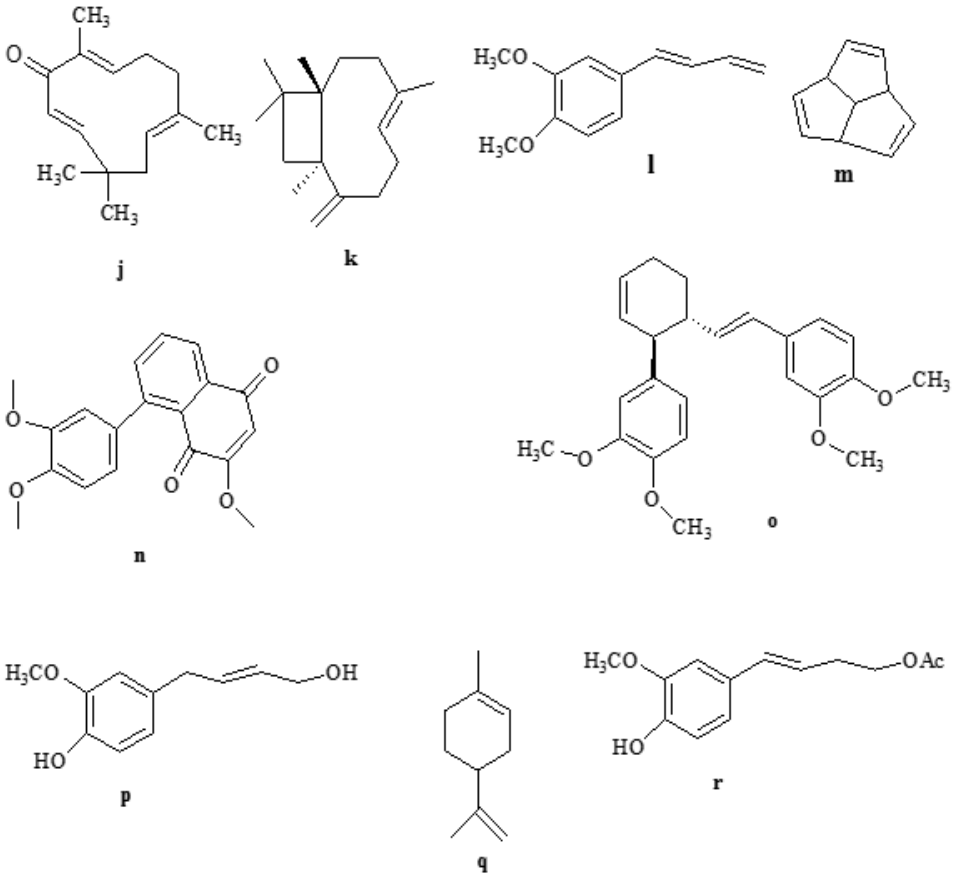

Fig 1 (B): Chemical structures reported from *Z. cassumnar* Roxb. - (j) zerumbone; (k) Caryophyllene; (l) (E)-1-(3, 4-Dimethoxyphenyl) butadiene, DMPBD; (m) triquinacene; (n) Cassumunaquinone; (o) (+/-)trans-3-(3′,4′-dimethoxyphenyl)-4- [(*E*) 3‴, 4″ dimethoxystyryl] cyclohex-1-ene; (p) (E)-4-(4-Hydroxy-3- methoxyphenyl) but-2-en-1-ol ; (q) limonene; (r) (E)-4-(4-hydroxy-3-methoxyphenyl)-but-3-en-1-yl acetate.

2.3 Yield of essential oils from leaves and rhizome of *Z. cassumnar*

Sabinene was detected as the main component (14.99%) of the leaf essential oil on GC-MS analysis by GC-MS Electron Impact ionization (EI) method on GC-17A gas chromatograph (Shimadzu) coupled to a GC-MS QP 5050A mass spectrometer (Shimadzu). The remaining constituents, including β-pinene (14.32%), caryophyllene oxide (13.85%), caryophyllene (9.47%),γ-pinene (6.31%), methyl p-methoxy cinnamate (5.02%), triquinacene, 1, 4, bis (methoxy) (3.79%) and camphene (3.56%), were present at low concentrations whereas the main component of *Z. cassumunar* rhizome essential oil were triquinacene, 1,4-bis (methoxy), (Z)-ocimene and terpinen-4-ol. The rhizome oil was rich in triquinacene, 1, 4-bis (methoxy) (26.47%), (Z)-ocimene (21.97%), terpinen-4-ol (18.45%), γ-terpinene (3.86%), β-phellandrene (3.49%) and cis-sabinene hydrate (3.00%). Thailand gave 11.07mL/kg as the highest essential oil yield, whereas those from the east gave 4.95 mL/kg as the lowest yield [23].

3. Pharmacological properties of *Z. cassumnar*

3.1 Antimicrobial activity

A number of pure compounds isolated from the plants have been found to have antimicrobial activity. Terpinen-4-ol (32%), was responsible for its antimicrobial activities [24], Disc diffusion screening studies have shown that Plai (Thai name of *Z. cassumnar*) oil was very potent against dermatophytes and yeasts, whereas bacteria were the least susceptible organisms to it. The antimicrobial activities of Plai oil was also contributed by sabinene content (34%–44%), another main constituent of Plai oil [25]. The 5% Plai oil gel (pH 5.0) was potent against dermatophytes and yeasts at much lower concentrations than against Gram-positive and Gram-negative bacteria, which indicates that Plai oil and the 5% Plai oil gel should be more effective for the treatment of fungi rather than bacteria. Chemical investigation have shown that the rhizomes of *Z. Cassumunar* contains a sesquiterpene compound, called zerumbone fig.1(j) which exhibit strong anti-fungal activities against *Rhizoctonia solani*, the damping-off pathogen. Its minimum effective dose against *R. solani* was 1000 ppm, much lower than some commercial fungicides. Zerumbone has good anti-fungal activity, a narrow fungi toxic spectrum and is not phytotoxic [26]. In addition the rhizome oil of *Z. cassumnar* have been found to exhibit high activity against dermatophytes and yeasts while the leaves showed absolute toxicity (100% growth inhibition) against *B. cinerea* at 500 ppm (mg/L) [27].

3.2 Anti-oxidant activity

Two groups of compounds were found to be responsible for anti-oxidant activity of *Z. cassumunar.* The yellow colour of the rhizome is attributed to the presence of curcuminoids in the substance. New curcuminoids, cassumunin isolated from this plant showed significant anti-oxidant activity. Cassumunin A and B own a potent protective action against oxidative stress

[28]. New Phenylbutenoid that was isolated shows inhibitory effects to nitric acid production in mouse peritoneal macrophages. Amongst those with significant inhibitory effects are plain III (IC50=24 µM), (E)-1-(3, 4-dimethoxyphenyl) buta-1, 3-diene (69 µM), (E)-1-(2, 4, 5-trimethoxyphenyl) buta-1, 3-diene (83 µM), and Cassumunaquinone 1 (47 µM) [29].

3.3 Insecticidal-activity

Z. cassumunar Roxb. Exhibited significant insecticidal activity and caused strong larval mortality and /or reduction of larval weight at the lowest concentration (1250 ppm). The constituent derivatives of benzene or benzenoid including phenylbutenoids, cassumunins and cassumunarins reported previously were used as flavour and fragrance. In addition, the other minor compounds found in small amount in the oil assemble include p-cymene, α-phellandrene, terpinolene, curcumin, α-thujone, sabinene hydrate and terpineol. Bioassay- guide isolation of the rhizomes of *Z. cassumunar* afforded two phenylbutanoid derivatives which were shown to be responsible for the insecticidal activity of the crude extract. Both compounds were identified from their NMR and mass spectra and by comparision with previously published data [30]. The LC_{50} values of both compounds were 0.5 and 3.6 µgcm^{-2} respectively. DMPBD provide insecticidal activity in bioassays with brown dog ticks (Rhipicephalus sanguineus) [31].

3.4 Anti-cancer

(+/-)trans-3-(3′,4′-dimethoxyphenyl)-4-[(*E*)-3‴,4‴-dimethoxy-styryl] cyclohex-1-ene have shown anti- proliferative effects on A549 human lung cancer cells by inhibiting cell progression at the G0/ G1 phase and has also significant inhibitory effects on P-gp inhibitory activity making it a potent that could reverse the P-gp-mediated multidrug resistance in human cancer chemotherapy. Petroleum extract of *Z. cassumunar* containing ZC-B11 collected from hexane: EtOAc (8 : 2) by column chromatography, further washed with hexane and methanol to give white solid, *cis*-3-(3′,4′-dimethoxyphenyl)-4-[(*E*)-3‴,4‴-dimethoxystyryl]cyclohex-1-ene, a phenylbutenoid dimer having molecular weight 380.199 g/mol with molecular formula $C_{24}H_{28}O_4$ and melting point 91 °C – 92 °C was found to exert the most potent antiproliferative effect towards CEMss cells with IC_{50} value of 7.11 ± 0.24 μg/mL followed by HepG2, MCF-7, MDA-MB-231, and HeLa cells with IC_{50} values of 17.65 ± 0.32 μg/mL, 21.28 ± 0.25 μg/mL, 32.38 ± 0.41 μg/mL, and >50 μg/mL, respectively, after 72 h incubation. The antiproliferative activities of ZC-B11 on CEMss, HepG2, MCF-7, and MDA-MB-231 cell lines exhibited IC_{50} values below 30 μg/mL. However, the lowest IC_{50} value of ZC-B11 on CEMss suggested preliminarily that ZC-B11 possesses high anticancer activity against T-acute lymphoblastic leukemia without producing any cytotoxic effect on human blood mononuclear cells up to the concentration of 50 μg/mL [32].

3.5 Anti-cholinesterase activity

The enhancement of the cholinesterase inhibitory activity of *Z. cassumunar* oil was done by using a micro emulsion technique. Pseudoternary phase diagrams of the oil, water, and surfactant/co-surfactant mixture were constructed using a water titration method. Effects of co-surfactant, surfactant/co-surfactant ratio, ionic strength, and pH were examined by means of the microemulsion region which existed in the phase diagrams. The inhibition of acetylcholinesterase and butyrylcholinesterase were tested by Ellman's colorimetric assay. It was found that the oil possesses inhibitory activity against not only but also. Formulation of the oil as ME revealed that alkyl chain length and number of hydroxyl groups of co-surfactant exhibited a remarkable effect on the pseudoternary phase diagram. Longer alkyl chains and more hydroxyl groups gave smaller regions of MEs. Ionic strength also affected the ME region. However, the phase behaviour was hardly influenced by pH. The suitable *Zingiber cassumunar* oil ME was composed of Triton X-114 in combination with propylene glycol. The anti-cholinesterase activity of this ME was much higher than that of native *Zingiber cassumunar* oil. It exhibited twenty times and twenty five times higher inhibitory activity against acetylcholinesterase and butyrylcholinesterase, respectively [33].

3.6 Anti-inflammatory

The anti-inflammatory activity of (*E*)-4-(3′, 4′-dimethoxyphenyl) but-3-en-2-ol, a compound isolated from the hexane extract of *Z. cassumunar* Roxb. Was assessed using various inflammatory models in comparison with aspirin, indomethacin and prednisolone. The results obtained showed that the anti-inflammatory effect of this compound mediated prominently on the acute phase of inflammation. It exerted marked inhibition on carrageenin-induced rat paw edema as well as on the exudate formation, leukocyte accumulation and prostaglandin biosynthesis in carrageenin-induced rat pleurisy. In the rat paw edema model, carrageenan induces edema formation in three distinct phases according to the mediators involved [34]. Panthong and his co-worker in Thailand Institute of Scientific and Technological Research have isolated some compounds with known chemical structures from *Z. cassumunar* Roxb. Of which DMPBD (E)-1-(3, 4-dimethoxyphenyl) butadiene obtained from its hexane extract was found to possess a potent anti-inflammatory activity. The extract of *Z. cassumunar* was demonstrated to have anti-inflammatory activity in animal model induced rat paw edema [35]. Moreover, phenylbutenoids are typical non-polar substances in the rhizomes of *Z. cassumnar* and recent studies have reported that these phenylbutenoids also have anti-inflammatory activities.

4. Conclusions and future prospects

Among the genus of Zingiberaceae family, *Z. cassumnar* is believed to possess various biological activities starting from the various phytochemical contents. This review is an attempt that offers many opportunities to investigate the various functions of *Z. cassumnar* and its prospects in pharmaceutical industries. It is believed that detailed information as presented in this review on its phytochemistry and various pharmacological properties of the extracts and the constituents may provide incentive for proper evaluation of the use of the plant in medicine and in agriculture. Activities such as its effects on anti-cancer and anti-inflammatory properties of the phenylbutenoids isolated from the plant need to be studied. Although, the pharmacological properties of *Z. cassumnar* seems to have been determined, the mechanism of these principles is still unknown. The bioassay guided isolation and identification of the bioactive components is still needed and detailed researches are also required to reveal the structure activity relationship of these active constituents. Outcome of the future research in the aforementioned areas will provide a convincing support for the future clinical uses of *Z. cassumnar* in modern medicine.

5. Abbreviations

DMPBD: (E) -1-(3, 4-dimethoxyphenyl) butadiene,
PGE: Prostaglandin E,
CYP3A4: Cytochrome P450 3A4,
GC-MS: Gas chromatography–mass spectrometry,
ZC-B11: cis-3-(3′, 4′-Dimethoxyphenyl)-4-[(E)-3‴, 4‴-dimethoxystyryl] cyclohex-1-ene and
EtOAc: Ethyl acetate.

6. Competing interests

The authors declare that they have no competing interest.

7. Authors' contribution

CBS conceived the topic and planned the review. SBC, NSD and NMD did the literature searching, data collection, critically reviewed the literature and drafted the manuscript. All authors read and approved the final version of the manuscript.

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