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Article Review: The Potential Of Plants In The Zingiberaceae Family As Agents For Treating Acute Inflammation

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ABSTRACT: **Background:** Anti-inflammatory drugs suppress the inflammatory process. Common therapies use NSAIDs, but long- term use can cause side effects such as stomach and kidney disorders and an increased risk of cardiovascular disease, as well as cost constraints. Therefore, alternatives from natural ingredients with fewer side effects are needed, one of which is plants from the Zingiberaceae family, which are still widely used traditionally without adequate scientific evidence, so their effectiveness and safety are not yet fully recognized in modern healthcare systems. Literature search was conducted systematically through several scientific databases, namely PubMed, ScienceDirect, Google Scholar, and Semantic Scholar, with a maximum publication time limit of 10 years. **Methods:** Article data included species, plant parts, types of extracts/active compounds, inflammatory test models, doses, and inflammatory inhibition results. Data were analyzed descriptively to compare the potential between Zingiberaceae genera. **Results:** In vivo tests showed that bioactive compounds such as curcumin, 6-gingerol, and zerumbone inhibit inflammatory mediators such as nitric oxide (NO) and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), as well as suppressing the expression of key enzymes iNOS and COX-2 through the NF-κB and MAPK signaling pathways. In in vitro testing, extracts from these plants were able to significantly reduce swelling (edema), with species such as kecombrang (*Etlingera elatior*) showing inhibition rates of up to 82.29%, almost equivalent to the standard drug sodium diclofenac. **Conclusion:** The Zingiberaceae family has strong potential as an acute anti-inflammatory agent through the inhibition of key inflammatory mediators and pathways; however, further standardization and clinical trials are still required.

KEYWORDS: Zingiberaceae; bioactive compounds; natural anti-inflammatory agents.

1. INTRODUCTION

Inflammation is a complex biological response of vascular tissue to harmful stimuli such as pathogens, irritants, or cell damage that functions as a defense mechanism to remove the factors causing damage and initiate the healing process of the affected tissue [1]. Based on its duration and characteristics, inflammation is divided into two main forms, namely acute and chronic inflammation. Acute inflammation is a short process that lasts from several minutes to several days, characterized by plasma protein leakage and the movement of leukocytes to the extravascular area [2]. This reaction occurs in response to tissue damage, injury, infection, or exposure to irritants [3]. Meanwhile, chronic inflammation is a prolonged immune response due to unresolved stimuli, characterized by the activation of immune cells and excessive cytokine production, which can cause tissue damage and increase the risk of chronic diseases [2].

The Indonesian Ministry of Health, 2018, states that in Indonesia, many diseases with inflammatory components have a high prevalence, such as pneumonia in children <5 years old at 2.1%, dental and oral problems at 57.6%, gastroenteritis at 7–8%, and gouty arthritis at 7.3% in people aged ≥45 years. Anti-inflammatory drugs are a group of drugs that function to suppress or reduce the inflammatory process in the body. Commonly used therapies are non-steroidal anti-inflammatory drugs (NSAIDs) and several non- opioid

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drugs for acute and chronic inflammatory conditions. However, long-term use of NSAIDs can cause side effects such as stomach disorders, nausea, vomiting, dyspepsia, kidney dysfunction, and an increased risk of cardiovascular disease. In addition, patient compliance and treatment costs are also obstacles in conventional therapy. Therefore, alternative anti-inflammatory agents derived from natural ingredients with lower potential side effects compared to synthetic drugs are needed [3]. Indonesia's biodiversity makes it an important source of various types of traditional medicinal plants that are widely used by the community because they are considered safer than synthetic drugs, which can cause side effects if consumed in excess. One plant family that has potential as an anti-inflammatory agent is Zingiberaceae. Most of the use of plants in the Zingiberaceae family is still limited to traditional use without adequate scientific evidence, so their ectiveness and safety are not yet fully recognized in the modern health system. Therefore, evidence-based development is needed through the standardization of raw materials, phytochemical characterization, and preclinical and clinical trials to produce Standardized Herbal Medicines (OHT) that meet quality and safety criteria [4].

This review article aims to comprehensively review the potential of plants of the Zingiberaceae family as acute anti-inflammatory agents by highlighting bioactive components, mechanisms of action, and reported research results. The scope of the discussion focuses on strengthening the scientific evidence supporting the development of Zingiberaceae plants into safe, effective, and competitive standardized herbal medicine candidates in modern medicine.

2. METHODS

This study is a literature review that aims to analyze the acute anti-inflammatory activity of five plant genera belonging to the Zingiberaceae family, namely Curcuma, Alpinia, Zingiber, Kaempferia, and Etlingera. The genera Curcuma, Alpinia, Zingiber, Kaempferia, and Etlingera are the most extensively studied groups within the Zingiberaceae family, particularly regarding their acute anti-inflammatory activity. This limiation allowed researchers to utilize a sufficiently robust and relevant literature source.

Literature search was conducted systematically through several scientific databases, namely PubMed, ScienceDirect, Google Scholar, and Semantic Scholar, with a maximum publication time limit of 10 years.
Inclusion criteria included:

1. Original research articles evaluating the acute anti-inflammatory activity of extracts or bioactive compounds of plants of the Zingiberaceae family.
2. Only peer-reviewed journal articles were selected.
3. Research conducted in vivo or in vitro.
4. Articles published nationally or internationally between 2015 and 2025.

Exclusion criteria included:

1. Articles in the form of reviews, conference abstracts, or reports without experimental data.
2. Studies that did not focus on acute anti-inflammatory activity or did not include quantitative activity test results.

Data collected from each article included species name, plant part used, type of extract or active compound, inflammatory test model used, dosage, and results or percentage of inflammation inhibition. Data were analyzed descriptively to compare the anti-inflammatory activity potential between genera in the Zingiberaceae family.

3. RESULTS AND DISCUSSION

a. Pathophysiology of Acute Inflammation Inflammatory mediators (COX-2, LOX, iNOS, and TNF-α)

1. COX-2 (Cyclooxygenase-2) enzyme
   COX-2, curcumin inhibits prostaglandin production by competitively binding to the active site of the enzyme, thereby disrupting the conversion of arachidonic acid.
2. LOX (Lipoxygenase) pathway
   In this pathway, curcumin inhibits the activity of the 5-LOX enzyme. This inhibition prevents the conversion of arachidonic acid into leukotrienes (such as LTB4 and LTC4), which are mediators that cause smooth muscle contraction and immune cell migration.
3. iNOS (Inducible Nitric Oxide Synthase) Enzyme

In iNOS, curcumin works in two ways: by suppressing iNOS gene transcription (by modulating NF κB) and by directly inhibiting the activity of the formed iNOS enzyme. This combined effect reduces the excessive production of Nitric Oxide (NO), which is damaging to tissues.

4. TNF-α (Tumor Necrosis Factor-alpha)
   TNF-α production is suppressed through an indirect mechanism. Curcumin inhibits the activation of he NF-κB pathway by preventing the activation of the IKK/IκB kinase complex. As a result, NF-κB cannot enter the cell nucleus to activate the transcription of various pro-inflammatory genes, including the gene encoding TNF-α. Thus, the expression and release of TNF-α can be reduced [5].

NF-κB and MAPK signaling pathways

1. NF-κB pathway
   In this pathway, curcumin works by inhibiting the activation of the IKK/IκB kinase complex, which is the enzyme complex responsible for activating NF-κB. This inhibition causes NF-κB to remain bound in the cytoplasm and unable to migrate to the cell nucleus. As a result, the transcription of pro-inflammatory genes that are normally activated by NF-κB, such as the genes for COX-2, iNOS, TNF-α, and IL-6, is inhibited, preventing the inflammatory response from occurring.
2. MAPK pathway
   Jakukin inhibits the phosphorylation (activation) of protein kinases in the three main branches of this pathway, namely ERK, JNK, and p38. MAPK itself is a signaling pathway that responds to cellular stress and transmits signals to activate various pro-inflammatory transcription factors, including NF-κB. With the inhibition of MAPK activation, inflammatory signal transduction through this pathway is disrupted, which ultimately also contributes to suppressing the expression of genes that promote inflammation [5].

b. Mechanism of action of plant-based anti-inflammatory agents

Plant-based anti-inflammatory agents exert their effects by modulating key molecular pathways involved in inflammation; however, the strength of evidence varies across in vitro, in vivo, and limited clinical studies.

At the in vitro level, phytochemical compounds such as curcumin, flavonoids, and polyphenols have consistently demonstrated the ability to inhibit pro-inflammatory enzymes, including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). These effects lead to decreased production of inflammatory mediators such as prostaglandins and nitric oxide (NO). In addition, inhibition of lipoxygenase (LOX) activity has been observed, reducing leukotriene synthesis associated with immune cell recruitment and smooth muscle contraction. Mechanistically, in vitro studies also show that plant-derived compounds suppress nuclear factor kappa B (NF-κB) activation by preventing IκB phosphorylation and degradation, thereby inhibiting transcription of pro-inflammatory genes (e.g., COX-2, iNOS, and TNF-α). Furthermore, modulation of mitogen-activated protein kinase (MAPK) pathways—through reduced phosphorylation of ERK, JNK, and p38—has been widely reported in cell-based models [5],[6].

At the in vivo level, animal studies support these findings by demonstrating reductions in inflammatory markers, edema formation, and tissue damage following administration of plant extracts or isolated compounds. These studies provide functional validation of the molecular mechanisms observed in vitro, although variability in dosage, extract composition, and experimental models should be considered when interpreting results [6].

At the clinical level, evidence remains limited but emerging. Some studies suggest that plant-derived compounds, particularly curcumin, may reduce inflammatory biomarkers and improve clinical symptoms in certain inflammatory conditions. However, issues such as bioavailability, standardization of extracts, and study design heterogeneity limit the strength of current conclusions.

Overall, while in vitro and in vivo studies provide strong mechanistic and preclinical support, further well-designed clinical trials are required to confirm the therapeutic efficacy and safety of plant-based anti-inflammatory agents in humans [6].

Potential acute anti-inflammatory activity in plants of the Zingiberaceae family in vivo and in vitro

Table 1. In vitro analysis of acute anti-inflam matory activity in plants of the Zingiberaceae family

Plant Species	Plant Parts	Primary Bioactive	Test Method	Result	Reference
Curcuma Longa	Rhizoma	Curcuminoids	erythrocyte membrane stability in vitro using UV Vis spectrophotometry. This method is used because erythrocyte membranes are similar to lysosomal membranes, which can influence the inflammatory process	The results show that turmeric extract has anti-inflammatory potential, as seen from its ability to stabilize red blood cell membranes. At a concentration of 100 ppm, it provides the highest inhibition percentage, namely 65.64%.	[7]
Curcuma xanthorrhiza	Rhizoma	Xanthorrhizol	LPS- and HDM (house dust mite)-induced RAW 264.7 assay	Significantly reduced the expression of proinflammatory cytokines: TNF-α, IL-1β, and IL-6 ($p<0.05$–0.01)	[8]
Curcuma zedoaria R.	Rhizoma	zedoarondiol, isozedoarondiol, procurcumadiol, procurcumenol, dan curcumenol	RAW 264.7 macrophage cells were treated with LPS (lipopolysaccharide) to induce an acute inflammatory response.	dependent manner by up to 80% without affecting cell viability, and its maximum effect was almost equivalent to the positive control	[9]
Alpinia galanga	Rhizoma	1′S-1′-acetoxy chavicol acetate, 1′S-1′-acetoxy eugenol acetate, p-hydroxycinnamaldehyde	LPS-induced RAW 264.7 macrophage cells; measurement of NO (Griess assay), PGE_2 (ELISA), and TNF-α (ELISA)	• Inhibits NO production with $IC_{50} = 6.99 \pm 0.40$ µg/mL • Inhibits PGE_2 with $IC_{50} = 1.23 \pm 0.01$ µg/mL • TNF-α activity is not significant (>10 µg/mL) • Not toxic to RAW 264.7 cells.	[10]
Alpinia oficinarum	Rhizoma	diarylheptanoid dan flavonoid	RAW 264.7 mouse macrophage cells stimulated with Kdo_2-lipid A (KLA) to trigger an inflammatory response	KLA-stimulated RAW 264.7 cells.	[11]

Plant Species	Plant Parts	Primary Bioactive	Test Method	Result	Reference
Zingiber officinale	Rhizoma	6-Gingerol	RAW 264.7 macrophage cells stimulated with LPS	• Ginger extract and 6-gingerol significantly reduce NO production. • They inhibit the expression of COX-2 and iNOS, and suppress the activation of the NF-κB and p38 MAPK pathways, which play an important role in the inflammatory response.	[12]
Zingiber zerumbet L.	Rhizoma	Zerumbone	LPS-induced macrophage cells (RAW 264.7); NO and IL-6 production tests, iNOS and COX-2 expression	Decreases NO, IL-6, PGE_2 production, and suppresses iNOS and COX-2 expression through NF-κB and NLRP3 inflammasome inhibition	[13]
Zingiber cassumunar	Rhizoma	E)-1-(3,4-Dimethoxyphenyl)-5-hydroxy-7-methoxy-8-methyl-6-chromene (DMC)	In vitro testing RAW 264.7 macrophage cells stimulated with lipopolysaccharide (LPS)	The anti-inflammatory effect occurs through inhibition of the NF-κB, MAPK (p38, ERK), and Akt pathways	[14]
Kaempheria galanga L.	Rhizoma	Ethyl-p-methoxycinnamate (EPMC)	Colorimetric assay, inhibit the activity of COX-1 and COX-2 enzymes in a cell-free system.	EPMC was found to inhibit COX-1 and COX-2 non-selectively. In addition to inhibiting PG synthesis, Kaempferia galanga L. also inhibits several inflammatory mediators TNF-a, IL-1ß, and Nitric Oxide (NO)	[15]
Kaempferia parviflora	Rhizoma	flavonoid	*RAW 264.7* murine macrophage cells	K. parviflora extract decreased the expression of LPS-stimulated iNOS and COX-2 proteins.	[16]

Plant Species	Plant Parts	Primary Bioactive	Test Method	Result	Reference
Etlingera elatior	İnflorescence	Flavonoid (quercetin, kaempferol, apigenin, luteolin), asam fenolat (gallic acid, caffeic acid, chlorogenic acid), tanin, terpenoid.	Nitric Oxide (LPS-induced RAW 264.7 macrophages + Griess reagent), PGE_2 & TNF-α (EIA)	The 70% ethanol extract of E. elatior flowers is most potent as an anti-inflammatory (IC_{50} NO ≈ 16 µg/mL) and antioxidant (EC_{50} ≈ 25 µg/mL); the 95% extract is also effective against PGE_2.	[17]
Curcuma mangga	rhizoma	flavonoid, saponin, glikosida, terpenoid, steroid	RAW 264.7 cells were stimulated with LPS (1 µg/mL) and then C. mangga extract was added. The expression of cytokine genes (IL-6, IL-1β, TNF-α) was analyzed using RT-PCR. Cell viability was tested using the MTT assay (12.5–50 µg/mL).	C. mangga extract reduced the expression of pro-inflammatory cytokine genes IL-1β, IL-6, and TNF- α in LPS alone. This indicates the potential for inhibition of the inflammatory pathway at the gene level.	[18]

Table 2. Analysis of acute anti-inflammatory activity in vivo against plants of the Zingiberaceae family

Plant Species	Main bioactive/Type of extract	Dose	Test Model	Test Results	Reference
Curcuma longa	Curcumin	20 and 25 mg/kgBW	Mice were injected with 0.1 mL of a 1% carrageenan solution into the left paw pad.	Nanoemulsions of ethanol extract of turmeric rhizome at doses of 20 and 25 mg/kg BW exhibited anti-inflammatory activity using the 1% carrageenan-induced edema volume method, with average protection rates of 35.21% and 64.79%, respectively.	[19]
Curcuma xanthorrhiza	Curcuminoid	175 – 250 mg/kgBW	Male Sprague Dawley rats were induced with carrageenan (foot edema test)	Showed anti-inflammatory activity of 31.70%, equivalent to the positive control diclofenac	[20]
Curcuma	Phenols,	300, 600, dan	Curcuma zedoaria	Curcuma zedoaria	[21]

Plant Species	Main bioactive/Type of extract	Dose	Test Model	Test Results	Reference
zedoaria R.	Flavonoids, Triterpenoids, Steroids, Tannins	900 mg/kgBW	ethanol extract was administered orally, followed by inflammation induction using 1% carrageenan (0.1 mL, intraplantar) 1 hour after administration.	ethanol extract significantly inhibited carrageenan-induced edema, with the best efficacy at a dose of 600 mg/kgBW, which is equivalent to diclofenac.	
Alpinia galanga	1'S-1'-Acetoxy chavicol acetate, Galangin, Eugenol	100 mg/kgBW p.o	*Carrageenan-induced paw edema and cotton pellet granuloma in albino Wistar rats*	Methanol and acetone extracts of galangal at a dose of 100 mg/kgBW showed significant anti-inflammatory effects ($p<0.05$). In the paw edema model, maximum inhibition was achieved at 1–3 hours (approximately 17–24%). In the granuloma model, the wet and dry weight reductions were approximately 18–19% and 16–17%, respectively.	[22]
Alpinia Officinarum	Diarylheptanoid	Doses of Rhizoma Alpinia Officinarum ethanol extract: 200, 500, and 1000 mg/kgBW	*Induced by subcutaneous injection of 1% carrageenan into the hind paws of Sprague-Dawley rats*	The extract significantly reduced leg edema within 1–5 hours after induction. The supporting mechanism is the indication of suppression of the iNOS/NO-mediated inflammatory pathway.	[23]
Zingiber officinale Roscoe	6-Gingerol	25, 50, and 100 mg/kgBW (p.o., oral)	Model of acute paw edema inflammation in rats (carrageenan-induced paw edema)	6-Gingerol showed a significant reduction in rat leg edema ($p < 0.05$) compared to the negative control. Tissue analysis showed a decrease in PGE2 and TNF-α levels in inflamed tissue.	[24]
Zingiber zerumbet L.	Zerumbone	10–50 mg/kgBW, intraperitoneal	Carrageenan-induced paw edema mouse model	Reduces edema by up to 70% at a dose of 50 mg/kg; suppresses	[25]

Plant Species	Main bioactive/Type of extract	Dose	Test Model	Test Results	Reference
		injection		the expression of TNF-α, IL-1β, COX-2, iNOS	
Zingiber cassummunar	Terpenoids, phenylbutanoids	1%, 2,5%, and 5%	Female mice induced with carrageenan to cause skin inflammation, then applied with ethanolic extract cream	The administration of Zingiber cassumunar extract significantly reduced skin swelling; even at a concentration of 1%, it had an anti-inflammatory effect.	[26]
Kaempheria galanga L.	Flavonoids, essential oils, ethyl p-methoxycinnamate	3.15 grams, 6.3 grams, and 12.6 grams.	Intraplantar induction of carrageenan in the left paw of mice	Doses of Kaempferia galanga extract (6.3 mg/kgBW, 12.6 mg/kgBW, and 25.2 mg/kgBW). The strongest reduction in edema was observed at a dose of 25.2 mg/kgBW, with a reduction percentage of 27.90%.	[27]
Kaempferia parviflora	Flavonoid	50 mg/kgBW, 150 mg/kgBW, 250 mg/kgBW	Carrageenan was injected subplantarly to induce paw edema in white mice (leg swelling) as a sign of acute inflammation.	Ethanol extract of Kaempferia galanga rhizome at a dose of 250 mg/kg BW significantly reduced the volume of carrageenan-induced edema in rat paws. By inhibiting the COX-2 enzyme → reducing prostaglandins	[16]
Etlingera elatior	flavonoids, phenolics, tannins, saponins, alkaloids, and triterpenoids.	200 mg/kgBW	*Carrageenan-induced paw edema test in Wistar rats*	The ethanol extract of Etlingera elatior leaves at 200 mg/kgBW provided 82.29% edema inhibition, which was almost equivalent to 4.5 mg/kgBW sodium diclofenac (83.48%) in a carrageenan-induced paw edema model (n = 5/group). This makes kecombrang leaves a viable candidate for further research as a	[28]

Plant Species	Main bioactive/Type of extract	Dose	Test Model	Test Results	Reference
				source of natural anti-inflammatory agents.	
Curcuma mangga	flavonoids, saponins, glycosides, terpenoids, steroids.	100 mg/kgBW 200 mg/kgBW 400 mg/kgBW	Normal and immune-suppressed rats (cyclophosphamide) were sensitized with Salmonella typhimurium. The delayed-type hypersensitivity (DTH) response was measured using the paw edema method. IgG and IL-4 were measured from serum using ELISA after treatment with the extract (100, 200, 400 mg/kgBW).	The extract increased DTH response and IgG production, indicating stimulation of cellular and humoral immunity. The extract also decreased IL-4 levels, indicating modulation of the Th2 cytokine pathway .	[29]

Toxicity testing on plants of the Zingiberaceae family

1. *Curcuma longa* L.

The main component of C. longa that plays a role in inhibiting the inflammatory process is curcumin, a polyphenolic compound with strong antioxidant and anti-inflammatory activities. Based on research acute toxicity tests were conducted by administering a single dose orally at a dose of 0.075-5000 mg/kg BW over a period of 14 days. C. longa extract did not have a toxic effect on the platelet count of Wistar rats. Based on research by Mulyani et al. (2022), subchronic toxicity tests of C. longa rhizome extract was conducted on Wistar rats with doses of 50, 100, and 200 mg/kg BW orally for 28 days. The results showed no signs of toxicity in liver and kidney biochemical parameters, hematology, and histopathological examination of major organ at all doses, indicating that turmeric extract is not toxic [30].

2. *Curcuma xanthorrhiza* Roxb.

C. xanthorrhiza contains a main compound that plays a role in inhibiting the inflammatory process, namely nanocurcumin (nanocurcuminoid). This compound, especially curcumin formulated in the form of nanoparticles and coated with palmitic acid, shows increased bioavailability and effectiveness in suppressing the inflammatory response. The results of the study indicate that the combination extract containing C. xanthorrhiza does not exhibit acute or subchronic toxic effects. In the acute oral toxicity test on rats, administration of doses up to 5000 mg/kg BW did not cause death or symptoms of toxicity, resulting in an LD_{50} value > 5000 mg/kg BW. Furthermore, in the 90-day subchronic toxicity test, administration of the extract at doses up to 1000 mg/kg BW did not cause significant changes in body weight, hematological parameters, blood biochemistry, or histopathological findings of organs. Therefore, the combination extract was declared safe, with a NOAEL value of 1000 mg/kg BW [31].

3. *Curcuma zedoaria* (Christm.) Roscoe.

C. *zedoaria* was identified as having zedoarondiol as its main active compound. The study by Tandanu et al. (2022) was an acute experimental study with a 14-day observation period. White rats were divided into a negative control group with distilled water and a positive control group with

1% Na CMC, and four treatment groups with white turmeric extract at doses of 250 mg/kg BW, 500 mg/kg BW, 750 mg/kg BW, and 2000 mg/kg BW. The results showed that white turmeric extract (C. *zedoaria*) did not exhibit acute toxicity effects on the pancreas of white rats, as evidenced by the absence of necrosis, edema, and inflammatory cells in the histological picture of the pancreas [32]. Based on the research by Armayanti D (2018), a subchronic toxicity test was conducted by administering C. *zedoaria*

ethanol extract for 28 days at a dose of 250 mg/kg BW, which proved to have no toxic effects on SGOT parameters and liver histopathology, while it had toxic effects on SGPT parameters [33].

4. *Alpinia galanga* (L.) Willd.

Galangal (*Alpinia spp*.) is a rhizome plant from the Zingiberaceae family that is widely used as a cooking spice and traditional medicine in Southeast Asia. In Indonesia, there are two main varieties, namely red galangal (*Alpinia officinarum* Hance) and white galangal (*Alpinia galanga*) [34]. A. galanga has been shown to have strong anti-inflammatory activity through its flavonoid and diarylheptanoid content, with the main compounds being galangin and acetoxychavicol acetate (ACA), which are the focus of mechanistic studies. Based on R. J. Das et al, (2017), an acute oral toxicity study was conducted in which herbal extracts at different doses up to 2000 mg/kg were administered and the animals were observed for behavioral changes. The animals were then observed for another 14 days to look for signs of delayed toxicity. All A. *galanga* extracts mentioned above have a good safety margin and did not show lethal effects in animals up to a dose of 2000 mg/kg [35].

5. *Alpinia officinarum*

A. *officinarum*, also known as red galangal, contains key bioactive compounds including flavonoids, phenolics, diarylheptanoids, and essential oils. Some specific components that have been identified include galangin, kaempferol, quercetin, and pinocembrin. Based on research by Alasmary et al. (2019), acute and subchronic toxicity tests were conducted on Swiss albino rats. In the acute test, the extract was administered orally at a single dose of up to 4000 mg/kgBW. No deaths or toxic symptoms were found during the 14-day observation period, so the LD_{50} value was estimated to be more than 4000 mg/kgBW. For the subchronic test, the extract was administered orally for 35 consecutive days at a daily therapeutic dose of 400 mg/kgBW. The evaluation included hematological parameters, serum biochemistry, and liver and kidney histopathology. The results showed no significant changes in all parameters tested, and no pathological lesions were found in the target organs [36].

6. *Zingiber officinale Roscoe*

The main component of Z. *officinale Roscoe*. is 6-Gingerol. Ginger extract contains 6-gingerol, which is effective in significantly reducing NO production. Based on research conducted by V. E. Villarreal-La Torre et al. (2024), an evaluation of the acute toxicity of Z. *officinale Roscoe* rhizome ethanol extract in rats showed histopathological changes, especially at a dose of 2000 mg/kg. The liver showed mild lymphocytic portal inflammation, condensed hepatocyte nuclei, eosinophilia, and moderate hepatic steatosis. The kidneys showed mild lymphocyte infiltration and some polymorphic cells around the renal tubules and glomeruli at the same dose. The brain showed a slight increase in the number of astrocytes with focal glial reactions, and the stomach and heart also showed mild inflammatory processes. Biochemical parameters such as cholesterol, triglycerides AST, ALT, ALP, urea, and creatinine in rat serum showed statistically significant differences between the 2000 mg/kg/day dose and the control group [37].

7. *Zingiber zerumbet* (L.) Roscoe

The main anti-inflammatory compound in Z. *zerumbet* is zerumbone. In an LPS-induced RAW 264.7 macrophage cell model, zerumbone showed a decrease in theproductionof pro-inflammatory cytokines such as TNF-α and IL-1β through the inhibition of the NF-κB signaling pathway and modulation of the MAPK pathway, as well as suppressing the expression of pro-inflammatory enzymes such as iNOS and COX-2. Based on research by Fatmawati & Rohmah (2022) conducted using albino mice given graduated doses (4000 mg/kg, 5000 mg/kg, and 6000 mg/kg BW). The results of this study showed that the varying doses administered did not cause toxic effects on bilirubin and alkaline phosphatase levels in the liver of mice. The LD50 value obtained from the toxicity test was greater than 6000 mg/kg BW, which falls into category 5 (practically non-toxic) [38]. Based on the study by Wen Chan et al (2024), the subchronic toxicity test of Z. *zerumbet* extract was conducted using albino rats that were given doses of 1000-3000 mg/kg BW once a day for 28 days orally. The results of this study showed no abnormalities in the body weight of the test animals, hematological parameters, and necropsy and histopathological tests. This is consistent with previous studies, where Z. *zerumbet* extract did not cause toxic effects and was classified as category 5 (practically non-toxic) [39].

8. *Zingiber cassumunar* Roxb.

The main component of Z. cassumunar that exhibits anti-inflammatory activity is phenylbutanoid, with dominant compounds such as (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-ol and its derivatives. Based on research conducted by Gundom et al. (2025) In acute toxicity tests, the extract was tested on RAW264.7

and C2C12 cells at concentrations of up to 100 µg/mL. The MTT assay results showed that the extract did not cause a significant decrease in cell viability, with viability levels remaining above 80%, indicating that the extract was not cytotoxic at that concentration. In the subchronic test, C2C12 cells were repeatedly exposed to phenylbutenoids and their derivatives. The extract did not trigger an increase in the expression of apoptotic proteins such as Bax and Bcl-2, and significantly decreased the cleaved/pro-caspase-3 ratio. A decrease in the expression of p-p38/p38, pERK/ERK, and pAkt/Akt was also observed, indicating that the extract was able to inhibit inflammatory and apoptotic pathways without causing systemic toxic effects [40].

9. *Kaempferia galanga* L.

The bioactive compounds in K. galanga are chalcones, flavonoids, and terpenoids. Based on research conducted by Nurmala (2017), acute toxicity tests of ethyl-p-methoxycinnamate compounds were administered orally to groups of test rats with varying doses of 50, 100, 500, 1000, and 2000 mg/kg BW. The test results showed that the median LD50 value was achieved at a dose of 3,652 mg/kg BW, concluding that this compound is classified as moderately toxic [41]. Ethanol extract of K. *galanga* rhizome was tested sub-acutely for 30 days with a daily dose of 1000 mg/kg BW in ICR rats. The results showed no significant toxic effects on body weight, behavior, food and water consumption, and no histopathological abnormalities in vital organs such as the liver and kidneys compared to the control group. At higher doses (3000 and 5000 mg/kg BW), symptoms such as lethargy and piloerection (bristling) appeared, but there were no mass deaths and no significant histopathological changes in vital organs compared to the control group [42].

10. *Kaempferia rotunda* L.

Toxicological study exhibits that the ethanol K. *parviflora* extract (at the doses of 60, 120, and 240 mg/kg for 60 days) does not induce significant changes in hemoglobin, white blood cells, or differential cell count. No any negative effects on renal and hepatic functions have been found at the tested doses. Subchronic toxicological study shows that administration of Fitnox (at the dose of 1000 mg/kg/day for 90 days) to rats exhibits no any drug-related toxicity or mortality in either sex and no significant changes between the control and Fitnox treated groups in all parameters at the hematological, biochemistry, and histological levels. In vivo, the hexane and chloroform fractions of K. *parviflora* extract show greater activity in decrease of rat paw edema than ethyl acetate, ethanol and water fractions. Consistently, the compounds isolated from KP have been tested for inhibitory effects on NO, PGE2, and TNFα release. Compound-10 has been demonstrated the highest activity against LPS-induced NO release (IC50 = 16.1 nM) and PGE2 production (IC50 = 16.3 nM) in RAW 264.7 cells, butitis inactive on TNFα expression (IC50 > 100 nM) [43].

11. *Etlingera elatior* (Jack) R.M. Smith.

Specifically, the flavonoids contained in E. elatior are kaempferol, quercetin, and myricetin. The leaves of E. elatior contain the compounds quercetin 3-glucoside, quercetin 3-glucuronide, quercetin 3-rhamnoside, and kaempferol 3-glucuronide, while the flowers and stems produce kaempferol-3-O-glucoside, kaempferol, and quercetin. The rhizome extract has the potential to inhibit Nitric Oxide (NO) production in RAW 264.7 [44]. Based on research conducted by Sholihah et al (2025), acute oral toxicity testing of 96% ethanol extract on Balb/C mice showed that even at the highest dose tested (600 mg/kg body weight), no mortality or significant toxicity symptoms were observed in the test animals during the 14-day observation period, indicating that the lethal dose 50% (LD50) is above 600 mg/kg [45].

12. *Curcuma mangga* Val

C. *mangga* extract contains terpenoids and steroids, as well as other compounds that may have anti-inflammatory effects, such as flavonoids, saponins, and glycosides. The main compound in C. *mangga* is demethoxycurcumin. Based on research by Sari et al (2016), subchronic toxicity studies showed that administration of ethanol extract of C. mangga rhizome at low doses (100 mg/kgBW) did not show significant changes in liver function indicators (SGOT and SGPT levels) and relative liver weight compared to the control, implying safety at that dose. However, at higher doses (200 and 300 mg/kgBW), significant differences in SGOT and SGPT levels were observed, indicating the need for safe dose limits in therapeutic use. Therefore, anti-inflammatory efficacy must always be balanced with toxicity safety profiles [46].

Regulation and Development of Standardized Herbal Medicines

a. Definition of OHT according to BPOM

Standardized herbal medicines are natural preparations that have undergone extraction and consistent formulation, with scientific proof of their safety and efficacy through preclinical testing. According to BPOM regulations, standardized herbal medicines must meet quality requirements that include identification of raw materials, standardization of production processes, and testing for microbial contamination, heavy metals, and solvent residues. This standardization aims to ensure the consistency of active ingredient content in each product batch, so that its effectiveness and safety can be scientifically accounted for.

b. Quality requirements

In the development of standardized herbal medicines, the raw material validation process is a crucial stage. The raw materials used must come from botanically identified sources and have undergone harvesting and post-harvesting processes in accordance with Good Agricultural Practices. Furthermore, the extraction process is carried out using controlled methods, using solvents that are safe and comply with pharmaceutical standards. The extract is then tested chemically and biologically to ensure the presence of active compounds that contribute to the expected pharmacological effects. BPOM regulations also emphasize the importance of proving efficacy through preclinical tests, such as toxicity and biological activity tests, before a product can be categorized as a standardized herbal medicine. In addition, scientific documentation supporting efficacy claims must come from valid and reproducible research results. Thus, standardized herbal medicines not only fulfill traditional aspects, but also scientific and regulatory aspects, so that they can be accepted in the formal health care system as an alternative or complement to conventional therapy [47].

c. Preclinical testing

In the context of standardized herbal medicine (OHT) development, preclinical testing is an essential stage for scientifically proving the safety and efficacy of natural extracts before testing on humans. Preclinical testing aims to evaluate the safety, effectiveness, and biological effects of drug candidates before testing on humans. These tests include in vitro and in vivo studies conducted in accordance with Good Laboratory Practice (GLP) guidelines, as well as pharmacokinetic, pharmacodynamic, and toxicity assessments as a basis for eligibility for clinical trials [48].

CHALLENGES AND PROSPECTS

The development of plant-based anti-inflammatory agents still faces a number of limitations, particularly in terms of pharmacodynamics. Variability in phytochemical composition between specimens and extraction processes means that the concentration of active compounds is greatly influenced by species, geographical origin, harvest season, and drying and extraction methods, making it difficult to reproduce pharmacodynamic results between laboratories. In addition, many studies still use crude extracts or different fractions without standardizing pharmacodynamic biomarkers, such as determining the levels of certain active compounds, making it difficult to quantitatively compare the relationship between dose and acute inflammatory response. Low bioavailability and pharmacokinetics, especially in phenolic compounds such as gingerol, shogaol, and curcumin, which undergo rapid phase II metabolism, also cause in vivo effects to often be weaker than in vitro results. The use of heterogeneous preclinical models with inconsistent protocols and outcome parameters also limits the translation of research results to acute inflammation in humans [49].

Another significant challenge is the standardization and reproducibility of the pharmacological effects of herbal products. The natural diversity of bioactive content, limitations in quality control systems, and suboptimal implementation of regulations lead to inconsistencies in quality and potency between batches and manufacturers. Therefore, strengthening the implementation of Good Agricultural Practices (GAP) and Good Manufacturing Practices (GMP), along with standardizing phytochemical composition, is a strategic step to ensure that herbal products have stable, safe, and scientifically replicable pharmacological effects [50]. In line with this, the validation of the efficacy and safety of plant-based anti-inflammatory agents requires measurable clinical trials. The development of herbal medicines begins with the documentation and standardization of ingredients, including botanical species identification, batch specifications, and the determination of active markers, followed by preclinical data linking pharmacokinetics and pharmacodynamics in acute inflammatory models, as well as adequate acute and subacute toxicity tests. These documents form the basis for clinical trial registration and compliance with quality requirements in accordance with the principles of botanical drug development recommended by regulators.

Despite still facing a number of challenges, herbal medicine is predicted to have a bright future. Developments in genomics, biotechnology, and analytical chemistry are also playing an important role in improving the quality of herbal products. These innovations enable the creation of extracts with more stable, standardized, and high-quality compositions. In addition, the application of the concept of integration between traditional and modern medicine is now increasingly accepted because it has been proven to improve the effectiveness of therapy and patient clinical outcomes. Regulatory reform efforts at the global level are also continuing to ensure the safety, quality, and effectiveness of herbal products, while supporting innovation in the field of phytotherapy. Several areas that are considered to have great prospects include the development of herbal medicines tailored to individual genetic profiles, nutraceutical innovations with specific health benefits, and phytopharmaceuticals that combine modern pharmaceutical technology with traditional knowledge. Additionally, treatment systems such as Traditional Chinese Medicine (TCM) and Ayurveda also show great potential due to their comprehensive approach that focuses on body balance and disease prevention [51].

4. CONCLUSION

Plants from the Zingiberaceae family have strong potential as acute anti-inflammatory agents. Various genera such as Curcuma, Zingiber, Alpinia, Kaempferia, and Etlingera have been shown to contain key bioactive compounds such as curcuminoids, gingerols, zerumbone, flavonoids, phenylbutanoids, and terpenoids that can suppress acute inflammatory responses both in vitro and in vivo. The anti-inflammatory mechanism of Zingiberaceae plants generally involves the inhibition of major inflammatory signaling pathways such as NF-κB and MAPK, as well as a decrease in the expression of proinflammatory mediators such as TNF-α, IL-1β, IL-6, NO, iNOS, and COX-2, thereby contributing to a reduction in edema and inflammatory responses. With efficacy comparable to conventional anti-inflammatory drugs and lower potential side effects, Zingiberaceae plants have the potential to be developed as standardized herbal medicines, although further standardization and clinical trials are still required.

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