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Review Article

Protective effects of zerumbone on chemical compound and drugs-induced hepatotoxicity in preclinical studies: a systematic review

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Abstract

Objective: Hepatotoxicity induced by pharmaceuticals, environmental toxins, and industrial chemicals represents a critical public health concern, necessitating effective protective strategies. This systematic review evaluates the hepatoprotective efficacy of zerumbone, a bioactive compound derived from *Zingiber zerumbet* L., against drug-induced liver injury through comprehensive analysis of experimental and preclinical studies.

Materials and Methods: Following PRISMA guidelines, the literature search was done across PubMed, Scopus, Web of Science, and Google Scholar focusing on studies examining zerumbone effects on biochemical markers, oxidative stress, and histopathological outcomes. The search strategy employed MeSH terms up to January 2025.

Results: Key findings demonstrate zerumbone multifaceted mechanisms: 1- Antioxidant activity through reactive oxygen species (ROS) reduction vs. controls, superoxide dismutase (SOD)/catalase (CAT) activities enhancement, and lipid peroxidation (MDA) inhibition. 2- Anti-apoptotic effects via caspase-3 suppression and Bcl-2 upregulation, as well as preserving hepatocyte viability. 3- Anti-inflammatory action by nuclear factor kappa B (NF-κB) inhibition, reducing tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2) and 5-Lipoxygenase (5-LOX) suppression. 4- Functional recovery evidenced by normalized liver enzymes aspartate transaminase (AST) and alanine aminotransferase (ALT) as well as reduction of bilirubin levels. Notably, zerumbone showed dose-dependent efficacy across diverse hepatotoxicants (paracetamol, carbon tetrachloride (CCl_4), and cisplatin).

Conclusion: These findings underscore zerumbone translational potential in managing drug-induced hepatotoxicity while highlighting critical research gaps that need to be addressed for clinical implementation.

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Introduction

Unintentional fatal poisonings resulting from exposure to toxic agents such as pesticides, heavy metals, environmental pollutants, and microbial and fungal toxins, as well as certain pharmaceuticals and cosmetic products pose a serious threat to public health. It is estimated that approximately 385 million cases of unintentional acute pesticide poisoning occur annually worldwide, including about 11,000 fatalities (Boedeker et al. 2020). Among these, hepatotoxicity has emerged as one of the most dangerous consequences, drawing significant attention from researchers and medical professionals (Yousaf et al. 2019). The liver, due to its central role in the metabolism and detoxification of chemical compounds, is particularly vulnerable to damage caused by self-medication, drug overdosing, and exposure to industrial and natural chemicals (Li et al. 2023). Notably, even some medications at therapeutic doses can induce liver injury (Di Giacomo et al. 2023).

Comprehensive research in hepatotoxicology has documented more than 900 pharmaceuticals linked to liver injury (Björnsson, 2016). For example, investigations have elucidated the underlying mechanisms of drug-induced hepatotoxicity across diverse agents, highlighting the imperative for hepatoprotective measures (Gulati et al., 2018). Furthermore, Andrade et al. reported that hepatotoxicity arising from pharmacotherapeutics and environmental xenobiotics constitutes a significant fraction of acute liver failure cases. Collectively, these observations emphasize the urgency of developing effective prophylactic and therapeutic modalities. Moreover, liver damage caused by narcotics and environmental toxins accounts for a substantial proportion of hepatic failures (Andrade et al., 2019).

Current mechanistic concepts of drug-induced liver injury limits to three main ways of initial injury such as direct cell stress, mitochondrial permeability, and specific immune reactions. The mitochondria play a fundamental role in events leading to apoptotic vs. necrotic cell death (Russmann et al. 2009). Oxidative stress plays a critical role in the course of inflammatory pathway, and proliferative chronic liver disease (fibrosis, necrosis and cirrhosis) (Ezhilarasan 2018). Furthermore, reactive oxygen species play central roles in the activation of the inflammatory signaling pathways via IκB (an inhibitor of nuclear factor-κB), thereby linking oxidative stress, inflammation and fibrosis (Ramos-Tovar and Muriel 2020).

In this context, innovative approaches for predicting and mitigating hepatotoxicity including drug toxicity prediction models (DTI) and the use of stem cell-derived hepatocytes, have gained attention (Kia et al. 2013). DTI redefines drug toxicity as scaled biphasic and exponential functions of pharmacodynamic, pharmacokinetic and physicochemical parameters. These contributions are then scaled by molar dose and oral bioavailability and the logarithm of the sum of scaled contributions is DTI (Dixit 2019).

However, many early-stage liver injuries can only be detected through enzymatic assays and may remain undiagnosed until severe complications arise. Alterations in serum enzyme activities are not mechanistically informative, that can occur for a variety of reasons unrelated to hepatic injury and can be observed with drugs that do not have the potential to cause significant drug-induced liver injury (Harrill et al. 2012).

Recently, there has been a growing global shift toward herbal remedies as a treatment for various disorders (Aslam and Kim 2025; Beigoli et al. 2021; Mortazavi Moghaddam et al. 2020).

Plant-derived compounds demonstrate broad-spectrum therapeutic effects with minimal toxicity, but their progression to clinical applications is limited by poor bioavailability, unclear mechanisms, and insufficient models. The preclinical modeling could be enhancing translational

relevance and support repositioning phytochemicals as precision-targeted agents (Kim et al. 2025).

Consequently, the search for natural protective agents particularly phytochemicals with antioxidant and anti-inflammatory properties, has become a research priority (Khazdair et al. 2024).

Zingiber zerumbet L. (*Z. zerumbet*) is a species in the Zingiberaceae family and is commonly known as bitter ginger has a wide range of traditional uses including treatments for typhoid, poisoning, stomach ailments, hemorrhoids, asthma, and skin diseases (Sharifi-Rad et al. 2017). Various pharmacological activities of *Z. zerumbet* including analgesic, anti-diabetic, anti-inflammatory, antioxidant, anti-hyperlipidemic, immunomodulatory, hepatoprotective, nephroprotective, and gastroprotective effects were also reported (Chan et al. 2024). Rhizome extract of *Z. zerumbet* has been used in traditional herbal medicine across the globe for the treatment of numerous diseases like worms, cough, leprosy and asthma. A total of nine compounds were obtained out of which zerumbone was found to be the major constituent covering 64.58 % of the total area by Gas Chromatography-Mass Spectrometry (GC/MS) analyses (Dash et al. 2020). A previous study indicated that zerumbone is abundantly present (70.60%) in essential oils extracted from the rhizomes of *Z. zerumbet* (Raina and Misra 2022).

It has been reported that the genus of ginger contains various chemical ingredients including phenolic compounds, terpenes, polysaccharides and active compounds such as gingerols, shogaols, and zingerone, and exhibits multiple pharmacological effects including antioxidant, anti-inflammatory, and hepatoprotective properties (Mao et al. 2019). Zerumbone is a major active compound found in the rhizomes of *Z. zerumbet* and has been reported to have an anti-inflammatory, anti-microbial, anti-tumor, and anti-oxidant properties (Ruslay et al. 2007).

Administration of zerumbone on zearalenone induced hepatotoxicity in mice significantly decreased the level of alkaline phosphatase and alanine aminotransferase. The levels of inflammatory mediators; interleukin (IL)-1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) and hepatic malondialdehyde (MDA) concentration were significantly reduced, while the levels of hepatic superoxide dismutase (SOD), hepatic glutathione (GSH), and hepatic catalase (CAT) improved after treatment of mice with zerombone. Moreover, it significantly ameliorated induced liver damage and histological hepatocyte changes (AbuZahra et al. 2021). Given the existing scientific evidence and the significance of hepatotoxicity, this study comprehensively reviewed the protective effects of zerumbone against drugs-induced hepatotoxicity in preclinical studies.

Methods and materials

Study design

This systematic review study adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA to evaluate the hepatoprotective effects of zerumbone (the active compound in bitter ginger) against drugs-induced liver toxicity. The study followed a library-based (documentary) research approach, and synthesizing evidence from experimental studies.

Data sources and search strategy

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, without temporal or geographical limitations. The search strategy employed MeSH terms (Zerumbone OR *Zingiber zerumbet* extract) AND (Drug Induced Liver Injury [Mesh] OR hepatotoxicity OR liver damage) AND (protective effect OR hepatoprotective), combined with free-text terms (ginger liver protection, drug-induced hepatotoxicity, and zerumbone

mechanism). Boolean operators (AND/OR/NOT) were used to refine the search. The search strategies employed in some database is summarized in Table 1.

Inclusion/exclusion criteria

Inclusion: Original studies (*in vitro*/*in vivo*) on zerumbone effects on drug-induced hepatotoxicity; published in English; administered zerumbone alone and not in combination with other compounds, experimental model of induced hepatotoxicity, published in peer-reviewed journals until January 2025.

Exclusion: The studies lacking quantitative outcomes. Also, several type of studies such as, review articles, conference abstracts, letters as well as full article published in a language other than English without English abstract.

Study selection and data extraction

Initial screening: Titles/abstracts were screened against criteria using EndNote X20 (duplicates removed). Full-text review: Two independent reviewers assessed eligibility. Discrepancies were resolved via discussion with a third reviewer. Data extraction: A standardized form captured: Study design (animal model/cell line/dosage). Hepatotoxicity inducer such as, paracetamol, and carbon tetrachloride (CCl_4). Key outcomes (biochemical markers, and oxidative stress indices). Due to heterogeneity in study designs, a thematic analysis categorized findings by: Mechanisms: Antioxidant (e.g. SOD and GSH modulation), anti-inflammatory (e.g. TNF-α and IL-6 suppression). Models: Rodent studies (e.g. Wistar rats), human cell lines (e.g. HepG2). Efficacy: Key finding and outcome.

Quality and risk of bias assessment

A modified version of the (CAMARADES) scale was employed to assess the quality of studies and the risk of bias in animal studies. A score of one point was awarded for each criterion that was met, while a score of zero was assigned if the information was lacking, inadequate, or ambiguous. Consequently, the final score could range from 0 (lowest quality) to 10 (highest quality) (Maity et al. 2025).

Table 1. Search strategies used in different databases

Database/search engine	Search strategy
Scopus	(TITLE-ABS-KEY (zerumbone) OR TITLE-ABS-KEY (zerumbone AND derivative) OR TITLE-ABS-KEY (zingiber AND zerumbet AND extract) AND TITLE-ABS-KEY (drug AND induced AND liver AND injury) OR TITLE-ABS-KEY (chemical AND induced AND liver AND injury) OR TITLE-ABS-KEY (liver AND injury) OR TITLE-ABS-KEY (hepatotoxicity) OR TITLE-ABS-KEY (hepatotoxicity AND testing) OR TITLE-ABS-KEY (liver AND damage))
Pubmed	((((((Zerumbone[Title/Abstract]) OR (Zingiber zerumbet extract[Title/Abstract])) AND (Drug Induced Liver Injury[Title/Abstract])) OR (hepatotoxicity[Title/Abstract])) OR (liver damage[Title/Abstract])) AND (protective effect[Title/Abstract])) OR (hepatoprotective[Title/Abstract])
Web of Science	Zerumbone* (Title) OR Zingiber zerumbet extract* (Title) AND Drug Induced Liver Injury* (Title) OR hepatotoxicity* (Title) OR liver damage (Title) AND protective effect* (Title) OR hepatoprotective (Title)

Results

Study selection

Our systematic search yielded 8895 scientific outputs globally pertaining to ginger (*Zingiber zerumbet* or zerumbone) and hepatotoxicity. This vast body of research included 3,554 journal articles, 1,912 conference papers, 1,336 theses/dissertations, and 9 books (print and digital). Significantly, over 138 peer-reviewed articles on *Zingiber zerumbet* or zerumbone hepatoprotective potential have been published in indexed journals internationally during the past five years (2020–2025), indicating a growing research interest in this area. This selection process was conducted after a thorough review of the titles and abstracts of the extracted studies, as illustrated in Figure 1.

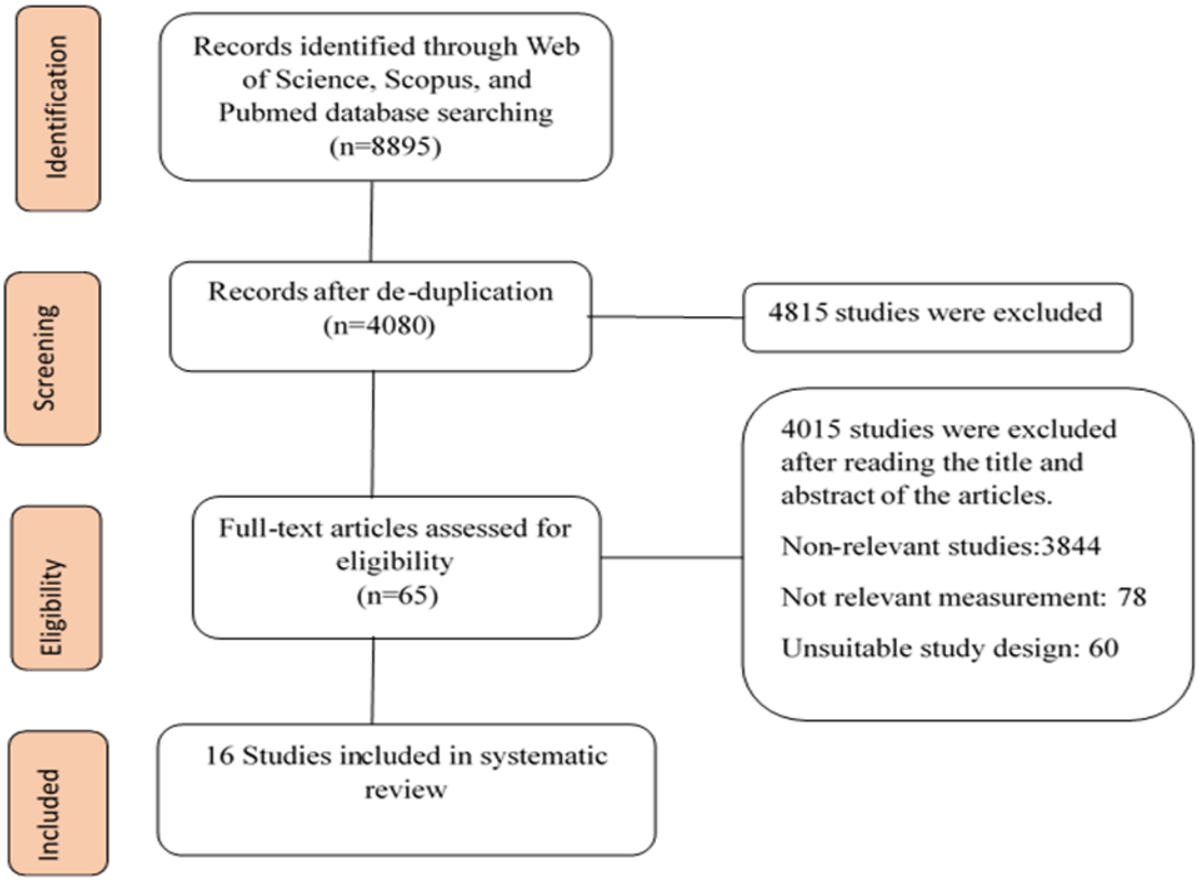

Figure 1. Flowchart of the literature search and strategy for the selection of relevant studies.

Risk of bias of the studies

It was recognized that 13 studies had a low risk of bias and three studies had a medium risk (Table 2). Many studies did not provide clear descriptions of allocation concealment procedures or randomization methods (Abuzahra et al. 2021; Asmah Hamid et al. 2011; Fakurazi et al. 2009; Hamid et al. 2018; Ibrahim et al. 2010; Kim et al. 2019; Samad et al. 2019; Sharkawi et al. 2019; Srimathi Devi et al. 2022; Taha et al. 2010; Wang et al. 2019; Wenhong et al. 2012; Zhang and Xu 2023). Some studies had medium risk, did not provide appropriate animal model, randomization or compliance with animal welfare regulations (Jegannathan et al. 2022; Samad et al. 2015; Sharifah Sakinah et al. 2007; Srimathi Devi et al. 2022).

Study characteristics

Classification of included articles describing zerumbone alleviated histopathological damage, inflammation and oxidative stress levels on hepatotoxin-induced liver injury. The total number of articles included in this systematic review is 16. The articles were classified according to the models of study applied; *in vitro* and animal models. Two *in vivo* studies investigated the effects of *Z. zerumbet* on chemical compound and drugs -induced hepatotoxicity, improved liver function test and oxidative stress parameters, 3 *in vitro* studies inhibition of cell proliferation in hepatocellular carcinoma and induced apoptosis.

Eleven *in vivo* studies investigated the effects of zerumbone on chemical compound and drugs in animal models showed elevated antioxidant parameters, and reduced pathological changes and expression levels of IL-1β and TNF-α in injured livers. Most of the papers originate from tropical countries where ginger is abundant. Malaysia contributed the largest number of articles on this compound, as summarized in Table 3.

Table 2. Quality assessment of the included studies

Study	1	2	3	4	5	6	7	8	9	10	Score
Sharkawi et al. 2019	Y	Y	Y	Y	N	Y	Y	N	Y	N	7
Asmah Hamid et al. 2011	Y	Y	Y	Y	N	Y	Y	N	Y	N	7
Sharifah Sakinah et al. 2007	Y	N	Y	Y	Y	N	N	N	N	Y	5
Samad et al. 2015	Y	N	Y	Y	Y	N	N	N	N	Y	5
Jegannathan et al. 2022	Y	N	Y	Y	Y	N	N	N	N	Y	5
Srimathi Devi et al. 2021	Y	Y	Y	Y	N	NC	Y	NC	NC	Y	6
Ibrahim et al. 2010	Y	Y	Y	Y	N	Y	Y	NC	Y	N	7
Samad et al. 2019	Y	Y	NC	Y	N	Y	Y	NC	Y	Y	7
Kim et al. 2019	Y	Y	NC	Y	N	Y	Y	NC	Y	Y	7
Wang et al. 2019	Y	Y	Y	Y	N	Y	Y	NC	Y	Y	8
Taha et al. 2010	Y	Y	Y	Y	N	Y	Y	NC	Y	NC	7
Hamid et al. 2018	Y	Y	Y	Y	N	Y	Y	NC	Y	Y	8
Fakurazi et al. 2009	Y	Y	Y	Y	N	Y	Y	NC	Y	N	7
AbuZahra et al. 2021	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8
Wenhong et al. 2012	Y	Y	Y	Y	N	Y	Y	N	Y	N	7
Zhang and Xu 2023	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8

(1) publication in a peer-reviewed journal; (2) statement of temperature control; (3) random allocation to groups; (4) allocation concealment; (5) blinded assessment of outcome; (6) use of anesthetic without significant intrinsic cardioprotective activity; (7) appropriate animal model (aged, diabetic, or hypertensive); (8) sample size calculation; (9) compliance with animal welfare regulations; (10) statement of potential conflict of interests.

Table 3. Characteristics of the included studies

Author/Year	Country	Study design	Intervention	Outcome
Sharkawi et al. 2019	Malaysia	*In vivo*	Zerumbet extract	Improvements in liver function test Improvements in oxidative stress parameters
Asmah Hamid et al. 2011	Malaysia	*In vivo*	Zerumbet extract	Improvements in liver function test Improvements in oxidative stress parameters
Sharifah Sakinah et al. 2007	Malaysia	*In vitro*	Zerumbone	Inhibited cell proliferation Inducing apoptosis
Samad et al. 2015	Malaysia	*In vitro*	Zerumbone	Induced apoptosis Induced mitochondrial- apoptosis Activities of caspase-3 and caspase-9.
Jegannathan et al. 2022	India	*In vitro*	Zerumbone	Inhibition of cell proliferation in hepatocellular carcinoma Enhanced the upregulation of the bax/bcl-2 ratio
Srimathi Devi et al. 2021	India	*In vivo*	Zerumbone	Reduction in the body weight of the treated fish and the size of tumors present in the liver and abdomen
Ibrahim et al. 2010	Malaysia	*In vivo*	Zerumbone	Improvements in oxidative stress parameters
Samad et al. 2019	Malaysia	*In vivo*	Zerumbone	Reduction in cancerous liver tissue and the total number of cancer cells
Kim et al. 2019	Republic of Korea	*In vivo*	Zerumbone	Improvements in liver function test Improvements in oxidative stress parameters Induced apoptosis
Wang et al. 2019	China	*In vivo*	Zerumbone	Reduction in the release levels of pro-inflammatory cytokines Improvements in oxidative stress parameters
Taha et al. 2010	Malaysia	*In vivo*	Zerumbone	Improved liver function test Improved oxidative stress parameters Increased expression of the pro-apoptotic protein
Hamid et al. 2018	Malaysia	*In vivo*	Zerumbone	Improvements in inflammatory processes Improvements in oxidative stress parameters
Fakurazi et al. 2009	Malaysia	*In vivo*	Zerumbone	Improvements in liver enzyme activities Improved liver function test
AbuZahra et al. 2021	Saudi Arabia	*In vivo*	Zerumbone	Improved oxidative stress parameters Improvements in inflammatory processes Improved histopathological findings
Wenhong et al. 2012	China	*In vivo*	Zerumbone	Improved liver function Improvements in inflammatory processes Improvements in histopathological changes
Zhang and Xu 2023	China	*In vivo*	Zerumbone	Improvements in liver enzyme Improvements in inflammatory processes

Mechanistic insights

Zerumbone exhibits hepatoprotective effects through several mechanisms. These include antioxidant activity, demonstrated by increased SOD and GSH levels alongside decreased lipid peroxidation, and neutralization of reactive oxygen species (ROS) in hepatocytes. Furthermore, zerumbone exhibits anti-inflammatory effects by suppressing TNF-α, IL-6, and NF-κB pathways. Finally, zerumbone contributes to detoxification by enhancing the clearance of various hepatotoxic substances including arsenic, CCl_4, and certain chemotherapeutic agents (e.g. doxorubicin).

Reactive oxygen species (ROS) produce due to oxidative stress procedure. The excess ROS produced can structurally modify proteins and genes so as to trigger signaling cascades that can lead to progression of inflammation process (Chatterjee 2016). The majority of the studies indicated that zerombone exerts protective effect against drugs-induced hepatotoxicity through modulation of oxidative stress and suppression of cytokines production.

Possible therapeutic effects of zerombone on drugs-induced liver toxicity are shown in Figure 2.

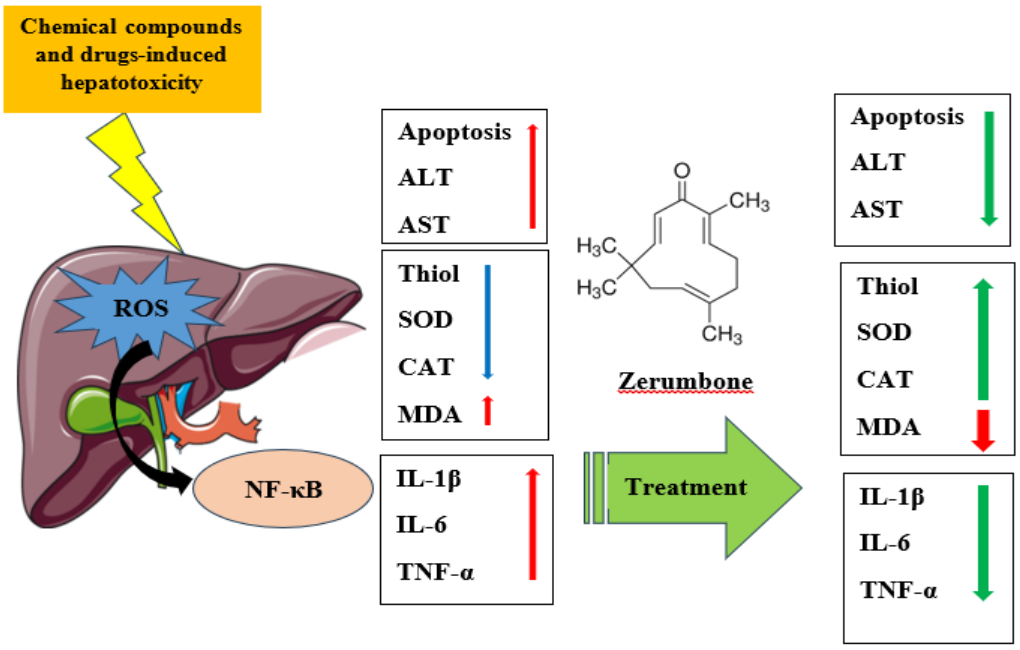

Figure 2. Possible therapeutic effects of zerombone on induced hepatotoxicity.

Effects of *Z. zerumbet rhizomes* extract on paracetamol induced hepatotoxicity

Oral administration of *Z. zerumbet* extract at doses of 250, 350, and 450 mg/kg for a week following paracetamol-induced hepatotoxicity demonstrated significant improvements in liver function test parameters including alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total protein levels, compared to the negative control group. The extract also significantly enhanced oxidative stress parameters, specifically SOD and reduced GSH activity, in the liver, kidney, and cardiac tissues of induced hepatotoxicity in rats(Sharkawi et al. 2019). In another study, intraperitoneal administration of ethyl acetate *Z. zerumbet* extract at doses of 200 and 400 mg/kg conferred protection against paracetamol-induced hepatotoxicity. This protection was characterized by significantly reduced serum ALT, AST, and ALP activities. Additionally, the treatment with *Z. zerumbet* extract notably increased ($p< 0.05$) SOD activities and GSH levels in liver homogenates. The extract also effectively inhibited the increase of MDA and protein carbonyls in liver homogenate, indicating a reduction in oxidative stress. The 400 mg/kg dose displayed superior hepatoprotective effects compared to the 200 mg/kg dose (Asmah Hamid et al. 2011).

Zerumbone-induced apoptosis in hepatic malignancies (*in vitro*)

In vitro studies demonstrated that zerumbone (3.45 µg/ml) significantly inhibited HepG2 cell proliferation with an IC50 of 3.45±0.026 µg/ml, inducing apoptosis through modulation of the Bax/Bcl-2 ratio (Sharifah Sakinah et al. 2007).

Zerumbone demonstrated a dose-dependent (20-100 µg/ml) inhibition of HepG2 cell proliferation and induced cell cycle arrest at the G2/M phase. Additionally, it triggered mitochondrial-mediated apoptosis in HepG2 cells in a time-dependent manner, evidenced by chromatin condensation, cell shrinkage, and the formation of apoptotic bodies. Furthermore, zerumbone stimulated the activities of caspase-3 and caspase-9 in these cells (Samad et al. 2015).

Cells treated with zerumbone and cisplatin (CIS), both individually and in

combination, demonstrated a significant inhibition of cell proliferation in hepatocellular carcinoma, with IC50 values of 10 μM for zerumbone and 3 μM for CIS. The combination therapy of zerumbone and CIS produced a synergistic effect, indicated by a combination index value of less than 1. Treatment with CIS, whether alone or in conjunction with zerumbone, resulted in cell cycle arrest in the S phase. Notably, the combination of zerumbone and CIS further enhanced the upregulation of the Bax/Bcl-2 ratio, which contributed to the activation of the caspase cascade (Jegannathan et al. 2022). The effects of *Z. zerumbet* rhizomes extract and zerombone on chemical compound and drugs induced hepatotoxicity are summarized in Table 4.

Table 4. *Z. zerumbet* extract and zerumbone effects on hepatotoxicity and apoptosis in hepatic cancer cells

Model of study	Zerumbone Doses	Reference drug	Type of uses	Key findings compared to control	Reference
Rats	250, 350, and 450 mg/kg, zerumbet extract	Paracetamol	Oral	Improvements in ALP, ALT, AST, and total protein levels Enhancement in SOD and GSH level	(Sharkawi et al. 2019)
Rats	200 and 400 mg/kg, zerumbet extract	Paracetamol	Intraperitoneal	Reduced serum ALT, AST, and ALP activities. Increased SOD activities and GSH levels in liver Inhibited the increase of MDA	(Asmah Hamid et al. 2011)
HepG2 cells	3.45 μg/ml	Cisplatin	Exposure	Inhibited cell proliferation Inducing apoptosis through modulation of the bax/bcl-2 ratio	(Sharifah Sakinah et al. 2007)
HepG2 cells	20-100 μg/ml	Cisplatin	Exposure	Induced cell cycle arrest at the G2/M phase Triggered mitochondrial-mediated apoptosis Chromatin condensation Cell shrinkage	(Samad et al. 2015)
liver cancer cells	3 and 10 μM	Cisplatin	Exposure	Stimulated the activities of caspase-3 and caspase-9. Inhibition of cell proliferation in hepatocellular carcinoma Enhanced the upregulation of the bax/bcl-2 ratio	(Jegannathan et al. 2022)

Effects of zerumbone on oxidative stress, inflammation and liver enzyme

The antineoplastic properties of zerumbone were assessed in a wild-type zebrafish model of hepatic cancer induced by cisplatin (CIS). The findings indicated that the combination of CIS and zerumbone at doses of 1.4 and 2.8 μg significantly inhibited the progression of hepatocellular carcinoma (HCC) cells. Zerumbone treatment resulted in a partial reduction in the body weight of the treated fish and the size of tumors present in the liver and abdomen. Furthermore, co-administration of zerumbone with CIS demonstrated therapeutic efficacy against human HCC cells introduced into the zebrafish model (Srimathi Devi et al. 2021).

Intraperitoneal administration of zerumbone at dosages of 100 and 200 mg/kg, utilizing corn oil as a vehicle, over a four-day period prior to cisplatin injections mitigated liver damage and upheld hepatic function, as corroborated by microscopic examinations and lesion

scoring. Zerumbone treatment was shown to elevate levels of glutathione (GSH) while simultaneously lowering malondialdehyde (MDA) levels in the liver, following cisplatin administration at a dose of 45 mg/kg (Ibrahim et al. 2010). The antiproliferative and anti-angiogenic effects of zerumbone were evaluated in rats with diethylnitrosamine-induced hepatocellular carcinoma. The expression levels of vascular endothelial growth factor (VEGF), matrix metalloproteinases, and Ki-67, which were elevated in untreated HCC rats, were found to be downregulated following treatment with zerumbone at doses of 30 and 60 mg/kg body weight. This treatment was associated with a reduction in both the levels of cancerous liver tissue and the total number of cancer cells (Samad et al. 2019). The downregulation of VEGF expression in zerumbone-treated rat models of HCC suggests that zerumbone effectively inhibits liver cancer growth. Oral administration of zerumbone at doses of 10 and 50 mg/kg during CCl_4-induced acute and chronic liver injury resulted in an increase in anti-apoptotic protein levels, while concurrently decreasing chronic liver damage and the associated fibrogenesis in murine models, as assessed through histopathological analysis. Zerombone treatment significantly decreased CCl_4-induced elevation of serum ALT and AST levels, expression levels of IL-1β and TNF-α were significantly down- regulated in injured livers of mice administered with high dose of zerombone (Kim et al. 2019). In a separate study, pre-treatment of mice with intraperitoneal zerumbone for five days, followed by CCl_4 injection two hours after the last zerumbone administration, demonstrated that zerumbone restored the activities of antioxidant enzymes SOD and glutathione peroxidase (GSH-Px), replenished the GSH pool, and decreased MDA production in a dose-dependent manner. Moreover, *in vivo* treatment with zerumbone led to a reduction in the release levels of pro-inflammatory cytokines, specifically IL-6 and TNF-α, and inhibited increases in the protein expression levels of Toll-like receptor 4 (TLR4), nuclear factor kappa B (NF-κB) p-p65, and cyclooxygenase-2 (COX-2) (Wang et al. 2019).

The administration of zerumbone via intraperitoneal injection (i.p.) at doses of 15, 30, or 60 mg/kg body for 11 weeks, following exposure to diethylnitrosamine (DEN) that induces hepatocarcinogenesis, demonstrated that zerumbone provided protective effects against the carcinogenic impacts of DEN and 2-acetylaminofluorene (AAF) on hepatic tissue in a rat model. Notably, serum levels of ALT, AST, alkaline phosphatase (AP), and alpha-fetoprotein (AFP) were significantly lower ($p < 0.05$) in rats treated with zerumbone compared to untreated rats with liver cancer. In untreated DEN/AAF rats, MDA concentrations in the liver were significantly elevated; indicating enhanced hepatic lipid peroxidation, whereas levels of hepatic glutathione (GSH) exhibited a significant decrease. Histopathological analysis revealed a high expression of proliferating cell nuclear antigen (PCNA) in the liver sections of untreated DEN/AAF rats. In contrast, zerumbone-treated rats showed a significant reduction in PCNA expression. The TUNEL assay indicated a significantly higher number of apoptotic cells in the livers of DEN/AAF rats treated with zerumbone compared to those that were untreated. Additionally, zerumbone treatment was associated with an increase in the expression of the pro-apoptotic protein Bax and a reduction in the expression of the anti-apoptotic protein Bcl-2 in the livers of DEN/AAF rats, suggesting a promotion of apoptosis (Taha et al. 2010). Further studies indicated that treatment with zerumbone (25 mg/kg, i.p.) significantly reduced levels of ALT, AST, and total hepatic protein compared to rats induced with paracetamol (PCM). Rats receiving zerumbone treatment exhibited a normal hepatocyte architecture, devoid of vacuolization or necrosis, alongside a significantly reduced neutrophil count,

implying its potential to mitigate inflammatory processes resulting from PCM overdose and to diminish the susceptibility of hepatocytes to necrosis (Hamid et al. 2018). In another investigation, rats were administered with zerumbone (0.2%) through oral intubation for 14 days prior to a 3 g/kg PCM challenge. No significant alterations in liver enzyme activities or histological assessments were observed 4 hr post-PCM administration. However, 24 hr after paracetamol injection, levels of ALT, AST, ALP were found to be reduced in the zerumbone-pretreated group compared to those treated with PCM only (Fakurazi et al. 2009).

Oral administration of zerumbone (15 mg/kg) resulted in decreased levels of ALP and ALT. Concurrently, zerumbone was found to attenuate the inflammatory response by significantly reducing the serum concentrations of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α. Pretreatment with zerumbone also lowered hepatic MDA concentrations and mitigated the depletion of hepatic antioxidant enzymes such as SOD, GSH, and CAT. Furthermore, it significantly alleviated zearalenone -induced hepatic damage and histopathological changes in hepatocytes, likely by modulating the PI3K/AKT signaling pathway and enhancing the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1). Additionally, zerumbone treatment increased Bcl-2 expression and inhibited markers of apoptosis (AbuZahra et al. 2021).

The potential effects of zerumbone (10 mg/kg) pretreatment in a rat model of acute necrotizing pancreatitis induced by sodium taurocholate were also evaluated. The results demonstrated a significant reduction in plasma amylase, serum secretory phospholipase A2, ALT, and AST levels, along with improved histopathological findings in pancreatic and hepatic tissues following zerumbone administration. Additionally, zerumbone was shown to inhibit the activity of NF-κB protein and downregulate the mRNA levels of Intercellular Adhesion Molecule-1 and IL-1β (Wenhong et al. 2012). In a separate study, varying concentrations of zerumbone (10, 20, and 40 mg/kg) were administered via femoral vein puncture 30 min prior to the 5% sodium taurocholate solution injected into the biliopancreatic duct for inducing severe acute pancreatitis. Zerumbone at doses of 10, 20, and 40 mg/kg was effective in alleviating pancreatitis, decreasing ascites volume, reducing lung wet/dry weight ratio, improving pancreatic pathology scores, and ameliorating oxidative stress and inflammatory damage. Notably, high doses (20 and 40 mg/kg) of zerumbone induced hepatorenal toxicity, while the 10 mg/kg dosage was effective in reducing liver enzyme levels, mitigating pathological liver damage, and offering protection against extrapancreatic organ damage in the context of severe acute pancreatitis. Furthermore, zerumbone did not exhibit significant side effects in normal rat models. Ultimately, the study demonstrated that the anti-inflammatory effects of zerumbone in severe acute pancreatitis may be mediated through the ROS/NF-κB signaling pathway (Zhang and Xu 2023).

The possible therapeutic effects of zerombone on chemical compound and drugs induced oxidative stress, inflammation and liver enzyme were showed in Table 5.

Effects of zerumbone on induced hepatotoxicity

Table 5. Effects of zerumbone on oxidative stress, inflammation and liver enzyme

Chemical compound and drugs -induced hepatotoxicity	Zerumbone Doses	Type of administration	Effects	Reference
Cisplatin	1.4 and 2.8 µg	-	Inhibited the progression of hepatocellular carcinoma (HCC) cells. Reduction in size of liver tumors present	(Srimathi Devi et al. 2021)
Cisplatin	100 and 200 mg/kg	Intraperitoneal	Mitigated liver damage Elevate levels of glutathione (GSH) Lowering malondialdehyde (MDA) levels in the liver	(Ibrahim et al. 2010).
Diethylnitrosamine	30 and 60 mg/kg	Intraperitoneal	Downregulated the expression levels of vascular endothelial growth factor (VEGF), matrix metalloproteinases, and Ki-67 Reduced the levels of cancerous liver tissue and the total number of cancer cells	(Samad et al. 2019).
Tetrachloride (ccl4)	10 and 50 mg/kg	Oral administration	Increased anti-apoptotic protein levels Decreased chronic liver damage Decreased ccl4-induced elevation of serum alt and ast levels	(Kim et al. 2019).
Tetrachloride (ccl4)	(20 µmol/Kg)	Intraperitoneal	Significantly down- regulated expression levels of il-1β and tnf-α Restored the activities of antioxidant enzymes SOD and glutathione peroxidase (GSH-Px) Decreased MDA production Reduction in the release levels of IL-6 and TNF-α Inhibited increases in the protein expression levels of TLR4, NF-κb and COX-2 Reduced the levels of ALT, AST, alkaline phosphatase (AP), and alpha-fetoprotein (AFP)	(Wang et al. 2019).
Diethylnitrosamine and 2-acetylaminofluorene	15, 30, or 60 mg/kg	Intraperitoneal	Reduced in PCNA expression Increased the expression of the pro-apoptotic protein Bax Reduced the expression of the anti-apoptotic protein Bcl-2	(Taha et al. 2010)
Paracetamol	25 mg/kg	Intraperitoneal	Reduced levels of ALT, AST, and total hepatic protein Reduced neutrophil count, implying its potential to mitigate inflammatory processes	(Hamid et al. 2018)
Paracetamol	(0.2%)	Oral intubation	Reduced levels of ALT, AST Reduced alkaline phosphatase (ALP)	(Fakurazi et al. 2009)
Zearalenone	15 mg/kg	Oral	Decreased levels of alkaline phosphatase and ALT. Reduced IL-1β, IL-6, and TNF-α. Lowered hepatic MDA concentrations and mitigated the depletion of hepatic antioxidant enzymes such as SOD, GSH, and CAT. Increased Bcl-2 expression and inhibited markers of apoptosis	(AbuZahra et al. 2021)
Sodium taurocholate	5, 10, 20, and 40 mg/kg	Injected via femoral vein	Reduced plasma amylase, serum secretory phospholipase A2, ALT, and AST levels Improved histopathological findings in pancreatic and hepatic tissues inhibited the activity of NF-κb protein and downregulate the mrna levels of intercellular adhesion molecule-1 and IL-1β	(Wenhong et al. 2012).
Sodium taurocholate solution	10, 20 and 40 mg/kg	Injected via femoral vein	Improved pancreatic pathology scores, and ameliorating oxidative stress and inflammatory damage through the ROS/NF-κb signaling pathway	(Zhang and Xu 2023)

Discussion

The results of this systematic review demonstrate that zerumbone significantly reduced ROS and enhanced antioxidant enzyme activity (e.g. SOD and CAT), corroborating earlier reports on ginger antioxidative properties (Ghanbari et al. 2021). The compound ability to inhibit lipid peroxidation preserved hepatocyte integrity, preventing the histopathological changes (e.g. steatosis and necrosis) typical of non-alcoholic fatty liver disease (NAFLD) a condition linked to obesity and diabetes (Rajabi et al. 2017). This aligns with clinical observations where oxidative imbalance drives liver dysfunction (Ghanbari et al. 2021).

Zerumbone administration markedly lowered serum ALT, AST, and ALP biomarkers of hepatocyte damage. These findings mirror studies showing that ginger extracts mitigate drug-induced enzyme leakage (Yang et al. 2024). Notably, reductions in total and direct bilirubin further underscore zerumbone role in improving hepatic detoxification, critical in toxin clearance (Delli Bovi et al. 2021).

The results of the reviewed studies indicated that zerumbone significantly reduced the expression of caspase-3 (a key protein in the programmed cell death pathway) while increasing Bcl-2 levels (an anti-apoptotic protein). This mechanism prevents the destruction of hepatocytes when exposed to chemical toxins. Previous studies have confirmed that zerumbone inhibits mitochondrial apoptotic pathways, thereby preventing liver tissue necrosis induced by chemotherapeutic drugs such as cisplatin (Fatoki and Badmus 2022). Notably, these effects were observed not only in acute models but also in cases of chronic exposure to hepatic toxins. Furthermore, zerumbone stabilizes mitochondrial membrane potential, preventing cytochrome c leakage into the cytoplasm. This finding is particularly significant because the accumulation of cytochrome c in the cytoplasm is a major trigger for caspase activation and subsequent apoptosis. Essentially, zerumbone creates a barrier-like effect at the mitochondrial level, making liver cells more resistant to oxidative stress caused by chemical drugs. These findings align with research by Rajabi et al. which demonstrated that oxidative stress from toxins directly impacts the mitochondrial integrity of hepatocytes (Rafie et al. 2020).

Moreover, zerumbone was identified as a potent anti-inflammatory agent that acts by inhibiting the transcription factor NF-κB. This factor plays a central role in the expression of pro-inflammatory cytokines such as TNF-α and IL-1β. This mechanism provides a molecular explanation for zerumbone protective effects against chemical-induced hepatitis (Hafezizadeh et al., 2024). Another noteworthy aspect is zerumbone ability to inhibit inflammatory enzymes COX-2 and 5-Lipoxygenase (5-LOX) which are involved in the synthesis of prostaglandins and leukotrienes key contributors to chronic liver inflammation and fibrosis. Clinical studies have shown that ginger-derived compounds (e.g. gingerol) can reduce inflammatory markers in patients with non-alcoholic fatty liver disease (Haque and Harikrishnan 2018). These findings support the hypothesis that zerumbone could serve as a complementary therapeutic option for inflammatory liver conditions (Slama et al. 2020). Additionally, zerumbone reduces the accumulation of inflammatory macrophages in liver tissue, thereby preventing the progression of steatohepatitis. This effect is likely mediated through modulation of the JAK/STAT pathway, which plays a role in hepatic stellate cell (HSC) activation and fibrosis progression (Thibaut et al. 2022). Such mechanisms distinguish zerumbone from other anti-inflammatory compounds, as it simultaneously targets multiple molecular pathways in the inflammatory process.

This study demonstrates that zerumbone exhibits significant hepatoprotective effects against drug-induced liver toxicity through multiple mechanisms. The findings of reviewed articles revealed that zerumbone modulated oxidative stress, MDA reduction and SOD/CAT enhancement, normalized liver enzymes (ALT, AST, and ALP), modulated apoptosis (caspase-3 inhibition and Bcl-2 upregulation), and suppress inflammation (NF-κB inhibition). Furthermore, the translational potential of these findings is limited by the scarcity of human clinical trials and incomplete understanding of zerumbone pharmacokinetics in different populations.

Current evidence positions zerumbone as a potent natural adjuvant for hepatoprotection, though future research should prioritize: (i) Standardized clinical trials, (ii) Pharmacokinetic profiling, and (iii) Combinatorial therapies.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Author contribution statement

Mehrdad Ghafoori: Conceptualization, Methodology, and the writing the original draft. Zahra Ghiravani: Conceptualization, help to the methodology, Review & editing. Mohammad Reza Khazdair: Conceptualization, Methodology, Writing – original draft, Review & editing, and Supervision.

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