Thieme

Zingiber zerumbet: A Scoping Review of its Medicinal Properties

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ABSTRACT

Zingiber zerumbet, a plant native to tropical and subtropical Asia, has a vast range of traditional uses and has been continuously studied for its medicinal properties. However, a systematic methodological approach in evidence synthesis on the plant's efficacy is lacking, and there is a need to elicit the current research status of this plant. This scoping review was conducted to systematically explore and collate the available scientific evidence on the efficacy of *Z. zerumbet* and its main phytoconstituents in various formulations, their biological mechanisms, and their safety. Results included 54 articles consisting of animal studies, while there were no published human studies. Only half of the included studies provided adequate reporting on the quality-related details of *Z. zerumbet* formulations. Identified pharmacological activities were analgesic, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, anti-neoplastic, immunomodulatory, antioxidant, antipyretic, hepatoprotective, nephroprotective, gastroprotective, and locomotor-reducing activities. Notably, the ethanolic extract of *Z. zerumbet* was found to be well tolerated for up to 28 days. In conclusion, *Z. zerumbet* and zerumbone have various pharmacological effects, especially in analgesic and anti-inflammatory models. However, there is still a pressing need for comprehensive safety data to conduct clinical trials.

Introduction

Zingiber zerumbet (L.) Roscoe ex Sm. is a species in the Zingiberaceae family and is commonly known as *lempoyang* in Malay and, among others, bitter ginger [1] and shampoo ginger in English [2]. It is native to tropical and subtropical Asia [3] and has spread throughout the Pacific [4] due to cultivation for ornamental and medicinal purposes, as well as naturalisation [5]. The rhizomes of *Z. zerumbet* are especially known for their medicinal properties. *Z. zerumbet* has a wide range of traditional uses, including treatments for typhoid, stomach ailments, allergies, poisoning, appetite enhancement, constipation, haemorrhoids, asthma, skin diseases, and postnatal care [6, 7].

Over the past decade, numerous narrative reviews have discussed various aspects of *Z. zerumbet*, including its botanical qualities, phytochemistry, pharmacognosy, pharmacological activities, and biological qualities, with the most recent comprehensive review dating back to 2017 [8–11]. A mini-review of *Z. zerumbet* in 2023 reported on its potential osteoinduction properties [12]. However, a consistent limitation among these works is the lack

LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine
ACO	acyl-CoA oxidase
ACOX1	peroxisomal acyl-coenzyme A oxidase 1
AEZZ	aqueous extract of *Z. zerumbet*
AgNORs	silver-stained nucleolar organiser regions protein
AMPK	adenosine monophosphate-activated protein kinase
ATP	adenosine triphosphate
Bax	B-cell lymphoma protein 2- associated X
Bcl-2 protein	B-cell lymphoma protein 2
bFGF	basic fibroblast growth factor
C/EBPα	cytosine-cytosine-adenosine-adenosine-thymidine enhancer-binding protein alpha
CB-1	cannabinoid receptor 1
cGMP	cyclic guanosine monophosphate
COX-2	cyclooxygenase-2
CPT-1	carnitine palmitoyl transferase 1
EEZZ	ethanol extract of *Z. zerumbet*
ELEZZ	diethyl ether layer extract of *Z. zerumbet*
EOZZ	essential oil of *Z. zerumbet*
ERK1/2	extracellular signal-regulated kinase ½
ETBF	enterotoxigenic *B. fragilis*
FGFR1	fibroblast growth factor receptor 1
FOXO1	forkhead box protein O1
GLUT4	glucose transporter type 4
HL-60	human promyelocytic leukaemia cell
Hmox1	heme oxygenase 1 gene
HO-1	heme oxygenase-1
HSP27	heat shock protein 27
i.p	intraperitoneal
ICAM-1	intercellular adhesion molecule-1
IL-10	interleukin 10
IL-1β	interleukin 1 beta
IL-6	interleukin-6
iNOS	inducible nitric oxide synthase
IκB	I kappa B
LOAEL	lowest-observed-adverse-effect level
LPS	lipopolysaccharide
MCP-1	monocyte chemoattractant protein-1
MIP-2	macrophage inflammatory protein 2
miR-146b	microRNA-146b
MMP	matrix metalloproteinase
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
Nrf2	nuclear factor-erythroid factor 2-related factor 2
p.o	per oral
p38 MAPK	p38 mitogen-activated protein kinase
P388D$_1$	murine lymphoid neoplasm cell line
PEPCK-C	cytosolic phosphoenolpyruvate carboxykinase
PGC1-α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PGD$_2$	Prostaglandin D2
PGE$_2$	prostaglandin E$_2$
PKCδ	protein kinase C delta
PPARα	peroxisome proliferator-activated receptor alpha
s.c	subcutaneous
SIRT1	sirtuin (silent mating type information regulation 2 homolog) 1
SREBP-1c	sterol regulatory element-binding protein 1
TGF-β1	transforming growth factor beta 1
TNF-α	tumour necrosis factor alpha
TRPV1	transient receptor potential vanilloid 1
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
w/w	weight for weight

of a systematic methodological approach in evidence synthesis, with a majority focusing on *in vitro* studies. In view of the rising interest in the health benefits of *Z. zerumbet*, this scoping review aims to systematically explore, consolidate, and provide an overview of both animal and human studies concerning *Z. zerumbet* and its major phytoconstituents related to its pharmacological efficacy, the potential biological mechanisms involved, and their safety profile. With this information, the potential areas of its therapeutic use that remain unexplored will be uncovered.

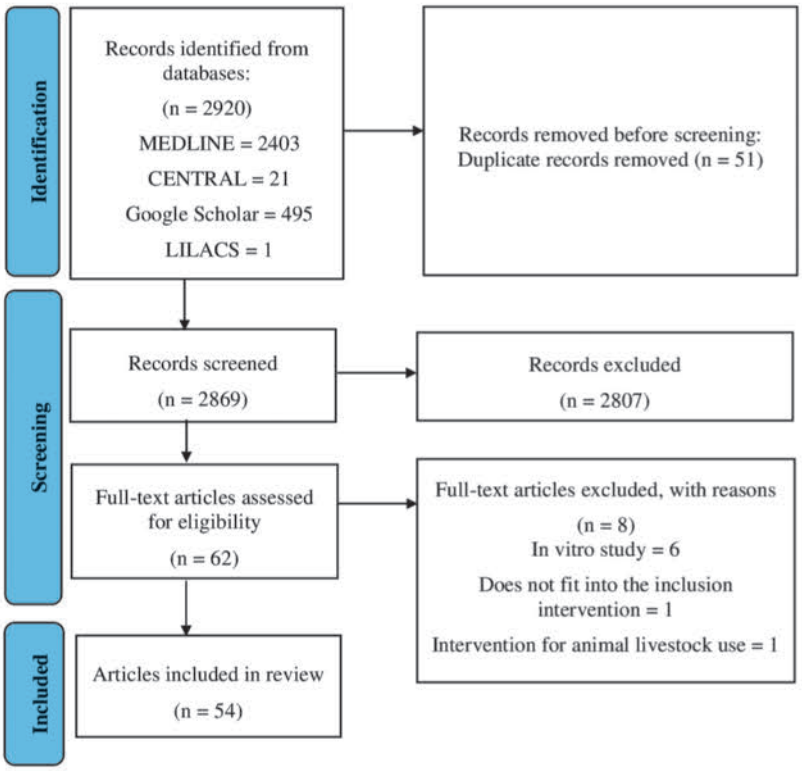
Results

Study Inclusion

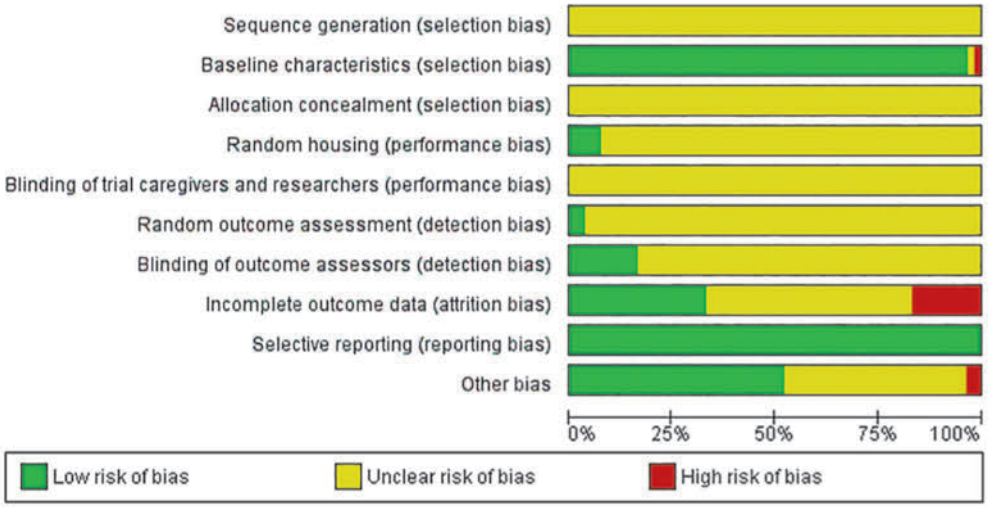
A total of 54 articles were selected from an initial pool of 2920 records. All included studies were preclinical *in vivo* studies, as no published clinical studies were identified. The study selection process is presented in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [13] flowchart, as shown in ▶ **Fig. 1**.

Characteristics of included studies

Overall, the studies examined the efficacy and safety of *Z. zerumbet* in the form of extracts and its primary phytoconstituent, zerumbone. These extracts and zerumbone were sourced from the rhizomes of the *Z. zerumbet* plant. Out of the included studies, 26 underwent an authentication process through the deposition of a voucher specimen of the plant. A total of 33 studies reported a qualitative analysis to identify the phytochemicals associated with *Z. zerumbet*, while 25 studies carried out a quantitative analysis to ascertain the composition of these phytochemicals in *Z. zerumbet*. Only one study utilised a standardised formulation of the ethanolic extract of *Z. zerumbet* (EEZZ). The interventions were administered via topical, oral, subcutaneous, intraperito-



▶ **Fig. 1** PRISMA flowchart.

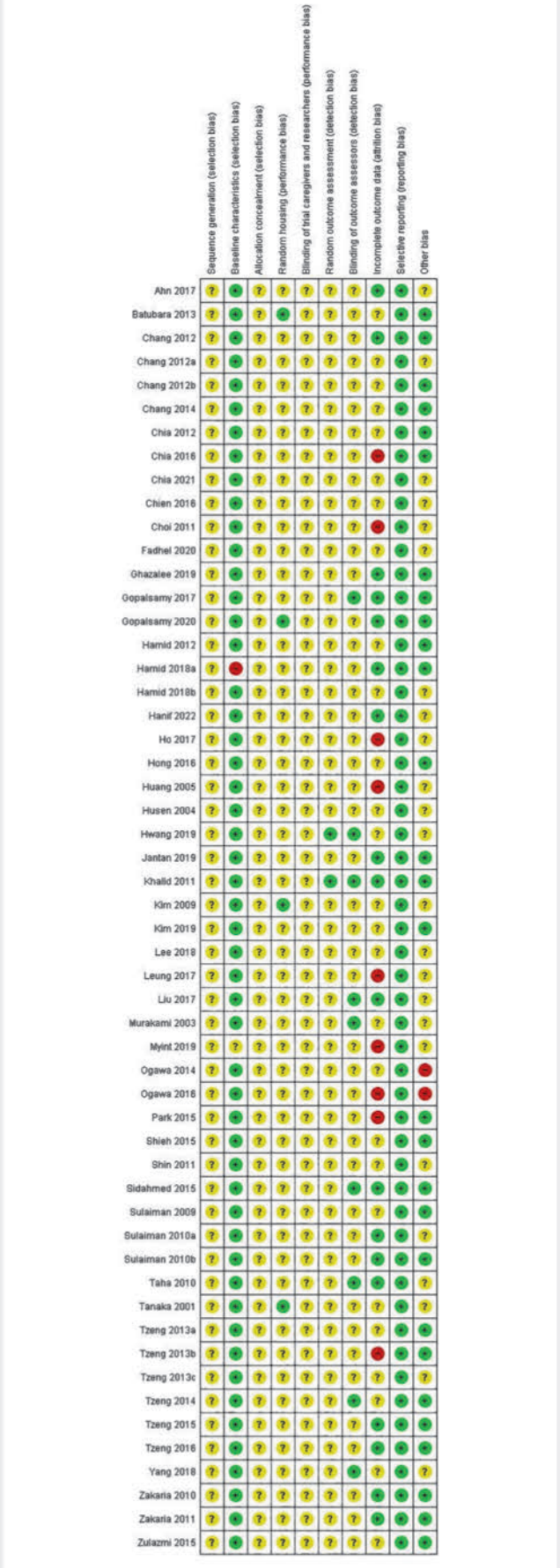


▶ **Fig. 2** Risk-of-bias assessment graph.

neal, intraduodenally, and inhalation routes. The checklist for the qualitative, quantitative, and standardisation of the herbal interventions for all included studies can be found in Supplementary material: **Table 1S**.

Risk of Bias Assessment

The risk of bias (ROB) assessment for the studies is presented in ▶ **Fig. 2** (ROB graph) and ▶ **Fig. 3** (ROB summary). Over 75% of the studies exhibited a low ROB in baseline characteristics and selective reporting. However, half of the studies showed an unclear



▶ **Fig. 3** Risk-of-bias summary.

ROB with regards to sequence generation, allocation concealment, random housing, blinding of trial caregivers and researchers, random outcome assessment, and blinding of outcome assessors. This suggests that many animal studies related to *Z. zerumbet* show concerns regarding selection, performance, and detection bias. Nearly 25% of the studies displayed a high ROB for incomplete outcome data (attrition bias).

Efficacy

All 54 included studies were preclinical *in vivo* studies, with 38 further supported by additional *in vitro* findings that explored potential mechanisms of action. The main pharmacological activities identified from the studies encompassed analgesia, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, anti-neoplastic, immunomodulatory, antioxidant, antipyretic, hepatoprotective, nephroprotective, gastroprotective, and reduced locomotor activities. The scientific evidence detailing the pharmacological properties of *Z. zerumbet* and its phytoconstituent is presented in the tables and in the subsequent narrative. Only data with a statistically significant p-value of less than 0.05 were included, while results with insignificant findings were omitted.

Analgesia

The analgesic effects of *Z. zerumbet* methanol extract, *Z. zerumbet* essential oil, and zerumbone were reported via intraperitoneal, oral, and subcutaneous routes. Detailed findings on the analgesic effects of *Z. zerumbet* and zerumbone are presented in ▶ **Table 1**.

Anti-inflammatory

The anti-inflammatory properties of *Z. zerumbet* were reported in the form of essential oil via the intraperitoneal route and zerumbone through topical, intraperitoneal, and oral administration. Detailed findings on the anti-inflammatory properties of *Z. zerumbet* and zerumbone are presented in ▶ **Table 2**.

Anti-diabetic

Ethanol extract of *Z. zerumbet* and zerumbone was reported to have anti-diabetic properties. Detailed findings of the anti-diabetic effects of *Z. zerumbet* and zerumbone are presented in ▶ **Table 3**.

Anti-hyperlipidaemia

EEZZ and zerumbone administered orally showed anti-hyperlipidaemic properties. Detailed findings on the anti-hyperlipidaemic properties of *Z. zerumbet* and zerumbone are presented in ▶ **Table 4**.

Anti-neoplastic

Z. zerumbet was shown to have anti-angiogenetic and anti-tumour properties. Detailed findings on the anti-neoplastic properties of *Z. zerumbet* extracts and zerumbone are presented in ▶ **Table 5**.

▶ **Table 1** The mechanisms by which *Z. zerumbet* formulations can contribute to analgesic and antinociceptive effects.

Animal	Intervention	Disease model	Administration details	Mechanism	Ref.
1A. Acute					
Rat	Zerumbone	Osteoarthritis	10–50 mg/kg single dose, i.p	Suppress NO, PGE_2, and MMP production	Chien, 2016 [45]
1–5 mg/kg/day, p.o, 7 days					
Mice	80% methanol extract of *Z. zerumbet*	Inflammation and nociception	25–100 mg/kg, single dose, s.c	Inhibit opioid receptors, bradykinin, prostaglandin, and histamine-mediated actions	Zakaria, 2010 [46]
1B. Neuropathic pain					
Mice	Zerumbone	Chronic constriction injury-induced	10 mg/kg single dose, i.p	Stimulate serotonergic inhibitory pathway (5-HT receptor subtypes 1A, 1B, 2A, 3, 6, and 7)	Chia, 2016 [47]
Mice	Zerumbone	Chronic constriction injury-induced	10 mg/kg single dose, i.p	Agonist of potassium channels (voltage-dependent K^+, ATP-sensitive K^+ and Ca^{2+}-K^+ channels) Agonist of the non-selective opioid receptors and selective opioid receptors (μ-opioid receptors, δ-opioid and κ-opioid)	Gopalsamy, 2020 [36]
Mice	Zerumbone	Neuropathic pain	5–50 mg/kg, once daily, 14 days, p.o	Agonist of CB-1 receptor	Chia, 2021 [48]
Mice	Zerumbone	Neuropathic pain	5–50 mg/kg, once daily, 14 days, p.o	Inhibit production of IL-1β, IL-6 and TNF-α in blood plasma and spinal cord tissues	Gopalsamy, 2017 [37]
Mice	Zerumbone	Neuropathic pain	5–100 mg/kg, once daily, 7 days, i.p	Inhibit mechanical allodynia, thermal allodynia, and hyperalgesia. The mechanism of action was not reported	Zulazmi, 2015 [49]
1C. Mixed (General anti-nociception)					
Mice	*Z. zerumbet* essential oil	General anti-nociception	50–300 mg/kg, single dose i.p and p.o	Activate L arginine/NO/cGMP/ATP-sensitive K^+ channel pathway Inhibit glutamatergic system and TRPV1 receptors Activate opioidergic system by acting as an agonist to the non-selective opioid receptors Inhibit the inflammatory mediators, prostaglandin, histamine, serotonin, and bradykinin	Khalid, 2011 [50] Sulaiman, 2010b [30]
Mice	Zerumbone	General anti-nociception	10–100 mg/kg, single dose, i.p	Agonist of the non-selective opioid receptors	Sulaiman, 2009 [38]

Abbreviations: i.p: intraperitoneal; s.c: subcutaneous; p.o: per oral; NO: nitric oxide; PGE_2: prostaglandin E_2; MMP: matrix metalloproteinase; 5-HT: 5-hydroxytryptamine; CB: cannabinoid; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumour necrosis factor alpha; cGMP: cyclic guanosine monophosphate; ATP: adenosine triphosphate; TRPV1: transient receptor potenzial vanilloid 1

Immunomodulatory

Three studies reported the immunomodulatory properties of *Z. zerumbet* and zerumbone. In male BALB/c mice, zerumbone was observed to suppress macrophage phagocytosis (part of the innate immune system) and inhibit nitrous oxide production in a concentration-dependent manner at dosages ranging from 25 to 100 mg/kg when administered orally, once daily for 14 days) [14]. In female BALB/c mice with ovalbumin (OVA)-induced T helper 2 (Th2)-mediated asthma, zerumbone improved airway hyperresponsiveness and reduced airway inflammation. This was noted at dosages of 0.1 to 10 mg/kg, administered orally three times daily for 17 days) [15]. Studies on male Wistar rats revealed that an 80% ethanol extract of *Z. zerumbet* has mild immunosuppressive effects by reducing the phagocytic activity of neutrophils (another component of the innate immune system). Additionally, the ethanol extract of *Z. zerumbet* influenced the adaptive immune system by inhibiting neutrophil migration, CD11β/CD18 integrin expression, and production of reactive oxygen species (ROS) in a dose-dependent manner, at dosages ranging from 100 to 400 mg/kg when given orally daily for 15 days [16].

Antioxidant

Three articles reported on the antioxidant properties of *Z. zerumbet* and zerumbone. These antioxidative properties have been re-

▶ **Table 2** The mechanisms by which *Z. zerumbet* formulations can contribute to anti-inflammation.

Animal	Intervention	Disease model	Administration details	Mechanism	Ref.
2A. Acute					
Rat	Zerumbone	Excisional wound (for wound-healing effects)	0.5 mg/mL, once daily, 15 days, topical	Downregulate IL-6, TNF-α, and COX-2 gene, while increasing IL-10 expression in wound tissues	Fadhel, 2020 [51]
Mice	Zerumbone	Excisional wound (for wound-healing effects)	0.01 or 1% (w/w), once daily, 15 days, topical	Increase VEGF, TGF-β1, and collagen IV expressions which correlates with increase fibroblast proliferation and collagen synthesis	Liu, 2017 [52]
Mice	Zerumbone	Acute lung injury	0–10 mmol/kg, single dose, i.p	Inhibit expression of TNF-α, IL-6, iNOS, and COX-2 Reduce activation of NFκB	Ho, 2017 [53]
Mice	Zerumbone	Acute lung injury	0–2183.4 µg/kg, single dose, i.p	Reduce neutrophil infiltration by decreasing expression of ICAM-1 Prevent LPS-induced adhesion molecule expression by decreasing IL-1β and MIP-2 expressions Inhibit NFκB activation through NFκB phosphorylation and IκB degradation	Lee, 2018 [54]
2B. Chronic					
Mice	Zerumbone	Enterotoxigenic *Bacteroides fragilis* (ETBF) infection	30–60 mg/kg/day, 7 days, p.o	Inhibit NFκB signalling that decreases ETBF-induced colitis Zerumbone shown to not inhibit E-cadherin cleavage	Hwang, 2019 [32]
2C. Mixed					
Mice	Zerumbone	Ulcerative colitis	0.1%, ad libitum, 14 days, p.o	Reduce PGE_2 formation in colonic mucus membrane Reduce TNF-α formation	Murakami, 2003 [55]
Mice	Zerumbone	Acute and chronic inflammation	5–100 mg/kg, single dose, i.p	Inhibit fibroblasts activity and synthesis of collagen with mucopolysaccharide, in granulation tissue formation	Sulaiman, 2010a [29]
Rat	EOZZ	General anti-inflammatory activity	Acute inflammation: 30–300 mg/kg, single dose, i.p Chronic inflammation: 30–300 mg/kg, once daily, 7 days, i.p	Reduce oedema, acute inflammation, chronic inflammation, and inflammatory- and noninflammatory-mediated pain. Mechanism of action was not reported	Zakaria, 2011 [56]

Abbreviations. w/w: weight for weight; COX-2: cyclooxygenase-2; EOZZ: essential oil of *Z. zerumbet;* VEGF: vascular endothelial growth factor; TGF-β1: transforming growth factor beta 1; IL-10: interleukin 10; iNOS: inducible nitric oxide synthase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; IκB: I kappa B; LPS: lipopolysaccharide; ICAM-1: intercellular adhesion molecule-1; IL-1β: interleukin 1 beta; MIP-2: macrophage inflammatory protein 2; ETBF: enterotoxigenic *B. fragilis*; NR: not reported

ported in animal models of brain, lung, and skin damages. In male Wistar rats with induced brain damage, the treatment of ethyl-acetate *Z. zerumbet* extract significantly reduced the level of oxidative stress markers such as malondialdehyde (MDA) and protein carbonyl in the brain homogenate. This treatment given at dosages of 200 to 400 mg/kg, once daily by oral gavage 30 minutes before ethanol exposure via intraperitoneal route for 14 consecutive days, also enhanced the activities of serum superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities, as well as glutathione (GSH) levels in a dose-dependent manner [17]. In adult male pathogen-free Institute of Cancer Research mice with lipopolysaccharide (LPS)-induced acute lung injury (ALI), zerumbone pretreatment ameliorated histopathological lung changes, such as neutrophil infiltration, increased alveolar wall thickness, haemorrhage, and hyaline membrane formation. Zerumbone at dosages from 1 to 10 µmol/kg suppressed LPS-induced activation of myeloperoxidase (MPO), metalloproteinase-9 (MMP-9), and lipid peroxidation in the lungs, reversed the LPS-induced reduction in antioxidative enzyme (superoxide dismutase, catalase, and glutathione peroxidase) activities in a concentration-dependent manner, and reduced LPS-induced oxidative stress through the mechanism of nuclear factor erythroid 2-related factor (Nrf2) and heme oxygenase (HO-1) [18]. In a separate study on athymic female nude mice (BALB/c-nu) exploring skin damage from UVA radiation, topical zerumbone pretreatment significantly countered the damage. Applied at 55 or 110 µg/day for 14 days, the treatment upregulated Nrf2- and Nrf2-dependent antioxidative genes, particularly HO-1 and γ-glutamyl cysteine ligase (γ-GCLC). This protective action functioned in a dose-dependent manner, further involving the downregulation of the Bax/Bcl-2 ratio in keratinocytes and the prevention of DNA fragmentation [19].

▶ **Table 3** The mechanisms by which *Z. zerumbet* formulations can affect diabetic-related diseases.

Animal	Intervention	Disease model	Administration details	Mechanism	Ref.
3A. Microvascular effects					
Rat	EEZZ	Diabetic retinopathy	200–300 mg/kg, once daily, 3 months, p.o	Stabilise tight junction proteins, leading to decreasing blood-retinal-barrier permeability Reduce p38 MAPK enzyme in the retina Inhibit retinal NFκB activation Decrease retinal expression of TNF-α, IL-1β, IL-6, Vascular cell adhesion molecule-1	Tzeng, 2015 [57]
Rat	EEZZ	Diabetic retinopathy	200–300 mg/kg, once daily, 3 months, p.o	Prevent activation of ERK1/2 phosphorylation and NFκB, downregulating pro-inflammatory mediators	Hong, 2016 [58]
Rat	Zerumbone	Diabetic retinopathy	40 mg/kg, once daily, 8 weeks, p.o	Inhibit NFκB activation and reduce VEGF expression in retinal tissue, thereby inhibiting retinal inflammation	Tzeng, 2016 [59]
Rat	EEZZ	Diabetic nephropathy	200–300 mg/kg, once daily, 8 weeks, p.o	Inhibit AMPK dephosphorylation in the kidneys	Tzeng, 2013 [60]
Rat	Zerumbone	Diabetic nephropathy	20–40 mg/kg, once daily, 8 weeks, p.o	Reduce upregulation of protein expression of TNF-α, IL-1β and IL-6 in the kidneys Reduce renal MCP-1 and ICAM-1 protein expression Reduce TGF-β1 protein expression Inhibit macrophage infiltration through reducing levels of p38-mediated inflammatory response in the kidneys	Tzeng, 2013 [61]
3B. Insulin resistance					
Rat	EEZZ	Insulin resistance	100–300 mg/kg, once daily, 8 weeks, p.o	Agonist of GLUT4 translocation from intracellular vesicles to the plasma membrane, thereby reversing the abnormal responsiveness to insulin seen in diabetes Inhibit hepatic PEPCK-C expression, thereby reduces the rate of gluconeogenesis in the liver	Chang, 2012a [62]
3C. Anti-hyperglycemic					
Rat	AEZZ	Hyperglycemia	50–150 mg/kg, 10 days, p.o	Reduce blood glucose and body weight. The mechanism of action was not reported	Husen, 2004 [63]

Abbreviations: EEZZ: ethanol extract of *Z. zerumbet*; AEZZ: aqueous extract of *Z. zerumbet*; AMPK: adenosine monophosphate-activated protein kinase; p38 MAPK: p38 mitogen-activated protein kinase; ERK1/2: extracellular signal-regulated kinase ½; MCP-1: monocyte chemoattractant protein-1; GLUT4: glucose transporter type 4; PEPCK-C: cytosolic phosphoenolpyruvate carboxykinase

Antipyretic

One study involving albino rats reported on the antipyretic properties of the EEZZ at doses of 1 to 4 g/kg and zerumbone at 0.75 g/kg of body weight, administered orally. Both EEZZ and zerumbone were found to reduce the rectal temperature in rats by about 1.3 °C within 2 hours. However, this reduction was not as pronounced as that produced by paracetamol, which lowered the temperature by 1.7 °C within 3 hours [20].

Weight gain

In male Sprague-Dawley rats on a high-fat diet, the inhalation of *Z. zerumbet* essential oil and zerumbone was observed to further increase body weight. While the inhalation of zerumbone decreased brown adipose tissue (BAT) sympathetic nerve activity, inhalation of *Z. zerumbet* essential oil did not have any effect on the BAT activity. It has been suggested that this decrease in BAT sympathetic nerve activity could lead to diminished thermogenesis. As a result, there might be a decrease in the conversion of fatty acids, ultimately contributing to an increase in body weight [21].

Hepatoprotective effects

Two studies investigated the hepatoprotective properties of zerumbone in male Sprague-Dawley rats and C57BL/6 mice. In both studies, zerumbone was found to restore neutrophil levels, to reduce ALT and AST levels, and to maintain normal hepatic tissue histology [22, 23]. At high doses of 50 mg/kg, zerumbone was observed to downregulate the expression levels of IL-1β and TNFα. It also reduces the terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL)-positive area in male C57BL/6 mice subjected to hepatotoxin-mediated acute and chronic liver injuries [23].

Nephroprotective effects

A study highlighted the nephroprotective effect of the ethyl acetate extract of *Z. zerumbet* against paracetamol-induced nephrotoxicity and oxidative stress in male Sprague-Dawley rats. When the *Z. zerumbet* extract was administered intraperitoneally at doses of 200 and 400 mg/kg for 7 days, there were marked reductions in creatinine elevations and oxidative stress indicators. Specifically, there were decreased levels of renal homogenate, plasma

▶ **Table 4** The mechanisms by which *Z. zerumbet* formulations can affect hyperlipidemia.

Animal	Intervention	Disease model	Administration details	Mechanism	Ref.
4A. Exogenous lipid metabolism					
Mice	Zerumbone	Hyperlipidemia	0.01–0.025%, ad libitum, 8 weeks, p.o	Increase AMPK phosphorylation in white adipose tissue by inhibiting acetyl-CoA carboxylase Inhibit the transcription factors C/EBPα and PPARγ, as well as the fatty acid synthase hence causing inhibition of adipogenesis differentiation caused by lipid accumulation Increase SIRT1 expression through inhibition of miR-146b expression and increasing the NAD^+/NADH ratio in white adipose tissue Inhibit deacetylation of FOXO1 and PGC1-α in the differentiated adipocytes	Ahn, 2017 [64]
4B. Endogenous lipid metabolism					
Rat	EEZZ	Hyperlipidemia	100–300 mg/kg, once daily, 8 weeks, p.o	Increase hepatic PPARα level which leads to increase hepatic fatty acid oxidation and reduced triglyceride content	Chang, 2012c [65]
Hamster	EEZZ	Hyperlipidemia	100–300 mg/kg, once daily, 8 weeks, p.o	Decrease plasma concentration of MCP-1, TNFα-, and IL-6 Suppress macrophage recruitment and inhibit release of inflammatory cytokines from hepatic macrophages, prevents hepatic steatosis, fibrosis and insulin resistance Inhibit SREBP-1c expression, thereby decreases transcription of target lipogenic genes which then decrease enzyme activity leading to reduced rate of lipid synthesis Increase hepatic PPARα mRNA and PPARα-mediated transcription of ACOX1, CPT-1, and ACO mRNA in hepatic cells	Chang, 2014 [66]
Hamster	Zerumbone	Hyperlipidemia	75–300 mg/kg, once daily, 8 weeks, p.o	Inhibit hepatic mRNA levels of sterol regulatory element-binding protein-1c and its lipogenic target genes (fatty acid synthase, acetyl-CoA carboxylase 1, and stearoyl-CoA desaturase 1) Upregulate hepatic mRNA expression of PPARα and its target genes (carnitine palmitoyl transferase-1, acyl-CoA oxidase, and acyl-CoA oxidase-1)	Tzeng, 2013 [67]
Hamster	Zerumbone	Hyperlipidemia	25–100 mg/kg, once daily, 8 weeks, p.o	Decrease hepatic mRNA levels of fatty acid synthase, malic enzyme, sterol-regulatory element binding protein and 3-hydroxy-3-methyl-glutaryl-CoA reductase Upregulate hepatic mRNA expression of PPARα and its target gene (CPT-1 and ACO)	Tzeng, 2014 [68]

Abbreviations: AMPK: adenosine monophosphate-activated protein kinase; C/EBPα: cytosine-cytosine-adenosine-adenosine-thymidine enhancer-binding protein alpha; EEZZ: ethanol extract of *Z. zerumbet*; FOXO1: forkhead box protein O1; PGC1-α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; miR-146b: microRNA-146b; SIRT1: sirtuin (silent mating type information regulation 2 homolog) 1; PPARα: peroxisome proliferator-activated receptor alpha; PPARγ: peroxisome proliferator-activated receptor gamma; SREBP-1c: sterol regulatory element-binding protein 1; ACOX1: peroxisomal acyl-coenzyme A oxidase 1; CPT-1: carnitine palmitoyl transferase 1; ACO: acyl-CoA oxidase

malondialdehyde (MDA), plasma protein carbonyl, and renal advanced oxidation protein product (AOPP). Additionally, the histological evaluation indicated better protection of the kidneys, especially in the appearance of glomeruli and tubules, when compared to the untreated group. This protection was observed to be dose-dependent [24].

Gastroprotective effects

One study reported on the gastroprotective property of zerumbone in an ethanol-induced gastric ulcer model using male Sprague-Dawley rats. When zerumbone was administered intraduodenally at doses of 5 and 10 mg/kg, there was a significant reduction in the acidity of gastric juice compared to the control group subjected to pylorus ligature. This effect was comparable to that of omeprazole at 30 mg/kg. Rats pretreated with zerumbone demonstrated a decrease in ulcer area formation, an increase in mucus production, and a reduction in both oedema and leukocyte infiltration. There was also a noticeable flattening of the mucosal fold and preservation of the gastric mucosa layer. Additionally, there was an overexpression of heat shock protein 70 (HSP-70) in the gastric tissue, suggesting enhanced protection of the gastric mucosa, since HSP-70 combats stress-induced protein denaturation. Following zerumbone treatment, there was a restoration in the levels of prostaglandin E_2 (PGE_2), glutathione (GSH), and lipid peroxidation in comparison to the ulcer control group [25].

▶ **Table 5** The mechanisms by which *Z. zerumbet* formulations contribute to anti-neoplastic effects.

Animal	Intervention	Disease model	Administration details	Mechanism	Ref.
5A. Anti-angiogenesis					
Mice	Zerumbone	Angiogenesis	10–200 µM, single dose, s.c	Inhibit proliferation, migration and blood capillary formation Inhibit VEGF-induced VEGFR2 phosphorylation in primary endothelial cells Inhibit phosphorylation of FGFR1 induced by bFGF stimulation	Park, 2015 [69]
5B. Antitumor effect					
Mice	Zerumbone and ELEZZ	Lymphoma	Zerumbone: 0.5–2.0 mg/kg, once daily, 8 days, i.p (in vivo antitumor P388D_1 assay) ELEZZ: 1.25–10.0 mg/kg, once daily, 8 days, i.p (in vivo antitumor P388D_1 assay)	Prolong survival days in lymphoma animal model (mechanism unclear) Inhibit the G_2/M transition of the HL-60 cells (in vitro)	Huang, 2005 [70]
Mice	MEZZR	Ehrlich ascites carcinoma	10–20 mg/kg/day, 5 days, i.p	Cancer cell apoptosis in the presence of caspase-3, -8, and -9 inhibitors	Hanif, 2022 [71]
Mice	Zerumbone	Colon and lung cancer	Colon carcinogenesis 100–500 ppm, ad libitum, 17 weeks, p.o Lung carcinogenesis 100–500 ppm, ad libitum, 21 weeks, p.o	Reduce NFκB and HO-1 expression in tumours. Suppress cell proliferation Induce apoptosis	Kim, 2009 [33]
Mice	Zerumbone	Skin cancer	1–10 µmol, topical on dorsal skin, 24 hours	Increase HO-1 mRNA expression through transcriptional activation of *Hmox*1, mediated through the activation of Nrf2 signalling.	Shin, 2011 [72]
Mice	Zerumbone	Non-small-cell lung cancer	Mice treated 5 times (route, dose and duration of zerumbone not stated)	Inhibit the binding activity between HSP27 and PKCδ or cytochrome C in tumour tissue lysates, improving the effects of chemo- or radiation treatment	Choi, 2011 [73]
Rat	Zerumbone	Liver cancer	15–60 mg/kg, twice per week, 11 weeks, i.p	Induce apoptosis via increasing Bax gene while decreasing Bcl-2 protein expression	Taha, 2010 [34]
Rat	Zerumbone	Colon cancer	0.01–0.05%, ad libitum, 5 weeks, p.o	Reduce expression of COX-2, PGE_2 and PGD_2 in colonic mucosa Reduce cell proliferation activity (seen by decreased AgNORs number) in colonic cryptal cell nuclei	Tanaka, 2001 [35]

Abbreviations: VEGFR2: vascular endothelial growth factor receptor 2; FGFR1: fibroblast growth factor receptor 1; bFGF: basic fibroblast growth factor; ELEZZ: diethyl ether layer extract of *Z. zerumbet*; MEZZR: Methanol extract of *Z. zerumbet* rhizome; P388D_1: murine lymphoid neoplasm cell line; HL-60: human promyelocytic leukaemia cell; G_2/M: Gap 2 phase mitosis; ppm: parts per million; HO-1: heme oxygenase-1; ADC: Adenocarcinoma; AD: Adenoma; Hmox1: heme oxygenase 1 gene; Nrf2: nuclear factor-erythroid factor 2-related factor 2; HSP27: heat shock protein 27; PKCδ: protein kinase C delta; Bax: B-cell lymphoma protein 2- associated X; Bcl-2 protein: B-cell lymphoma protein 2; AgNORs: silver-stained nucleolar organiser regions protein; PGE_2: prostaglandin E_2; PGD_2: prostaglandin D2

Locomotor-reducing activity

Two studies investigated the locomotor-reducing effects of the phytoconstituents of *Z. zerumbet* rhizomes. Ogawa et al. reported a decrease in total spontaneous locomotor activity in mice after a 60-minute inhalation of zerumbone and its derivatives, with a concentration of 4.5×10^{-2} mg being the most significant [26]. Another study by the same primary author focused on inhaled hexahydrozerumbone derivatives and zerumbol. Hexahydrozerumbone significantly reduced the total spontaneous locomotor activity in mice at a dose of 4.5×10^{-3} mg, whereas zerumbol did not show any significant effects [27]. The mechanism behind this reduced locomotion was not determined in either of the studies.

Safety

General toxicity studies for the ethanol extract of *Z. zerumbet* and zerumbone were conducted in seven studies [14–16, 28–31], with results presented in ▶ **Table 6**. Overall, no deaths or severe abnormalities were observed for most of the investigated doses. In addition to these toxicity studies, four studies reported no adverse events from the use of *Z. zerumbet* extracts and zerumbone during efficacy studies [32–35], while three other studies indicated that zerumbone did not exert sedative effects [36–38]. The ethanolic extract of *Z. zerumbet* demonstrated no genotoxic effects in mice based on their bone marrow studies [31]. A summary of the

▶ **Table 6** Safety data of *Z. zerumbet* and zerumbone.

Animal	Intervention	Toxicity study type/ Disease model	Administration details	Safety findings	Ref.
Rat	EEZZ	General toxicity	Acute: 15 g/kg/day, in three times daily dose for one day, p.o Subacute: 1000–3000 mg/kg, once daily for 28 days, p.o	NOAEL (acute): 15 g/kg LOAEL (subacute): 3000 mg/kg No abnormalities in the body weight gain; food and water consumption; haematological parameters (blood counts, i.e., liver, renal, lipid, and glucose profile); and necropsy and histopathological examination.	Chang, 2012b [28]
Rat	EEZZ	General toxicity	100, 200, 400, and 2000 mg/kg, once daily for 14 days, p.o	Results reported for 100, 200, and 400 mg/kg: No abnormalities in weight, clinical, and gross organ examination	Ghazalee, 2019 [16]
Mice	EEZZ	General and genotoxicity	500, 1000, and 2000 mg/kg once daily for two days, p.o	No abnormalities in general appearance and body weight. No increased number of micronucleated polychromatic erythrocytes in the bone marrow indicating no genotoxic hazards	Chang, 2012d [31]
Mice	EOZZ	General toxicity	300, 100, and 300 mg/kg, single dose, p.o	No deaths observed up to the dose of 5000 mg/kg. No behavioural and locomotor changes.	Sulaiman, 2010b [30]
Mice	Zerumbone	General toxicity	25, 50, 100, and 200 mg/kg once daily for 14 days, p.o	No abnormalities in body weight and vital organs; spleen and liver; ALT, ALP, AST, and creatinine in all groups. Loss of appetite; lowered body temperature; changes in general behavioural activities; and colour of skin, hairs, teeth, and eyes in 200 mg/kg group	Jantan, 2019 [14]
Mice	Zerumbone	General toxicity	10 mg/kg, three times per day for 17 days, p.o	No deaths and no treatment-related organ abnormalities	Shieh, 2015 [15]
Mice	Zerumbone	General toxicity	10, 50, 100, and 1000 mg/kg, once daily for 7 days, i.p	No deaths and treatment-related organ abnormalities	Sulaiman, 2010a [29]

Abbreviations: EEZZ: ethanol extract of *Z. zerumbet*; NOAEL: no-observed-adverse-effect level; LOAEL: lowest-observed-adverse-effect level; EOZZ: essential oil of *Z. zerumbet*

preclinical *in vivo* safety studies done for *Z. zerumbet* and zerumbone can also be found in ▶ **Table 6**.

Discussion

The bulk of the evidence focused on the analgesic, anti-inflammatory, anti-diabetic, anti-hyperlipidemia, and anti-neoplastic properties of *Z. zerumbet* and zerumbone. A small number of studies reported their antioxidant, antipyretic, hepatoprotective, nephroprotective, and gastroprotective properties, as well as their locomotor-reducing activities. Among these pharmacological effects, the most researched areas were analgesia and anti-inflammation. In terms of formulations and dosages, three were commonly utilised: the methanolic extract of *Z. zerumbet* at dosages of 25–100 mg/kg administered via the intraperitoneal route; the essential oil of *Z. zerumbet* at dosages of 30–300 mg/kg given orally or intraperitoneally; and zerumbone derived from *Z. zerumbet* at dosages 5–100 mg/kg administered either orally or intraperitoneally. *Z. zerumbet* may exert its various pharmacological effects through the phytochemicals contained in the plant such as triterpenes, saponins, tannins, and other volatile oils, particularly the zerumbone compound, which is a sesquiterpenoid [11].

Based on the included studies, the ethanolic extract of *Z. zerumbet* appears safe in short-term animal toxicity studies for up to 28 days, with no evident safety concerns. The essential oil of *Z. zerumbet*, when administered intraperitoneally in up to doses of 5000 mg/kg, showed neither mortality nor adverse effects. Zerumbone, however, presented a more mixed picture. One study reported adverse effects at a dose of 200 mg/kg, but other studies using even higher doses of up to 1000 mg/kg did not confirm these findings. These adverse effects encompassed appetite loss, lowered body temperature, behavioural changes, and discolouration of skin, fur, teeth, and eyes. Among the pharmacological categories with five or more animal studies (i.e., analgesic, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, and anti-neoplastic effects) zerumbone-based interventions were more extensively examined. This preference might arise from the fact that zerumbone, being a compound, offers a clearer path to discerning the mechanism of its pharmacological action. In contrast, while *Z. zerumbet* extracts do show therapeutic effects, their mechanisms of action can be challenging to pinpoint due to the complex composition of natural products, which can contain a variety of compounds that influence therapeutic pathways.

Documented traditional uses of Z. *zerumbet* that we have access to include its use as an appetiser and as treatment for stomach aches [7], pain relief, toothaches, alleviation of a cough related to cavities, asthma, deworming, and various unspecified skin diseases [39]. Based on our findings, the most substantiated traditional claim through scientific studies is *Z. zerumbet*'s analgesic property. This can be linked, both directly and indirectly, to toothaches, cough, asthma, and skin diseases – primarily through its anti-inflammatory attributes. Modern research has identified claims for *Z. zerumbet* that are not documented in its traditional uses. These claims include anti-diabetic, anti-hyperlipidemic, anti-neoplastic, hepatoprotective, and nephroprotective effects, as well as the reduction of locomotor activity.

We found that approximately half of the studies reported, in detail, the qualitative and quantitative phytochemical analyses of the herbal interventions. A significant gap in the herbal medicine literature on safety and efficacy is the lack of comprehensive reporting on the quality details of the formulations under investigation [40,41]. Given that the phytoconstituents of medicinal plants can vary based on agroclimatic conditions and processing methods [41], it is vital to provide detailed reports on the quality-related components of a formulation being studied. Despite the substantial amount of preclinical evidence, we could not find any published clinical trial. The availability of such data will facilitate a more insightful interpretation of the dose-response relationship and enable extrapolation to similar formulations of the same plant, further bridging the gap towards successful clinical studies. Currently, based on the preclinical *in vivo* efficacy data, most of the research focuses on the anti-inflammatory and analgesic effects of *Z. zerumbet,* indicating a promising direction for future clinical trials.

One limitation of this review is the inclusion of only articles written in English. Due to the limited availability of human literature, a meaningful appraisal could not be conducted. Our safety data are derived primarily from animal toxicity studies and from the extraction of safety-related data within efficacy studies, given the design of our search strategy. This approach might not capture all safety-related data. Furthermore, our institution might not have access to all traditional medicinal claims related to Z. *zerumbet*, especially those from non-English sources or global traditional practices, potentially leading to certain oversights.

In conclusion, the outcomes the studies demonstrate that *Z. zerumbet* holds promise in the field of natural products with therapeutic claims, particularly in addressing pain and anti-inflammatory conditions. The combined effects of this plant could potentially offer comprehensive symptom relief for various diseases. However, the future prospects of this review suggest the need for further research. This includes standardising *Z. zerumbet* formulations, extending the safety studies based on its duration of use, and investigating its pharmacokinetic properties. A specialised review centred on the safety and potential herb–drug interactions of *Z. zerumbet* would further enrich the field. Furthermore, it is imperative to establish rigorous herbal quality standards to enhance the interpretation of results and pave the way for successful clinical trials in the future.

▶ **Table 7** Population, Intervention, Comparison, and Outcomes (PICO) framework.

Elements	Details
Population	Human and animal model in efficacy and toxicity studies.
Intervention	*Z. zerumbet* as a single herb, with any plant parts used, in any type of formulation.
Comparator	None, placebo, or standard medical treatment.
Outcome	▪ Pharmacological properties. ▪ Preclinical and clinical outcomes of efficacy studies. ▪ Mechanism of action of *Z. zerumbet* in efficacy studies. ▪ Toxicity results from animal toxicity studies.

Methodology

We conducted a scoping review according to the York framework of scoping studies by Arskey and O'Malley [42]. This framework was appropriate for the broad range of preclinical evidence comprising of the efficacy and safety of Z. *zerumbet*. This scoping review has been registered with the National Medical Research Register (NMRR) under the research ID 21–526–59312 with an *a priori* protocol prepared. To ensure the transparency and comprehensiveness of our scoping review, we followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, which involved using the PRISMA flowchart to document the screening and selection process, as well as the PRISMA scoping review checklist (Supplementary material: **Table 2S**), to ensure relevant items were included in the review [13].

Research Questions

This scoping review was based on the research question "What is the current scientific evidence on *Z. zerumbet* as a natural product?" and was further subdivided to categorise the types of evidence, which include the following:

1. What is the pharmacological scientific evidence of *Z. zerumbet*?
2. What is the safety profile of *Z. zerumbet* in animal toxicity studies and its potential harm to humans?

The population, intervention, comparison, and outcomes (PICO) framework shown in ▶ **Table 7** was used to approach the research study questions.

Search Strategy

A systematic search was conducted by two independent investigators on electronic databases including MEDLINE, CENTRAL, LILACS, and Google Scholar from the period since commencement to 31st March 2023. A predetermined combination of keywords that include "Zingiber zerumbet" and its synonyms, "medicinal", "therapeutic", "benefit", "effect", "properties", and "bioactive" were used. An example of the keyword search used in the databases is presented in the Supplementary material: **Table 3S-6S**.

The abstracts of the searched results were extracted with duplicates removed using the bibliographical software EndNote 20.

Article Inclusion and Data Extraction

The search result was transferred to a Microsoft Excel sheet. Title, abstract, and full-text article screening was performed by two independent investigators, with disagreements resolved by a third investigator. This review accounted for *Z. zerumbet* as a whole plant used in any formulation (crude, extract, and essential oil) and its major compound studied, zerumbone. Only English-language articles were included. The inclusion criteria comprised all published primary literature of animal and clinical studies on the efficacy and safety of *Z. zerumbet*, of animal studies that incorporate *in vitro* studies to elicit the mechanism of action, of any plant part, and of any formulations with *Z. zerumbet* as a sole active ingredient and its representative compound isolated from the plant (i.e., zerumbone). The exclusion criteria comprised review papers, book sections, combination products and formulation, and *in silico* and purely *in vitro* studies. A data extraction table of included studies (the table layout provided in Supplementary material: **Table 7S**) was created to record all the relevant data upon full-text screening.

Data analysis

Full-Text Analysis

Descriptive numerical analysis on the efficacy and safety of *Z. zerumbet* was performed. For efficacy, we focused on data related to its intended pharmacological effects, the underlying cellular and molecular mechanisms, and the range of doses shown to be effective. In terms of safety, the primary data was sourced from animal toxicity studies. This encompassed information about the dose range tested, any resulting morbidity or mortality, and other pertinent findings from clinical evaluations, histopathological examinations, and laboratory tests.

Risk of Bias Assessment

The risk of bias for each included study was assessed independently by two authors, TYCT and JSWC. For this assessment, we used the systematic review Centre for Laboratory Animal Experimentation risk of bias tool (SYRCLE's RoB) [43]. This tool has 10 domains:

1. Sequence generation;
2. Baseline characteristics;
3. Allocation concealment;
4. Random housing;
5. Blinding of trial caregivers;
6. Random outcome assessment;
7. Blinding of outcome assessors;
8. Incomplete outcome data;
9. Selective reporting;
10. Other biases.

For each criterion, the study was judged as having a 'low', 'unclear', or 'high' risk of bias. Justifications for each judgment were provided in a risk-of-bias table. Additionally, we visualised the overall results using the review manager application by Cochrane (RevMan 5.4.1) to generate the risk-of-bias graph and summary [44].

Supporting Information

The herbal intervention qualitative, quantitative, and standardisation checklist, the PRISMA scoping review checklist, the keyword search strategy, and the data extraction table layout are provided in the Supporting Information.

Contributors' Statement

All the authors were involved in the abstract and full-text screening of the included studies, crosschecked among pairs, and tabulated data from the included studies into the data extraction sheet. JSWC prepared the data extraction table for full text analysis, analysed and interpreted the results of the included studies, drafted the manuscript, designed the research framework, critically revised the manuscript, and discussed the results. XYL analysed, critically reviewed the interpreted data in the drafted manuscript, provided inputs on tabulating the interpreted data and discussion and interpreted the safety aspect section of the results. NJ and TYCT descriptively analysed and interpreted the data on several pharmacological efficacy aspects in the results section. TYCT provided input on the overall discussion. IFA contributed to the manuscript literature review, introduction, and proofreading. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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