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REVIEW ARTICLE

The Safety Evaluation of Some Plants of the Zingibereceae Family

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Abstract: The Zingiberaceae family has long been used by the community as a spice, cosmetic ingredient, spice ingredient, and as an ingredient in traditional medicine. Toxicity testing is also essential as the first step in drug safety parameters before being used as a human drug product. This review article aims to identify and review scientific information from research thatched regarding the safety of the use of plants, especially those from the Zingiberaceae family. A literature study is used as a method in writing this article review. Literature searches were conducted online through search engines such as Google Scholar, Pubmed, and NCBI using the keyword "Zingiberaceae". "Toxicity test" and "Toxicity" followed by each plant's Latin name. The library criteria used are international journals indexed in Scopus Q1 to Q4 and national journals indexed in Sinta S1 to S6 published in the last ten years (2012-2022). A literature search found that 18 plants from the Zingiberaceae family had their toxicity tested acutely, subacutely, and chronically including *Alpinia calcarata*, *Alpinia galanga*, *Alpinia malaccensis*, *Amomum compactum Sol. Ex Maton*, *Boesenbergia rotunda*, *Curcuma angustifolia*. *Curcuma caesia*, Curcuma longa, Curcuma xanthorriza, Curcuma comosa, Etlingera elatior, Globba pendula, *Hedychium spicatum*, *Kaempferia galanga*, *Kaempferia rotunda*, *Zingiber officinales*, *Zingiber zerumbet*, and *Zingiber cassumunar* are categorized as non-toxic.

Keywords: Acute, sub-acute, chronic, toxicity, Zingiberaceae

INTRODUCTION

Indonesia is known for having biodiversity in the form of plants that contain various types of chemical compounds that have the potential to be used as traditional medicine by the community to overcome different disease problems. Treatment is mainly derived from primary sources, such as

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plant leaves, bark, seeds, fruits, flowers, and roots.[2] In Indonesia, knowledge of the efficacy and safety of medicinal plants is typically based on empirical experiences passed down through generations rather than scientific testing.[3] For the legal health services to be increased, it is necessary to make research efforts on a medicinal plan so that the drug can be rugged safely and effectively.[4] One plant in the Zingiberaceae family that is widely used as a medicinal plant is ginger.[5]

The Zingiberaceae family is the largest of the Zingiberales tribe, and it grows in the tropics and subtropics in humid and dry conditions; 6 the Zingiberacea; 6 family contains 52 genera, and 1587 species is an annual, aromatic, spherical or rhizomes herbaceous rhizomes epiphytic, tubular, and usually has tubular roots, has a short stem, replaced by a pseudo-stem, alternate leaves, usually leafless at the base of the plant, and fused into a midrib.[8] Curcuminoids, flavonoids, alkaloids, tannins, saponins, quinones, and triterpenoids are among the compounds found in the Zingiberaceae family, which is widely distributed in Papua, Central Java, Sumatra, Sulawesi, and Maluku.[11]

The community uses the Zingiberaceae family as a seasoning, cosmetic ingredient, spice, and spaceline ingredient.[12] Some species of the Zingiberaceae plant that are often used by the community, including black temu (Curcuma aeruginosa Roxb), turmeric (Curcuma longa. L), Temu rapet (Kaemferia rotunda L. rhizome), Lempuyang (Zingiber zerumbet L.), Kecombrang leaf (Etlingera elator (Jack) R.M Smith), Bangle (Zingiber cassumunar). Several studies have shown that the Zingiberaceae family effectively treats headaches, loose stools, gout, measles, and sore drugs.[13]

There have been no reports of specific studies on toxicity studies from the Zingiberaceae family. Although culture is very supportive and low cost, sources of low-cost and knowledge must be obtained correctly. Understanding the effects present in medicinal plants is essential to ensure their safety anabolic be more selective in using traditional medicine.[14] Toxicity testing is also an essential first step in essentialising a drug's safety parameters before it is approved for human use.[15] This is because substantially to be toxic depending on the dose administered to the body. Several ages of toxicity testing are developed to determine a medicinal product's safety velocity tests, subchronic toxicity tests, and subchronic toxicity tests.[16] Based on the preceding, it is necessary to make additional efforts to study scientific information on the results of the toxicity of some plants in the Zingiberaceae family. This article aims to find and review scientific information from research on the safety of using plants, particularly those in the Zingiberaceae family.

METHODS

This article's reviews are written using a method called literature studies. Online

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library searches using the keyword "Zingiberaceae" use Google Scholar, Pubmed, and NCBI. "Toxicity test," "Toxicity," and then the Latin name of each plant were used. International journals indexed by Scopus Q1 to Q4, and national journals indexed by Sinta S1 to S6 published in the last ten years, were used as library criteria (2012-2022). After obtaining the articles, data such as plant species, plant parts used, solvents used, compound content, type of toxicity, the sage used, LD_{50} value, and toxicity category are collected.

RESULTS

According to the literature search, 18 plant species from the Zingiberaceae family have been tested for toxicity both acutely, subacutely, and chronically, as shown in Tables 1, 2, and 3:

Table 1. The results of the safety evaluation of some plants of the Zingiberaceae family of the acute toxicity category

No.	Plant species	The Parts of Plants Used	Solvents Used	Compound Content	Types of Toxicity	Dosage Used	LD_{50} Value	Toxic Categories
1	*Alpinia calcarata*	Rhizome	Ethanol, hot water	polyphenol, tannin, flpolyphenolglycoside steroid, alkaloid, and essential oils	Acute	1500 mg/BW	>1500 mg/BW[17]	Non-Toxic
2.	*Alpinia galanga* (Galangal)	Rhizome	Ethanol	Alkoloid, saponin, tannin, flavonoid, steroid, and terpenoid	Acute	5, 50, 300, 2000 mg/kg BW	>2000 mg/BW [18]	Non-Toxic
3.	*Alpinia malaccensis* (White galangal)	Rhizome	N-hexane	alkaloid, Flavonoid, steroid, karbohidrat, tannin, saponin and glikosida	Acute	300 mg/BW 2000 mg/BW	>2000 mg/BW[19]	Non-Toxic
4.	*Amomum compactum Sol. Ex Maton* (Cardamom)	Seed	Ethanol	Seskuitepen, monoterpenoia nd essential oils	Acute	300 mg/BW 2000 mg/BW	>2000 mg/kBB[20]	Non-Toxic

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5.	*Boesenbergia rotunda* (Temu kunci)	Rhizome	Ethanol 95%	alkaloid, esensial oil, flavonoid, fenolat., kuersetin	Acute	250,500 1000,2000 4000mg/BW	>4000 mg/BW[21]	Non-Toxic
6.	*Curcuma angustifolia*. (tikhur) (india)	Rhizome	Water	metil eugegenol, kamper, sineol	Acute	2200 mg/kg; 3300 mg/kg; 4400 mg/kg	>4400 mg/kg[22]	Non-Toxic
7.	*Curcuma caesia* (Black Turmeric)	Rhizome	Ethanol	alkaloid, phenolic compounds, flavonoid and tannin	Acute	2000 mg/BW	>2000 mg/BW[23]	Non-Toxic
8.	*Curcuma longa* (Turmeric)	Rhizome	Ethanol 95%	Flavonoid	Acute	10g/BW	LD_{50} fraksi etil asetat 27,98 g/BW. LD_{50} fraksi hexan 19,25 g/BW[24]	Non-Toxic
9.	*Curcuma xanthorriza* (Temulawak)	Rhizome	Ethanol	terpenoid, kurkuminoid, and fenolik	Acute	50-6400 mg/BW	>6400 mg/BW[25]	Non-Toxic
10.	*Etlingera elatior (Jack)* (Kecombrang)	Flower	Ethanol	Fenolik and flavonoid	Acute	dosis 1000, 1500 dan 2000 mg/BW	>2000 mg/BW[26]	Non-Toxic
11.	*Globba pendula* (Pedas Kancil)	Rhizome	Methanol	diterpene labdane, benzofuran, phenolate, steroid, and phenolate eal oils	Acute	6, 8, 10 g/BW	>500 mg/BW[27]	Non-Toxic

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12.	*Hedychium spicatum* (Gandasuli)	Rhizome	Ethanol	polifenolat, flavonoid, tannin, kuinon, monoterpenod iand sekuiterpenoid	Acute	200 mg/BW	>200mg/kg	Non-Toxic
13.	*Kaempferia galanga* (Kencur)	Rhizome	Ethanol	Flavonoid, kaempferol, etil p-metoksisinamat, eukaliptol, karvon pentadekan and metal sinamati	Acute	5000 mg/kg	>5000 mg/kg[28]	Non-Toxic
14.	*Kaempferia rotunda* (White turmeric)	Rhizome	Ethanol	atsiri oil, flavonoid, alkaloid, and sponin	Acute	250, 500, 1000 mg/kg	>1000 mg/BW[29]	Non-Toxic
15.	*Zingiber officinales* (Red ginger)		Ethanol	diarylheptanoid, fenilbutenoid, flavonoid, diterpenoid, sesquiterpenoid, gingerol and shagaol	Acute	1000, 3000,5000 mg/BW	>5000mg[30]	Non-Toxic
16.	*Zingiber zerumbet L.* (Lempuyang Gajah)	Rhizome	Ethanol 95%	alkaloid, saponin, flavonoid, tannin, terpenoid, fenol, polifenol, and sugar.	Acute	15g kg^{-1}	>15gKg^{-1} [31]	Non-Toxic
17.	*Zingiber cassumunar* (Bangle)	Rhizome	Ethanol	fenilbutanoid, terpenoid, sitosterol, and kurkuminoid	Acute	5000 mg/kg BW	>5000 mg/BW [32]	Non-toxic

Table 2. The results of the safety evaluation of several plants of the Zingiberaceae family of the sub-acute toxicity category

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No.	Plant species	The Parts of Plants Used	Solvents Used	Compound Content	Types of Toxicity	Dosage Used	Haematological and histopathological parameters	Toxic Categories
1.	*Curcuma comosa*	Rhizome	Ethanol	diarylheptanoid and acetophenones	sub acute	100, 250, 500 mg/kg/day	No effect on the haematological and chemical parameters of the blood. Alkaline phosphatase levels and serum potassium increased significantly at 500 mg/kg/day. Quantities of 250 and 500 mg/kg/day of CYP1A1 and CYP2B1/2B2 activity increased daily signifikan[33]	Non-toxic
2.	*Kaempferia galanga* (Kencur)	Rhizome	Ethanol	Flavonoid, kaempferol, etil p-metoksisinamat, eukaliptol, karvon pentadekan and metal sinamati	sub acute	1000,3000,5000 mg/BW	At doses of 5000 mg/BW and 3000 mg/BW, there was a decrease in activity, such as lethargy and piloerection, due to more significant dose levels, but showed no remarkable signs of toxicity, including weight, histopathology of vital organs, respiratory patterns, motor activity, regular drinking, and did not cause death[28]	Non-toxic

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3.	*Zingiber officinales* (Red Ginger)	Rhizome	Ethanol	diarylheptanoid, fenilbutenoid, flavonoid, diterpenoid, sesquiterpenoid, gingerol and shagaol	sub acute	1000, 3000,5000 mg/BW	Irritation of the abdominal part occurred, but the test animal recovered from symptoms within 1 hour after dosing. Food and water intake, comparable average body weight, no abnormal histopathology of vital organs.[30]	Non-toxic
4	*Zingiber zerumbet L.* (Lempuyang Gajah)	Rhizome	Ethanol 95%	alkaloid, saponin, flavonoid, tannin, terpenoid, fenol, polifenol, and sugar.	sub acute	1000, 2000 300 mg/kg	There are no signs of toxicity such as piloerection, changes in motion activity, or diarrhea[31]	Non-toxic
5.	*Zingiber cassumunar* (Bangle)	Rhizome	Ethanol	fenilbutanoid, terpenoid, sitosterol, and kurkuminoid	Chronic	0,3 , 3, 30, 11, 25, and 112,5 1.125 mg/BW	Showed no clinical symptoms of toxicity and mortality in experimental mice[32]	Non-toxic

Table 3. The results of the safety evaluation of several plants of the Zingiberaceae family of the chronic toxicity category

No.	Plant species	The Parts of Plants Used	Solvents Used	Compound Content	Types of Toxicity	Dosage Used	Haematological and histopathological parameters	Toxic Categories
1.	*Zingiber cassumunar* (Bangle)	Rhizome	Ethanol	Fenilbutanoid, terpenoid, sitosterol, and kurkuminoid	Chronic	0,3 , 3, 30, 11, 25, and 112,5 1.125 mg/BW	Showed no clinical symptoms of toxicity and mortality in experimental mice[32]	Non-toxic

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1. *Alpinia calcarata*

Alpinia calcarata Roscoe is a tropical plant in Sri Lanka, India, and Malaysia. *Alpinia calcarata* rhizomes have been shown to have antibacterial, deworming, antioxidant, and antifungal properties. *Alpinia calcarata* rhizome is used as an aphrodisiac, and its decoction is widely used to treat bronchitis, cough, respiratory diseases, diabetes, asthma, and arthritis. Chemical compounds found in *Alpinia calculate* you include polyphenols, tannins, flavonoids, steroid glycosides, alkaloids, and essential oils. In a toxicity study conducted by Rahman et al. (2015)[17] using ethanol solvents and hot water, testing the rhizomes of *Alpinia calcarata* for 42 consecutive days revealed no toxic effect. The effects of *Alpinia calcarata* rhizomes in male rats, with doses of 1500 mg/BW administered orally, showed no acute poisonous effects as evidenced by impact on liver function, nephritic function, RBC count, and haemoglobin concentration. There is no visible toxicity in the organ's external morphology or wet weight. No evidence suggests that hot ethanol extracts and hot water extracts of *Alpinia calcarata* cause toxic or side effects at the dosages used.[17]

2. *Alpinia Galanga*

Alpinia galanga, or galangal, grows in the tropics and can treat bronchitis and ulcers and clean the mouth. It also has antifungal, antiviral, antidiabetic, and antibacterial properties. Galangal contains numerous flavonoids and essential oils. Galangal rhizomes treat toothaches, muscle swelling, rheumatism, and abdominal pain. Saponins, terpenoids, phenolics, flavonoids, alkaloid carbohydrates, glycosides, and phytosterols are all found in Alpinia.[35] Subash et al. (2012) tested the acute oral toxicity of galangal *Alpinia galanga* rhizome for 14 days in an ethanol solvent. The dosage is 5, 50, 300, and 2000 mg/BW. There was no death, no excitation of the central nervous system, depression, autonomic nervous system, abnormal motor activity during the test, no significant differences in haematological or biochemical parameters, and no abnormalities in tissues or organs. The estimated LD_{50} ranges from 2000 to 5000 mg/kg.[18]

3. *Alpinia malaccensis*

Alpinia mallaccensis, also known as white galangal, grows in tropical or subtropical areas such as Indonesia, Malaysia, Bangladesh, Vietnam, Myanmar, and Thailand. *Alpinia malaccensis* can be used as a medicine for abdominal pain, flatulence, vomiting, cooking spice, and tea. Several studies have suggested that this plant has antibacterial and antioxidant properties.[36] White galangal contains alkaloids, flavonoids, steroids, carbohydrates, tannins, saponins, and glycosides.[37] Somarthana et al. (2021)[19] found that a single dose of 300 or 2000

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mg/kg of raw n-hexane extracts of white galangal rhizomes did not cause death, nor were there significant differences in body weight, behaviour, or histopathological aspects in test animals. There was no difference in the weight of the rat organs tested compared to the control group. The test animals given *Alpinia malaccensis* 200 mg/BW had significant liver weight, there was no significant difference in serum biochemical parameters between rats given *Alpinia malaccensis* and controls, and the dose that could cause death was estimated to be greater than 2000 mg/BW, resulting in LD_{50} values greater than 2000 mg/BW. Although all mice were given white Galangal usually behaved for 24 hours, some animals displayed mild disruption during the first four hours and drank excessively during the first three hours after oral administration. In the oral administration of preparations and chemicals, changes in body weight are considered markers of side effects.[19] Significant weight loss is losing more than 10% of one's starting body weight.[38] No animals were used in the study by Somarathana et al. (2021)[19] to demonstrate that plant extracts had no adverse effects on rat weight regarding acute toxicity. Assessing liver and kidney function is an essential indicator in determining plant toxicity. Serum urea concentration, creatinine, and blood liver enzymes (ALT, AST, and ALP) are indices used to assess kidney function. The creatinine, ALT, and AST results after 14 days of oral administration did not differ significantly from the control group, and no renal abnormalities were observed in any test animals.[19]

4. *Amomum compactum Sol. Ex Maton*

Cardamom grows in the tropics and has long been used as an aromatic herbaceous. The aroma produced is proportional to the number of volatile sesquiterpenoids or monoterpenoids at room temperature. *Amomum compactum* essential oil contains a high concentration of cineole, a bioactive that kills bacteria. Many people use it as aromatherapy because of its distinct aroma. It benefits respiratory treatments such as influenza, asthma, bronchitis, and nausea and strengthens the nervous system.[39] Acute toxicity of cardamom seed extract was given as the initial dose in the Raet al.t al (2020)[20] study at a dose of 300 mg / BW. Once observed, the rats were able to survive and showed no signs of poisoning, resulting in an increase in the amount to a high single amount of 2000 mg/kg body weight 48 hours after no symptoms of death or poisoning were observed. The examination of liver biochemical parameters (SGOT and SGPT) from the blood serum of all mice, both control and treatment groups, followed. The SGOT and SGPT tests revealed that a high single dose of kapalaga seed extract of 2000 mg/kg BB was not hepatotoxic based on liver transaminase

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enzyme parameters. At this dose, cardamom does not affect SGOT or SGPT. According to toxicity studies, cardamom is non-toxic and does not cause death or toxicity in all rats. Furthermore, SGOT and SGPT levels remain within the normal range. Cardamom does not affect liver function because SGOT and SGPT levels remain normal. The enzyme SGOT (AST) is found in many other tissues, including the heart, skeletal and smooth muscles, kidneys, and brain. While SGPT (ALT) is more specific to hepar because it is found in high hepatocyte concentrations and low concentrations in other tissues, its LD_{50} is estimated to be greater than 2000 mg/BW.[20]

5. *Boesenbergia rotunda* (L.) mansf

Boesenbergia rotunda, or temu kunci, is found in the tropics, particularly in South and Southeast Asia and China. Because its rhizome resembles a finger, it is known as a finger root in English. It is a traditional medicinal plant that can be used as a food ingredient. It has anti-allergic, anticancer, anti-inflammatory, antioxidant, and antiulcer activity and is commonly used to relieve stomach discomfort.[21] The phytochemical components it contains are alkaloids, essential oils, flavonoids, and phenolics,[40] quercetin.[21] Rosdianto et al. (2020) used 95% ethanol as the solvent and the rhizome with doses of 250 mg / BW, 500 mg / BW, 1000 mg / BW, 2000 mg / BW, and 4000 mg / BW given singly. There were no deaths or signs of toxicity behaviour during the 21-day toxicity study. Clinical, biochemical measurements of serum reflect normal kidney and liver function. It can be concluded that the LD_{50} is more significant than 4000 mg/BW. Key Encounter Extract may inhibit acetic acid-induced KT and NF-kappaB p65 expression in the stomach and intestines of test animals.[21]

6. *Curcuma comosa*

Curcuma comosa rhizomes have traditionally been used to relieve abnormal uterine pain symptoms and reduce uterine inflammation. Chemicals found in *Curcuma comosa* include diarylheptanoids and acetophenones. Sukketseri et al. (2017)[33] administered *Curcuma comosa* extract via oral and ethanol solvents at 100 mg/kg/day; 500mg/kg/day for 30 days. According to research, *Curcuma comosa* Roxb does not cause severe organ toxicity or affect body weight, food, or water. At all doses tested, there was no effect on hematologic or blood chemistry parameters, no death in test animals, and no apparent toxicity features. Only serum alkaline phosphatase and potassium levels were significantly elevated in animals given 500 mg/kg/day of the extract. Furthermore, curcuma coma Roxb does not affect the total CYP content of the liver or the activity of CYP1A2, CYP2E1, or CYP3A. However, after administration at doses of 250 and 500 mg/kg/day, the movement of CYP1A1 and CYP2B1/2B2 increased significantly. Possible herbal

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medicine interactions and increased risk of any bioactivation or bioactivated compounds via CYP1A1 and CYP2B1/2B2.[33]

7. *Curcuma angustifolia*

Tikhur contains methyl eugenol, camphor, and cineol, which are commonly used as sedatives, wound healing, hypoglycemia, anti-inflammatory, and antimicrobial agents.[41] Rajashekharan et al. (2014)[22] used a portion of the rhizome in a water solvent with a single oral dose of 2200 mg/kg, 3300 mg/kg, and 4400 mg/kg up to a maximum amount of 4400 mg/kg. There were no toxic symptoms or death after 72 hours and no significant changes. Because the administered dose does not produce potency at the dosage level used for therapy, the LD^{50} value is estimated to be greater than 4400 mg/kg.[41]

8. *Curcuma caesia*

Curcuma caesia, also known as black turmeric, is a popular spice in India. Black turmeric is a spice and medicinal ingredient in the pharmaceutical industry. Cysts, cancer, asthma, epilepsy, menstrual disorders, high fever, burns, allergies, toothache, acne, and burns are all common uses for black turmeric.[42,] is also an anti-inflammatory and anti-asthmatic, containing phytochemicals such as alkaloids, phenolic compounds, flavonoids, and tannins. Chakraborty et al. (2014) used part of the rhizome with ethanol solvent and was given orally at a dose of 2000 mg / BW, then observed for the first 4 hours and then every 4 hours for the next 24 hours, showing no toxic symptoms or death.[23]

9. *Curcuma longa*

Curcuma longa, also known as turmeric, has long been used as a medicinal plant for its antibacterial, anticancer, antioxidant, inflammatory, and wound-healing properties. In the study of Winarsih et al., (2012)[24], an analysis of acute toxicity of ethyl acetate and n-hexane fractions was conducted using 96% ethanol solvent at a dose of 10 g / BW with oral administration, did not cause toxic effects, the LD_{50} value of the ethyl acetate fraction was 27.98 g / BW, while the LD_{50} value of the hexane fraction the LD_{50} value was 19.25 g / BW. Turmeric rhizome ethanol extract is classified as non-toxic in the ethyl acetate fraction, likely due to the presence of flavonoids, which can protect cells from damage. Meanwhile, ethyl acetate and hexane turmeric rhizomes can increase the number of parietal cells in the stomach and cause degeneration and necrosis in kidney tubule cells and cells.[24]

10. *Curcuma Xanthorriza*

Curcuma xanthorrhiza, also known as temulawak or Javanese turmeric, is in the tropics. In addition to temulawak or Javanese turmeric, *Curcuma zanthorriza* has several regional names, including koneng gede (Sunda), tommo (Bali),

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common (South Sulawesi), and karbanga (Ternate). This plant can grow in the lowlands up to 2500 meters above sea level and is cultivated on nearly all large islands, including Java, Sumatra, Kalimantan, Sulawesi, and Maluku. Temulawak has been widely used as a medicinal and nutritional plant, as well as to treat various diseases, including rheumatism, and skin rashes,[43] and for treating hepatitis, diabetes, rheumatism, anticancer, hypertension, and heart disease. In this study, a portion of the rhizome was extracted to extract the starch,[25] an essential ingredient in the formulation of herbal medicines. Terpenoids, curcuminoids, and phenolics are active compounds in Temulawak.[43] Acute oral toxicity studies revealed that the solvent used in Anu et al. (2020)[25] study, ethanol, was non-toxic because there were no significant changes in body weight, food and water consumption, subcutaneous swelling, abdominal distension, dull eyes and opacity, ptosis, wet or dirty perineum, and respiratory abnormalities. Animals in all groups were given doses ranging from 50 to 6400 mg/BW. No mortality was observed even at the highest dose level, demonstrating that coarse starch powder derived from *Curcuma zanthorriza* had no significant toxic effect up to a dose of 6400 mg/BW. Raw starch powder extracted from temulawak is a powerful, essential and non-toxic ingredient in various food products.[25]

11. *Etlingera elatior (Jack)*

Etlingera elatior, also known as torch ginger, is a plant native to Southeast Asia with a high concentration of phenolic compounds and flavonoids and antioxidant, antimicrobial, and antifungal properties. The acute toxicity of ginger torch flower extract in an ethanol solvent was investigated. On day 14, the dose of kecombrang flower extract given in the study of Sungthong et al. (2018)[26], i.e., at doses of 1000, 1500, and 2000 mg/BW, no death or abnormal clinical signs of internal organs, including liver, kidneys, heart, and lungs did not differ significantly from the control group, including defecation or urination, estimated LD_{50} >2000 mg/BW.[26]

12. *Globba pendula.*

Pedas kancil is found throughout the tropics and subtropics, from India to southern China, the Philippines, and New Guinea, with distribution centres in Southeast Asia monsoon, specifically Thailand and Myanmar. *Globba pendula* Roxb rhizome is widely used to treat rheumatism, osteoporosis, and flatulence. Nitric Oxide (NO) is a signal molecule that plays a role in the pathogenesis of inflammation, producing anti-inflammatory effects under normal physiological conditions. The compounds in *Globba pendula* are diterpene labdane, benzofuran, phenolics, steroids, and essential oils with a moderate NO inhibitory effect. The acute toxicity test Le min et al. (2021)[27] was

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performed with methanol solvent at six g/BW, eight g/BW, and ten g/BW. After 72 hours of observation, the test animal was still alive and could consume food and drink normally. Joint histopathology revealed muscular oedema, inflammatory leukocytes, macrophages, and synovial hyperplasia. The administration of a dose of 500 mg/BW Pedas kancil extract reduces infiltration of inflammatory cells and oedema in the joints while not affecting the normal development of rats. It has good sound and reflection, and even *Globba pendula* extract has an LD_{50} value greater than 500 mg/BW; thus, Pedas kancil rhizome extract is considered non-toxic when taken orally.[27]

13. *Hedychium spicatum*

Hedychium spicatum, also known as spiny ginger lilies, van haldi, or kapoorkachari, is a plant native to Southeast Asian countries in temperate and subtropical regions with elevations ranging from 1000 to 2800 meters above sea level. They are used in traditional and modern medicine, cosmetics, and perfumery. Polyphenols, flavonoids, tannins, quinones, monoterpenoids, and sesquiterpenoids are among the secondary metabolites found in this plant. The ginger lily extract treats inflammations, pain, asthma, bad breath, fever, vomiting, diarrhoea, and bronchitis. Toxicity studies have not been widely conducted; only published reports state that hexane and benzene extract has a weak central nervous system depressant effect, as evidenced by a decrease in locomotor activity compared to the control group. Rawat et al. (2018)[44] discovered that 200 mg/kg of ethanol solvents did not cause death in test animals. An LD_{50} of more than 200 mg/kg from both extracts after 24 hours without cessation did not produce acute toxicity,[45] no harmful effects were observed on this plant's rhizome extract even after ten times the dose indicated the safety status of its rhizomes, test animals tolerated very high doses without producing harmful effects saying that ginger lily rhizome extract had a high level of safety.[44] Gandasuli is also used as a flavouring, fragrance, and cosmetic ingredient.[46]

14. *Kaemferia galanga*

Kaemferia galanga, known as kencur, grows in lowland or mountainous areas with loose soil. Urination can help reduce inflammation because urine contains anti-inflammatory compounds such as flavonoid compounds, kaempferol, the most abundant chemical in urine, ethyl p-methoxycinnamate, eucalyptol, carbon pentadekan, and metal synagogue.[47] Urination is a standard treatment for bacterial infections, ascariasis, cancer, rheumatism, and abdominal pain in women. Amuamuta et al. (2017)[28] kaempferol galanga lin rhizome extract with ethanol solvent given 5000 mg/BW caemferia rhizome extract, with no death during the 14-day observation period. Subacute

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toxicity testing was performed on doses of 5000 mg/BW (highest dose rate), 3000 mg/BW (moderate dose rate), and 1000 mg/BW (lowest dose rate). There were no significant changes in the test animal's general behaviour or other physiological activities such as breathing patterns, cardiovascular signs, motor activity, or eating and drinking activities, particularly at the lowest dose levels and in the control groups. However, at dose levels of 5000 mg/BW and 3000 mg/BW, there were transient signs of toxicity, including weight, histopathology of vital organs, respiratory patterns, motor activity, regular drinking, and death after 14 days.[28]

15. *Kaempferia rotunda* L.

Kaempferia rotunda L., or "Kunci pepet" or "white turmeric," is a fragrant medicinal plant with an aromatic yellow-white tuber rhizome. The plant's rhizomes and root tubers have a bitter, spicy, and camphor flavour. They have been widely used as vegetable and food flavouring seasoning seasonings in India and Southeast Asia, including Malaysia, Indonesia, and Thailand.[29] Pepet locks are frequently used to treat abdominal pain, fever, wound healing, and inflammation.[48] Essential oils, flavonoids, alkaloids, and saponins are among the compounds found in Kaemferia rotunda.[49] Toxicology test using ethanol solvents, Here et al. (2014)[29] re-dosed for 28 days at doses of 250 mg/kg, 500 mg/kg, and 1000 mg/kg did not cause death, changes in body weight and weight gain, or significant haematological, biochemical, and histopathological changes. As a result, the LD_{50} is estimated to be greater than 1000 mg / BW / day because 1000 mg / BW is still well tolerated and shows no toxicity.[29]

16. *Zingiber officinale*

Zingiber officinale, also known as red ginger, is an Indian plant that has spread throughout the country. The compounds found in *Zingiber officinale* include diarylheptanoid, phenylbutenoid, flavonoid, diterpenoid, sesquiterpenoid, and bioactive compounds gingerol and shagaol, which act as antibacterials; ginger also has antioxidant, anti-inflammatory, analgesic, diuretic, and antifungal properties.[50] Plengsuriyakarn et al. (2012) performed acute and subacute toxicity testing with ethanol solvents. Then it administered red ginger rhizomes at doses of 1000 mg/BW, 3000 mg/BW, and 5000 mg/BW, after being observed to cause no death and showing no significant toxicity at a maximum dose of 5000 mg/BW. However, stomach irritation occurred, but the test animal recovered from symptoms within 1 hour of dosing. Food and water intake were comparable, and there was no abnormal histopathology of vital organs.[30]

17. *Zingiber zerumbet* (L.)

Zingiber zerumbet, or pine seed or ginger shampoo, is a perennial tuber root

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herbaceous plant cultivated as a spice and a medicinal plant to treat headaches, swelling, colds, boils, wounds, loss of appetite, nausea, and menstrual discomfort. It contains chemical compounds such as alkaloids, saponins, flavonoids, tannins, terpenoids, phenols, polyphenols, and sugars.[31]

Acute toxicity studies revealed that shampoo ginger extract administered orally at doses of up to 15 g kg^{-1} produced no signs of toxicity or death in rats, with LD_{50} exceeding 15 g kg^{-1} via the oral route, indicating that orally administered zerumbet zingiber zerumbet extract is practically non-toxic.

Subacute toxicity research Chang et al. (2012)[31] used a 95% ethanol solvent to administer elephant lempuyang extract at doses of 1000 and 2000. Furthermore, 3000 mg kg^{-1} per day for 28 days did not result in death or clinical signs of toxicity. In the group of animals given shampoo ginger extract at any dosage, there were no significant changes in animal behaviour, food and water consumption, or weight gain. There were no significant changes in haematological and biochemical parameters, no changes in plasma urea and creatinine levels, and no effect on AST and ALT levels, which were considered sensitive indicators of hepatocellular damage and could provide a quantitative assessment of liver damage to some extent. As a result, shampoo ginger extract does not harm the liver or kidneys, plasma cholesterol levels remain unchanged, and there are no differences in the weight and structure of other organs. Overall, subchronic studies show that using ginger shampoo does not result in toxic estimated LD_{50} values greater than 3000 mg kg^{-1}.[31]

18. *Zingiber cassumunar*

The rhizome of *Zingiber cassumunar*, also known by the Thai name "plai," is widely cultivated in Thailand and tropical Asia. It has anti-inflammatory[53], antivirus, antiseptic, analgesic, and antioxidant properties.[52] The plant's rhizomes have been used in traditional medicine to treat inflammation, muscle and joint problems, menstrual disorders, ulcers, skin diseases, and wound healing. Its chemical compounds include phenylbutanoids, terpenoids, sitosterols, and curcuminoids. After 14 days of observation, there were no signs of toxicity or death at a 5000 mg/BW dose. As a result, the LD_{50} value exceeds 5000 mg/BW.

Chronic toxicity studies were carried out by Koontongkaew et al. (2014)[32] at doses of 0.3, 3, 30, 11, 25, and 112.5 mg/BW/day. It was administered orally for 270 days and did not cause clinical toxicity symptoms or death in rats. The body weight gain of the rats was no different when compared to the control group; additionally, there was no significant difference in body weight between the satellite and control groups; however, the number of red blood cells was significantly lower in female rats

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given *Zingiber cassumunar* rhizome extract at doses of 30 and 1.125 mg/BW/day for 270 and 298 days. After 298 days of treatment with 30 mg/BW/day, beta rats' hematocrit levels were significantly lower. However, the average haemoglobin concentration in rat blood cells was significantly higher than in the control group. Except for a decrease in haemoglobin levels in the group given Zingiber cassumunar extract at a dose of 30 mg/BW/day for 270 days, there were no haematological changes in the male rats. The number of neutrophils in female mice given a dose of 3 mg/kg/bb/day for 270 days was statistically higher than in the control group. Lymphocytes were statistically reduced in all female mice, and there was no discernible change in white blood cell count in male mice except for an increase in neutrophils after 270 days at a dose of 0.3 mg/BW. Overall, rats given zingiber cassumunar extract up to 1,125 mg/BW for 270 days showed no chronic toxicity regarding body weight, organ weight, haematology, or histology.[32]

CONCLUSIONS

According to several studies, the 18 plant species of the Zingiberaceae family that have been tested for safety acutely, subacutely, and chronically belong to the non-toxic category.

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