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Toxicity Assessment of *Allium sativa* and *Zingiber officinale* using *in vivo* and *in silico* Approaches in Mice

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ABSTRACT

The widespread use of *Allium sativa* (garlic) and *Zingiber officinale* (ginger) in traditional medicine and nutraceuticals has prompted increased interest in their safety profiles, particularly concerning dosage and long-term effects. This study employs both *in vivo* and *in silico* approaches to evaluate the potential toxicity of these plants. Phytochemical analysis identified key bioactive compounds such as allicin, ajoene, gingerol, and shogaol, known for diverse pharmacological effects, but also possessing toxicity risks at elevated doses. *In vivo* toxicity studies in mice, including acute and sub-chronic exposures, revealed dose-dependent alterations in liver and kidney function enzymes, hematological parameters, and histopathological changes in major organs. Simultaneously, *in silico* ADMET profiling and molecular docking against toxicity-relevant targets, such as cytochrome P450 enzymes and oxidative stress mediators, predicted hepatotoxicity and nephrotoxicity potential in some phytochemicals. Comparative analysis confirmed correlations between experimental and computational findings, supporting the integration of both models for comprehensive toxicological evaluation. This study underscores the dual nature of these botanicals, advocating for standardized dosing and further research into chronic toxicity, reproductive effects, and systems toxicology frameworks.

KEYWORDS

Allium sativa, *Zingiber officinale*, toxicity, *in vivo* studies, *in silico*, phytochemicals

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INTRODUCTION

Since ancient times, plants have played a key role in traditional medicine[1]. Today, herbal remedies are widely used, especially in developing countries where they are accessible and affordable. Many believe natural products are safer than synthetic drugs; however, this perception is misleading. Studies have shown that medicinal plants can cause adverse effects, and using them without toxicity evaluation poses health risks[2]. Toxicity testing, including acute and subacute studies, is essential to assess the safety of such compounds. Acute tests evaluate the impact of a single dose, while subacute tests examine repeated dosing to detect potential long-term organ or tissue damage[3]. These assessments are vital for identifying hazards and informing risk management. *Allium sativa* (garlic), belonging to the Liliaceae family, is a widely used herb valued for both its culinary and medicinal properties. It is rich in essential minerals, vitamins, and unique sulfur-containing compounds such as allicin, alliin, and diallyl sulfides, which are responsible for its characteristic odor and biological activities[4]. Garlic has demonstrated strong antioxidant, antimicrobial, and anti-inflammatory effects. Studies have shown that it can enhance immunity and reduce the risk of infections, cardiovascular diseases, cancer, and neurodegenerative disorders[5-7]. *Zingiber officinale* (ginger), a member of the Zingiberaceae family, is a perennial herb used both as a spice and a medicinal plant[8,9]. It grows up to 3-4 feet, with medicinal uses for its leaves, flowers, and rhizomes. Ginger contains over 400 compounds, including carbohydrates, lipids, terpenes (e.g., zingiberene, β-bisabolene)[10], and phenolic compounds (gingerol, paradols, and shogaol). The primary bioactive compounds, gingerols (23-25%)[11] and shogaols (18-25%)[12], are responsible for its pungency and characteristic flavor[13]. Ginger is widely used for gastrointestinal relief, including treating nausea, upset stomach, and indigestion, and is also effective in managing conditions like arthritis, muscle soreness, and respiratory infections. Its anti-inflammatory properties and use in reducing pain and high blood pressure have been well-documented[14-16]. Additionally, ginger is used in cosmetics and beverages for its flavor and fragrance. *Allium sativa* and *Zingiber officinale* are commonly utilized in ethnomedicine and nutraceutical formulations due to their therapeutic properties[17,18]. Despite their widespread use, uncertainties regarding appropriate dosage, long-term safety, and possible toxic effects highlight the need for thorough investigation. Fig. 1 and 2 depicted the structural formula of some compounds of *A. sativum* and *Z. officinale*. This review focuses on evaluating the toxicity profiles of *A. sativum* and *Z. officinale* through both *in vivo* and *in silico* methods.

Bioactivities of *A. sativa* and *Z. officinale*

Anti-inflammatory effects: Garlic extracts exhibit anti-inflammatory properties, reducing liver inflammation and injury caused by Eimeria papillata infections by inhibiting cytoskeleton assembly-disassembly processes[21,22]. A sulfur compound in garlic inhibits neuroinflammation and amyloidogenesis by blocking NF-κB activity, potentially aiding in treating neurodegenerative diseases like Alzheimer's disease[22,23], found that sulfur compounds in garlic reduce inflammation by suppressing inducible NO synthase (iNOS) and Cyclooxygenase-2 (COX-2) expression. Ginger is a popular herbal treatment for chronic inflammatory diseases. Aqueous *Zingiber officinale* extract showed significant anti-inflammatory activity in rats, making it a promising agent for further investigation[24-26]. Ginger's anti-inflammatory effects involve suppressing prostaglandin synthesis by inhibiting cyclooxygenase-1 and cyclooxygenase-2. Additionally, gingerol and its derivatives effectively inhibit PGE2 production, contributing to ginger's anti-inflammatory properties[27-29].

Cardiovascular benefits: Garlic compounds can help prevent atherosclerosis by suppressing LDL oxidation. Studies have shown that garlic powder supplementation effectively reduces total cholesterol levels, particularly at lower doses, and LDL-cholesterol levels[30]. Garlic has also been found to be an effective and safe approach for treating hypertension[31]. Similarly, ginger has demonstrated various cardiovascular benefits, including hypotensive, hypoglycemic, hypocholesterolemic, and hypolipidemic effects[32]. Aqueous ginger extract has been shown to inhibit arginase activity and prevent hypercholesterolemia in rats fed a high-cholesterol diet[33]. Additionally, ginger has been found to lower serum lipids, reducing total cholesterol, LDL, VLDL, triglycerides, and phospholipids in animals, with a generally dose-dependent hypotensive effect[34].

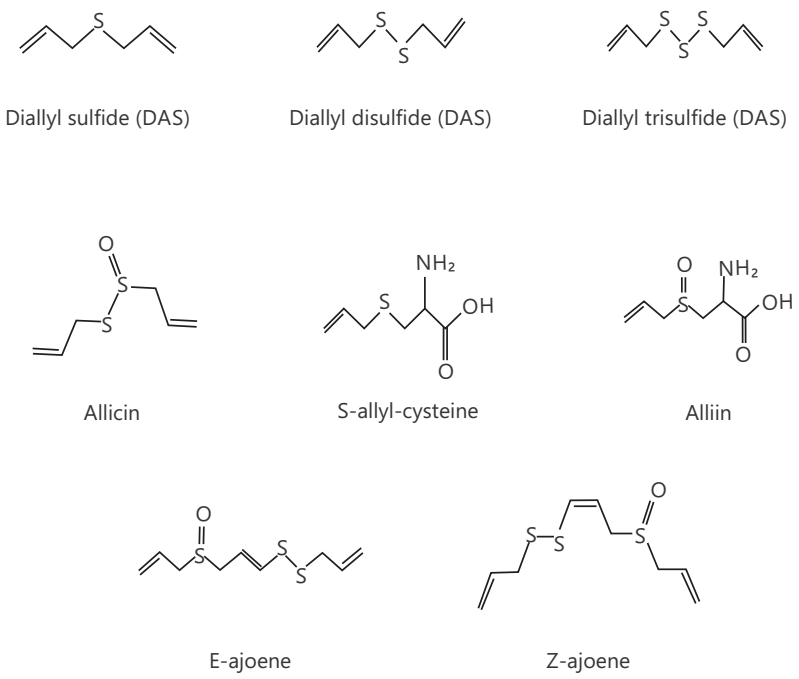

Fig. 1: Chemical structure of some compounds of *A. sativa*[19]

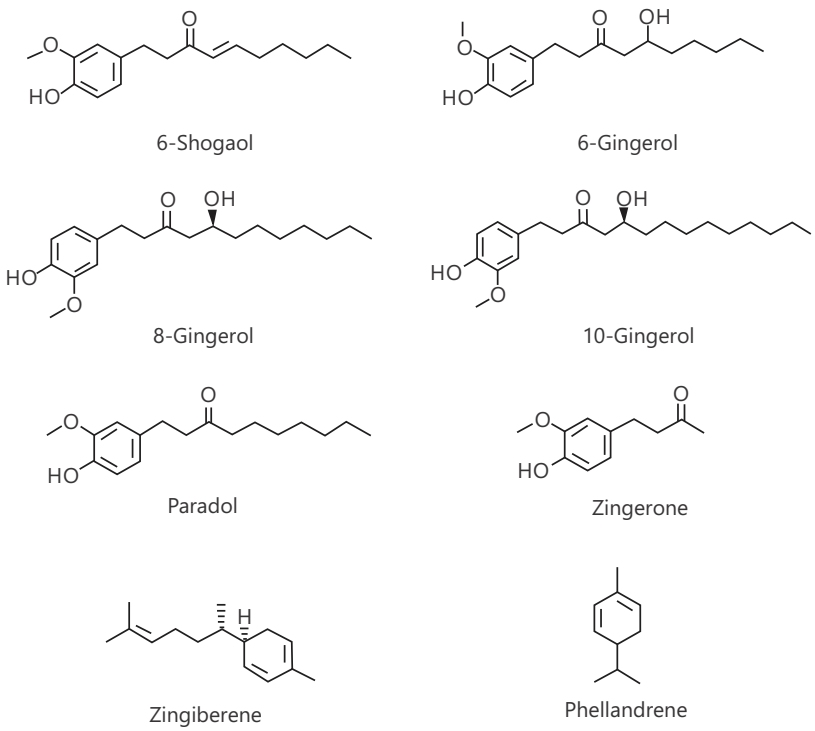

Fig. 2: Chemical structure of some compounds of *Z. Officinale*[20]

Anti-cancer: Epidemiological studies suggest that regular consumption of garlic may protect against certain cancers, particularly pancreatic cancer[35]. Meanwhile, ginger has shown promise in treating colorectal cancer by interfering with cell signaling pathways involved in cancer development[36]. Studies have demonstrated that ginger extract can reduce proliferation and increase apoptosis in colorectal epithelium. Ginger extract has been observed to inhibit cellular growth and enhance programmed cell death in colonic epithelial cells. *In vivo* studies have also demonstrated that whole ginger extract impedes the progression of human prostate cancer in mouse models[37]. The anticancer properties of ginger are attributed to compounds like [6]-gingerol, paradol, shogaols, and zingerone (Fig. 2), with [6]-gingerol being a key compound that inhibits skin carcinogenesis, colorectal cancer cell growth, and tumor growth[36].

[6]-gingerol, in particular, has been found to suppress skin tumor formation, colorectal cancer cell growth, and overall tumor expansion[38]. Its antitumor action is associated with targeting Leukotriene A4 Hydrolase (LTA4H), along with DNA binding and initiation of apoptosis via autophagy and caspase-3-dependent mechanisms

Anti-viral: Members of the *Allium* genus, notably garlic, possess broad-spectrum antimicrobial actions, including antiviral capabilities. Garlic extracts have been shown to inhibit the replication of viruses such as Influenza A (H1N1) and Herpes Simplex in cell culture studies. Allicin, a major sulfur-containing compound in garlic, is believed to be the principal antiviral agent[39]. Ginger has also demonstrated antiviral activity against various viruses, including Human Respiratory Syncytial Virus (HRSV)[40], caprine alpha Herpes Virus-1 (HSV-1)[41], and Feline Calicivirus, a surrogate for Human Norovirus. Fresh ginger has been found to dose-dependently inhibit HRSV-induced plaque formation, whereas dried ginger did not show similar effects[42]. The antiviral activity of ginger essential oil may be attributed to its ability to disrupt the viral envelope.

Anti-bacterial: Garlic and ginger have demonstrated significant antibacterial activity against a wide range of bacteria. *Allium sativa* has demonstrated inhibitory effects on a wide array of bacterial species, including *Aeromonas*, *Bacillus*, *Clostridium*, *Escherichia*, *Helicobacter*, *Klebsiella*, and *Mycobacterium*[43]. Its antibacterial activity has also been effective against resistant bacterial strains[44]. Additionally, garlic's antimicrobial properties have been investigated for their potential to combat *H. pylori* infections. Ginger has also exhibited antibacterial activity against several bacteria, including *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Escherichia coli*. Essential oils extracted from ginger leaves and rhizomes have displayed moderate antibacterial effects on both Gram-positive and Gram-negative bacteria[45]. Furthermore, ginger's active constituents, such as gingerols, have been effective *in vitro* against *Helicobacter pylori*[46]. Ginger extracts have also demonstrated antibacterial activity against anaerobic Gram-negative bacteria that cause periodontal diseases[47].

The qualitative phytochemical screening revealed the presence of alkaloids, flavonoids, tannins, and steroids in *Zingiber officinale*, while *Allium sativa* showed positive results for saponins, glycosides, flavonoids, and alkaloids, as summarized in Table 1.

Toxicity and adverse effects: Garlic and ginger have shown promise in preventing and treating various diseases, including cancer, cardiovascular disease, and bacterial infections. To ensure their safe and effective use, it's crucial to evaluate their toxicity and potential adverse effects using both *in vivo* and *in silico* approaches.

***In vivo* approach:** Acute toxicity studies in rodents, such as mice, play a crucial role in assessing the safety of substances, including herbal drugs. A key parameter in these studies is the LD_{50} dose, which is the dose lethal to 50% of the test animals[48]. The LD_{50} value serves as abenchmark for categorizing substances based on their toxicity levels: Extremely toxic (<5 mg/kg), highly toxic (5-50 mg/kg), moderately toxic (50-500 mg/kg), practically non-toxic (500-5,000 mg/kg), or relatively harmless (>15,000 mg/kg)[49]. Notably, many studies conclude at a dose of 5,000 mg/kg; however, determining the actual median lethal dose (LD_{50}) can provide valuable insights into the safety profile of substances, particularly herbal drugs[50]. This review highlights the importance of evaluating the LD_{50} of substances like *Zingiber officinale* (ginger) and *Allium sativa* (garlic), especially when used in combination, to inform potential clinical applications and consider herb-herb interactions in poly-herbal medicines. By understanding the LD_{50} values of these substances, researchers can better assess their safety and efficacy for therapeutic use. A recent study by Grzanna *et al.*[51], investigated the acute toxicity of ginger, revealing dose-dependent adverse effects. At higher doses (3200 and 4200 mg/kg), aqueous garlic extract induced behavioral signs such as loss of appetite, depression, partial paralysis, and death,

Table 1: Phytochemicals of *Allium sativa* and *Zingiber officinale* ethanol leaf extract[31]

Phytochemicals	*Zingiber officinale*	*Allium sativa*
Alkaloids	+	+
Saponins	-	+
Tanins	+	-
Flavonoids	+	+
Steroids and terpenoids	+	-
Glycosides	-	+

+: Present, -: Absent and adapted from Ihekwereme *et al.*[31]

with an LD_{50} of 3034 mg/kg and a maximum tolerated dose of 2200 mg/kg[52]. Another study confirmed the safety of garlic up to 2500 mg/kg, but observed toxicity signs at 5000 mg/kg, including weakness, erythema, tachycardia, and disorientation[53]. Excessive garlic consumption can cause gastrointestinal issues, such as burning sensations, diarrhea, flatulence, and changes in intestinal flora[54]. Other potential adverse effects include garlic odor, allergic reactions, contact dermatitis, and bronchial asthma. Garlic may also increase the risk of bleeding after surgery. In contrast, ginger has shown a relatively safe profile. Toxicity assessments in volunteers revealed no signs of toxicity, with minor gastrointestinal upsets being the primary adverse effects[55]. Subacute toxicity studies in albino rats found no mortalities or abnormalities, except for a calming effect[1]. Ginger administration during pregnancy did not cause maternal or developmental toxicity at doses up to 1000 mg/kg body weight. While ginger is generally well-tolerated, potential adverse effects include mild gastrointestinal issues, such as heartburn, diarrhea, and mouth irritation[56]. However, ginger has also demonstrated therapeutic benefits, including reducing menstrual blood loss. Overall, these studies highlight the importance of understanding the potential risks and benefits associated with garlic and ginger consumption. Another study by Ihekwereme *et al.*[31], on the acute toxicity of *Zingiber officinale* (ginger) and *Allium sativa* (garlic) revealed that ginger had a higher LD_{50} (8,660 mg/kg) than garlic (4,472 mg/kg), indicating greater safety. When combined, the LD_{50} of both herbs became 5,477 mg/kg, suggesting antagonistic interactions. The differing toxicity profiles may be attributed to the presence of steroids in ginger and glycosides in garlic. Despite this, the combination showed a high safety range, with potential benefits for therapeutic applications.

***In silico* approach:** The *in silico* ADMET analysis of bioactive compounds from *Zingiber officinale* (ginger) and *Allium sativa* (garlic) reveals favorable pharmacokinetic properties indicative of their therapeutic potential. Most compounds exhibit molecular weights within the optimal drug-like range (130-725 Da) as seen in Table 2 and 3, which supports adequate permeability and absorption[57-59]. Notably, gingerol derivatives (Z2-Z4) and paradol (Z5) show moderate to high molecular weights (278-350 Da) yet remain within the acceptable range, suggesting a balance between molecular complexity and bioavailability. Dipole moments for both ginger and garlic constituents lie between 0.125-5.973 Debye, a range that indicates sufficient polarity for solubility without compromising membrane permeability[28]. Hydrogen bonding capacity, measured through the number of hydrogen bond donors (HBD) and acceptors (HBA), also aligns with Lipinski's rule of five[28], with most compounds possessing $\leq$2 HBD and $\leq$5 HBA. This implies favorable passive diffusion across biological membranes. Lipophilicity, represented by QPlog o/w values, ranges between -2.289 and 6.644, where compounds such as zingiberene (Z7) and phellandrene (Z8) display high lipophilicity, facilitating membrane penetration, while more polar compounds like alliin (G1) may require transport mechanisms or formulation enhancements due to poor lipid solubility. The predicted number of metabolic reactions (*metab) for both ginger and garlic constituents suggests manageable metabolic transformation, with values ranging between 0 and 6. Gingerols and paradol typically undergo 5-6 predicted reactions, consistent with their phenolic structures that are known to be subject to conjugation and oxidation[60,61]. On the other hand, garlic sulfur compounds like diallyl trisulfide (G7) and allyl methyl sulfide (G8) exhibit lower predicted metabolism, possibly contributing to prolonged bioactivity. Human oral absorption (HOA) values further validate the bioavailability potential of these phytochemicals. Most compounds display high predicted absorption (>80%), with exceptions like alliin

Table 2: ADMET screening of some ginger compounds

Compound	Molecular weight	Dipole	Donor HB	Acceptor HB	QPlog o/w	*metab	Humano Oral absorption (%)
Z1_6Shogaol	276.375	4.336	1	3.5	4.014	5	100
Z2_6Gingerol	294.39	4.053	1	4.2	3.704	6	100
Z3_8Gingerol	322.444	5.247	1	4.2	4.594	6	100
Z4_10Gingerol	350.497	5.973	1	4.2	5.36	6	100
Z5_Paradol	278.391	4.307	1	3.5	4.239	5	100
Z6_Zingerone	194.23	4.527	1	3.5	1.892	4	95.103
Z7_Zingiberene	204.355	0.125	0	0	6.444	0	100
Z8_Phellandrene	136.236	0.325	0	0	6.644	0	100

Adapted from Veber *et al.*[64]

Table 3: ADMET screening of some garlic compounds

Compound	Molecular weight	Dipole	Donor HB	Acceptor HB	QPlog o/w	*metab	Humano Oral absorption (%)
G1_Alliin	177.213	4.693	2	5.5	-2.289	6	6.322
G2_Allicin	162.264	2.361	0	1.5	1.505	4	76.53
G3_E_Ajoene	234.389	5.895	0	2	2.566	4	82.418
G4_2Vinyl4H13dithiin	144.25	2.802	0	0	2.373	2	100
G5_Diallyl sulfide	114.205	1.15	0	0	2.742	2	100
G6_Diallyl disulfide	146.27	2.115	0	0	3.548	2	100
G7_Diallyl trisulfide	178.325	3.996	0	0	4.354	2	100
G8_Allyl methyl sulfide	88.167	1.261	0	0	2.76	2	100

Adapted from Veber *et al.*[64]

(6.322%) and allicin (76.53%) indicating that despite their biological activity, they may suffer from limited oral bioavailability-a limitation corroborated by *in vivo* studies[62,63]. Conversely, high HOA values in gingerols and sulfur-rich garlic compounds suggest they are well-suited for oral delivery, consistent with traditional use and modern pharmacological evidence. Overall, these *in silico* predictions affirm the drug-likeness of key ginger and garlic constituents, justifying their further development as therapeutic agents. Their favorable physicochemical properties and oral bioavailability align with previously reported pharmacokinetic evaluations of plant-derived compounds[64,65], reinforcing the value of computational tools in early-stage drug screening. Table 2 and 3 present the predicted pharmacokinetic properties of selected *Zingiber officinale* and *Allium sativum* compounds, respectively, including molecular weight, dipole moment, hydrogen bonding characteristics, lipophilicity (QPlog o/w), metabolic sites, and estimated human oral absorption, all of which indicate favorable oral bioavailability for most compounds.

Comparative evaluation (*in vivo* vs *in silico*): Both *in vivo* and *in silico* approaches are integral to advancing the therapeutic potential of ginger (*Zingiber officinale*) and garlic (*Allium sativa*). By combining empirical evidence from animal models with computational predictions, researchers gain a well-rounded understanding of how these plant-derived compounds interact with biological systems, providing valuable insights into their therapeutic applications. *In vivo* studies are crucial for confirming the efficacy of ginger and garlic in treating chronic conditions such as cancer and inflammation. For example, ginger's active compounds, like gingerol and shogaol, have shown promising results in reducing inflammation and slowing tumor growth in animal models. These effects are largely attributed to the modulation of pathways such as NF-κB and COX-2, which play a significant role in inflammatory responses[66-68]. Likewise, garlic's bioactive compound, allicin, has demonstrated potent anticancer and anti-inflammatory properties by influencing signaling pathways like MAPK and NF-κB[69,70]. These findings highlight the substantial therapeutic potential of both plants in managing chronic diseases. On the computational side, *in silico* techniques provide a deeper, molecular-level understanding of how these compounds interact with cellular proteins. Molecular docking studies have been particularly useful in identifying the key protein targets of gingerol, shogaol, and allicin, such as COX-2, BCL-2, and VEGF. These targets are pivotal in regulating inflammation, cell survival, and tumor progression[71,72]. Moreover, QSAR modeling and ADMET predictions help estimate the pharmacokinetic properties and potential toxicity of these compounds,

which can streamline the process of drug development[73]. By evaluating factors like absorption, distribution, metabolism, and excretion, these tools minimize the risk of adverse effects, making the transition from bench to clinic more efficient. Furthermore, bioinformatics tools used for pathway enrichment analysis have shed light on the broader biological impact of ginger and garlic. Through these analyses, researchers can pinpoint specific molecular pathways that are modulated by these compounds, such as those involved in apoptosis and oxidative stress regulation. For instance, gingerol has been found to interact with apoptosis-regulating proteins like BCL-2 and p53, which are critical in cancer therapy. Similarly, garlic's compounds influence various biological processes, including cell cycle regulation and oxidative stress, which could explain its anticancer and cardioprotective effects[14]. The integration of *in vivo* and silico approaches creates a comprehensive framework for drug discovery, allowing researchers to identify promising therapeutic candidates while ensuring safety and efficacy. Together, these methods enable a more precise and efficient development of plant-based therapeutics, offering hope for new treatments for a range of chronic diseases, including cancer, inflammation, and metabolic disorders[70].

Hepatotoxicity of *Allium sativa* and *Zingiber officinale:* Recent studies have explored the hepatotoxic potential and dose-dependent effects of garlic and ginger[71,72]. While both are widely recognized for their therapeutic benefits, excessive or prolonged consumption may pose risks to liver health. High doses of garlic have been associated with hepatocellular alterations and elevated liver enzymes in animal models, suggesting potential toxicity at supra-therapeutic levels[59,53,73]. Similarly, ginger, though generally considered safe, has shown hepatotoxic effects at high concentrations, including hepatic inflammation and oxidative stress in rodent studies[3,4]. These findings emphasize the importance of dose-response evaluations to establish safe therapeutic windows and avoid adverse hepatic outcomes.

CONCLUSION

The comprehensive assessment of *Zingiber officinale* (ginger) and *Allium sativum* (garlic) through both *in vivo* and *in silico* (ADMET) models underscores their broad therapeutic potential alongside important safety considerations. While both botanicals exhibit low toxicity at traditionally consumed doses and possess numerous pharmacological benefits, excessive or prolonged use may pose risks, such as hepatotoxicity or gastrointestinal irritation. *In silico* ADMET predictions support these findings by revealing favorable absorption and metabolic profiles, but also highlight the need for caution with certain bioactive compounds due to their potential for bioaccumulation or interaction with metabolic enzymes. Overall, integrating experimental and computational approaches provides a robust framework for evaluating the safety of medicinal plants, ensuring their effective and responsible use in both traditional medicine and modern therapeutic applications.

SIGNIFICANCE STATEMENT

Medicinal plants have been widely used for centuries in traditional medicine systems across the globe. The study assessed the acute and sub-chronic toxicity of *Allium sativum* and *Zingiber officinale* extracts in mice through *in vivo* experimentation. The comprehensive evaluation of *Allium sativa* (garlic) and *Zingiber officinale* (ginger) through both *in vivo* and *in silico* toxicity assessments in mice provides critical insights into their safety profiles, bridging traditional herbal medicine with modern pharmacological standards and underscoring the importance of integrative methodologies in validating the therapeutic and toxicological potential of natural compounds.

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