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Review Article

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Toxicological Profiling of Natural Bioactive Compounds Using PubChem Database and Relevant Literature

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Abstract: Natural bioactive compounds have gained increasing attention for their pharmacological properties and therapeutic potential. However, understanding their toxicological profiles is crucial for assessing their safety and potential applications. This study aimed to assess the toxicological profiles of selected natural compounds using LD_{50} values and literature-based evaluations. Toxicity data were collected from the PubChem database and scientific literature, covering various administration routes and model organisms. The toxicological assessment revealed varying LD_{50} values among bioactive compounds, with toxicity influenced by structure, organism, and administration route. Compounds like ellagic acid, swertiamarin, and verbascoside exhibited high safety margins, whereas angelicin, xanthotoxol, and senegenin showed lower LD_{50} values, indicating greater toxicity. Route of administration significantly influenced toxicity; for example, bakuchiol and osthol were more toxic via intraperitoneal or intravenous injection than oral administration. Literature findings further supported these trends, highlighting species and dose-dependent effects. Some compounds also showed model-specific toxicity despite therapeutic potential. Toxicity varied significantly depending on the route of administration; for example, bakuchiol and osthol exhibited higher toxicity when administered intraperitoneally or intravenously compared to oral administration, indicating the importance of the administration route in toxicity profiling.

Keywords: Toxicity analysis; Lethal dose 50; Bioactive compound; Natural sources

1. Introduction

Natural compounds play a vital role in drug discovery due to their diverse pharmacological properties, including antiinflammatory, anticancer, antimicrobial, antioxidant, and neuroprotective effects (Sharifi-Rad et al., 2020; Chowdhury et al., 2024; Al Hasan et al., 2024; Bhuia et al., 2025). They serve as valuable sources for new drug candidates and therapeutic agents. These compounds, derived from plants, fungi, marine organisms, and microorganisms, serve as valuable sources for new drug candidates and therapeutic agents (Jensen & Fenical, 2000). The importance of nature as a drug reservoir is highlighted by the fact that many effective medications in the past have come from natural sources (Bernardini et al., 2018). Their complex chemical structures and high biological specificity often surpass those of synthetic compounds, making them highly promising for pharmaceutical development (Atanasov et al., 2021). Some naturally occurring compounds are morphine, atropine, artemisinin, scopolamine, quercetin, kaempferol, etc. (Cadar et al., 2015; Saboon et al., 2019; Tsuchiya, 2017).

However, despite their benefits, it is essential to evaluate their toxicity to ensure their safety and efficacy. Toxicity analysis is a critical aspect of pharmacological studies, as it helps determine the potential risks, adverse effects, and unsuitable candidates early in the drug development pipeline (Mensah et al., 2019; Bulusu et al., 2016). A thorough toxicological assessment allows for the identification of safe dosage levels, minimizes unwanted side effects, and ensures compliance with regulatory guidelines for new drug development (Gad, 2016; Blomme & Will, 2016). Toxicological analysis is essential to identify potential harmful effects of bioactive compounds and ensure their safe use in humans. For example, despite its anticancer properties, aconitine, a compound from *Aconitum* species, can cause severe cardiotoxicity if not properly dosed (Jiang et al., 2022). This highlights the need for toxicity screening before clinical application. Acute toxicity studies and

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LD_{50} values are fundamental in drug discovery, providing initial toxicity screening for new compounds (Saganuwan, 2017). LD_{50} values help assess the lethal dose required to cause mortality in 50% of test subjects, offering insights into the compound's safety profile (Noga et al., 2024). These studies are critical for determining safe therapeutic doses and identifying potential toxicological concerns before progressing to clinical trials.

This study aims to assess the toxicological profiles of selected bioactive compounds from natural sources by analyzing their LD_{50} values across different test organisms and administration routes. The findings will contribute to a better understanding of their safety, inform risk assessments, and support their potential applications in the development of novel therapeutic agents.

2. Methodology

Data on toxicological properties were extracted from the PubChem databases (https://pubchem.ncbi.nlm.nih.gov/). Compounds were randomly selected based on their known bioactivity and reported toxicity data. The parameters analyzed include LD_{50} values, test organisms, and administration routes (oral, intravenous, intraperitoneal, subcutaneous, or dermal exposure). In addition, we have searched for the toxicity test, safe dose, higher dose, and mechanism of selected bioactive compounds from the literature.

3. Results and discussion

Toxicity profiles from the PubChem Database

The toxicological profiles of the studied compounds varied significantly, with differences observed in species susceptibility and route of administration. Among the compounds, senegenin demonstrated the highest toxicity, with an intraperitoneal LD_{50} of 3 mg/kg, highlighting its potential toxicity risks even at low doses. Conversely, cianidanol and swertiamarin exhibited high oral LD_{50} values (>10 g/kg), suggesting relatively lower acute toxicity.

Routes of administration significantly influenced toxicity levels. Intravenous administration generally resulted in lower LD_{50} values, indicating higher acute toxicity, as seen in bakuchiol (31 mg/kg), senegenin (45 mg/kg), and osthol (>40 mg/kg in dogs). Intraperitoneal administration also displayed relatively high toxicity, with angelicin (165 mg/kg in rats), osthol (190 mg/kg in mice), and bakuchiol (94 mg/kg in mice) exhibiting notable toxicity. In contrast, oral administration often resulted in higher LD_{50} values, indicating lower acute toxicity in many compounds, such as ellagic acid (>20 g/kg), cianidanol (>10 g/kg), and swertiamarin (>10 g/kg).

Species-specific differences were evident in compounds like Osthol, which had varying toxicities in rats (oral LD_{50}: 2905 mg/kg, intraperitoneal LD_{50}: 600 mg/kg) and mice (intraperitoneal LD_{50}: 190 mg/kg, subcutaneous LD_{50}: 16 mg/kg). Similarly, xanthotoxol demonstrated higher oral toxicity in rats (480 mg/kg) than in mice (>1 g/kg). These differences may be attributed to variations in metabolic pathways, enzyme systems, and pharmacokinetics among species.

Chronic toxicity assessments help identify cumulative toxic effects, delayed organ damage, or carcinogenic potential that are not apparent in acute LD_{50} studies (Chinedu et al., 2015). Numerous common chronic and sub-chronic animal toxicity assays are employed to describe chronic toxicity and meet regulatory information needs (Reichl & Schwenk, 2014). It is also stressed that future research should focus on repeated-dose toxicity studies in rodents and non-rodents that last 28 or 90 days (Hayes, 1967). We found little information regarding chronic toxicity in our investigation. For six months, the chronic toxicity of xanthotoxol in rats was studied at doses of 10, 40, and 80 mg/kg p.o. No adverse effects or anomalies in endocrine integrity or reproductive activity were observed (Sethi et al., 1992). Wistar rats were used to perform acute and sub-chronic toxicity tests with PAHE containing verbascoside, and no signs of toxicity were observed during sub-chronic exposure (Henn et al., 2019).

Overall, these findings provide valuable insights into the toxicity profiles of these compounds, aiding in their risk assessment and potential therapeutic applications. However, **Table 1** demonstrated PubChem CID, 2D structure, organism, test type, route, and dose of compounds.

Table 1. Pubchem CID, 2D structure, organism, test type, route, and dose of compounds.

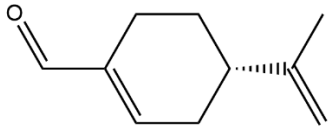
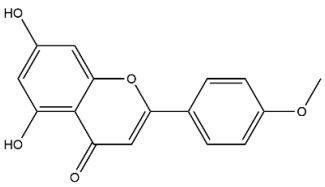
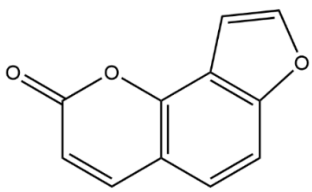
Compound Name	CID	2D structure	Organism	Test Type	Route	Dose
(-)-Perillaldehyde	16441		Mouse	LD_{50}	Oral	1720 mg/kg
			Guinea pig		Skin	> 5 gm/kg
Acacetin	5280442		Mouse		Intravenous	933 mg/kg
					Unreported	933 mg/kg
Angelicin	10658		Rat		Intraperitoneal	165 mg/kg
			Mouse		Intraperitoneal	254 mg/kg
			Rat		Oral	322 mg/kg

Table 1. *Continued*

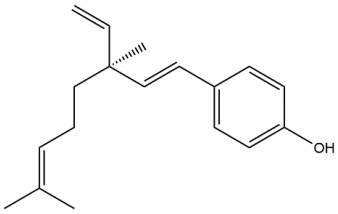
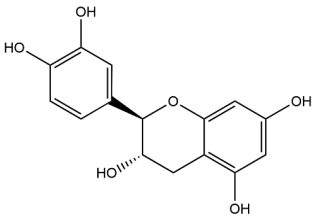
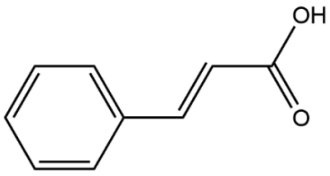
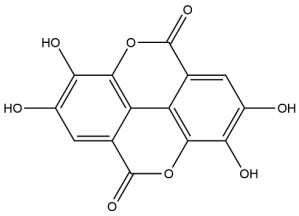
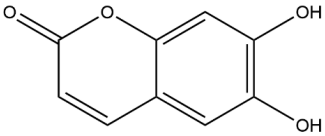
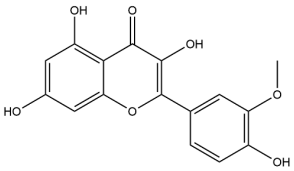
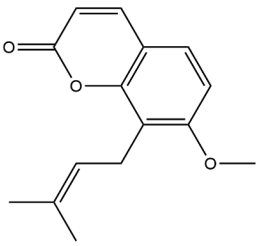
Compound Name	CID	2D structure	Organism	Test Type	Route	Dose
Bakuchiol	5468522		Rat	LD_{50}	subcutaneous	>1 gm/kg
			Mouse		Oral	2560 mg/kg
			Mouse		Intraperitoneal	94 mg/kg
			Mouse		intravenous	31 mg/kg
Cianidanol	9064		Rat		Oral	>10 gm/kg
					Intraperitoneal	1084 mg/kg
					Subcutaneous	>5 gm/kg
					Intravenous	>100 mg/kg
			Mouse		Oral	>10 gm/kg
Cinnamic Acid	444539		Bird - wild		Oral	100 mg/kg
Ellagic Acid	5281855		Rat		Oral	>20 gm/kg
				LDLo	Intraperitoneal	630 mg/kg
Esculetin	5281416		Mouse	LD_{50}	Intraperitoneal	1500 mg/kg
Isorhamnetin	5281654		Rat		Intravenous	11100 mg/kg
Osthol	10228		Rat		Oral	2905 mg/kg
			Rat		Intraperitoneal	600 mg/kg
			Mouse		intraperitoneal	190 mg/kg
			Mouse		Subcutaneous	16 mg/kg
			Dog	LD	intravenous	> 40 mg/kg

Table 1. *Continued*

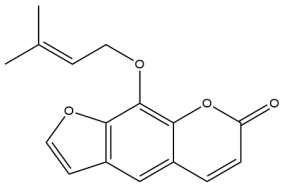
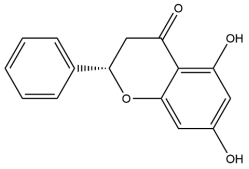
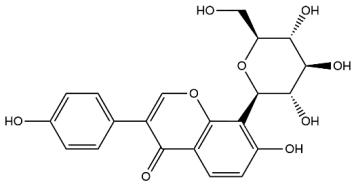
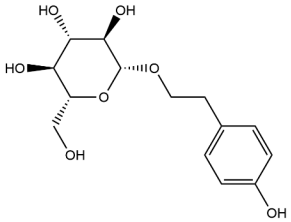
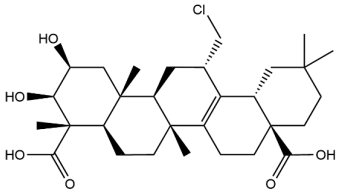
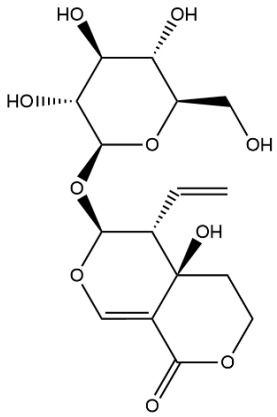
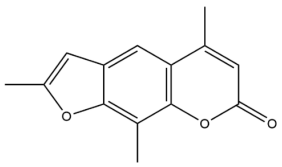
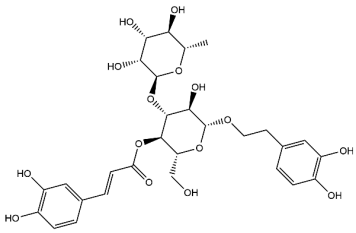
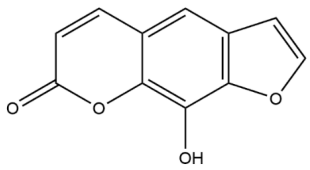
Compound Name	CID	2D structure	Organism	Test Type	Route	Dose
Pentosalen	10212		Mouse	LD_{50}	Intraperitoneal	330 mg/kg
				LDLo	Parenteral	600 mg/kg
Pinocembrin	68071			LD		>1500 mg/kg
Puerarin	5281807			LD_{50}	Intravenous	738 mg/kg
Salidroside	159278				Subcutaneous	28600 µL/kg
Senegenin	12442762			LDLo	Oral	1 gm/kg
				LD_{50}	Intraperitoneal	3 mg/kg
				LDLo	Subcutaneous	30 mg/kg
					Intravenous	45 mg/kg
Swertiamarin	442435			LD_{50}	Oral	>10 gm/kg
					Intraperitoneal	>8 gm/kg
					Intravenous	>5 gm/kg
Trioxsalen	5585				Oral	>7 gm/kg
					Intraperitoneal	>3 gm/kg
					Subcutaneous	>4 gm/kg
			Rat		Oral	>22 gm/kg

Table 1. *Continued*

Compound Name	CID	2D structure	Organism	Test Type	Route	Dose
Verbascoside	5281800		Rat		Oral	>5 gm/kg
			Rat		Intraperitoneal	>5 gm/kg
			Mouse	LD_{50}	Oral	>5 gm/kg
			Mouse		Intraperitoneal	>5 gm/kg
Xanthotoxol	65090		Rat		Oral	480 mg/kg
			Mouse	LD	Oral	>1 gm/kg
			Mouse	LD_{50}	Intraperitoneal	468 mg/kg

Toxicity profiles from the literature

The toxicological profiles of several natural compounds were evaluated using *in vitro* and *in vivo* models, highlighting a spectrum of safety and adverse outcomes. Through literature search, we found that (-)-perillaldehyde showed significant toxicity in zebrafish embryos (LC_{50}: 7.975 mg/L), including neurotoxicity, oxidative stress, and morphological defects. However, it was safe in NAFLD mice at 50 mg/kg with no adverse effects (Li et al., 2025; Niu et al., 2024). Acacetin and senegenin were non-toxic in rheumatoid arthritis and neuronal models, respectively, supporting their therapeutic potential (Wang et al., 2024; Ren et al., 2022). Angelicin induced liver injury via VKORC1 inhibition, indicating hepatotoxicity risk (Tang et al., 2024), while bakuchiol and cianidanol showed dual roles, offering protective effects in some systems but inducing cellular alterations in others (Xu et al., 2025; Jia et al., 2025). Ellagic acid and puerarin were well-tolerated in rodents even at high doses, showing no mortality or clinical toxicity (Tasaki et al., 2008; Chung et al., 2009). Xanthotoxol, salidroside, and swertiamarin exhibited cytotoxic effects in cancer or aquatic models, highlighting their potential as anticancer agents or environmental risks depending on concentration and model (Lin et al., 2022; Yu & Feng, 2024; Perumal et al., 2021). Osthol showed morphological toxicity in aquatic species (Yim et al., 2014), while trioxsalen, pinocembrin, and verbascoside were non-toxic and displayed promising biological activities (Sánchez Ruderisch et al., 2002; Punvittayagul et al., 2011; Etemad et al., 2015). Cinnamic acid reduced plant growth, indicating phytotoxicity (Jităreanu et al., 2011).

Overall, most compounds exhibited good safety margins at therapeutic doses, though some (e.g., (-)-perillaldehyde, swertiamarin, angelicin) presented dose or species-dependent toxic effects. However, **Table 2** shows overall toxicity data from the literature.

Table 2. Toxicity data of compounds from the literature

Compound Name	Experimental Model	Concentration / Dose (R/A)	LC_{50}/ LD_{50}	Observed Toxicities	References
(-)-Perillaldehyde	Zebrafish embryos, *in vivo*	0–20 mg/L	7.975 mg/L	↑ Glipr1a, Nox1, pericardial edema, neurotoxicity ↓Motor ability, angular velocity, activity of antioxidant enzymes, nestin, neurogenin1, Nrf2/HO-1, oxidative stress levels, body length, microphthalmia	Li et al., 2025
	NAFLD mice, *in vivo*	50 mg/kg	–	No significant side effects	Niu et al., 2024
Acacetin	Rheumatoid arthritis mice, *in vivo*	–	–	No significant toxicity. Excellent anti-inflammatory effects in RA	Wang et al., 2024
Angelicin	–	–		↑ Liver injury via inhibition of VKORC1	Tang et al., 2024
Bakuchiol	SH-SY5Y cell line, *in vitro*	–	–	↑ cerebral infarction/ischemia-reperfusion injury by activating AMPK/Nrf2	Xu et al., 2025
	MACO/R mice, *in vivo*	20 mg/kg			

Table 2. *Continued*

Compound Name	Experimental Model	Concentration / Dose (R/A)	LC_{50}/ LD_{50}	Observed Toxicities	References
Cianidanol	HEK293T, HK-2 cell lines, *in vitro*	–	–	↑Fat, histopathological changes, Dysfunction, ↓Obesity, oxidative stress, apoptosis, lipotoxicity	Jia et al., 2025
	Zebrafish, *in vivo*	50–100 mg/kg			
Ellagic Acid	F344/ DuCrj male and female rats, *in vivo* (n=10)	9.4– 39.1 g/kg (Male) 10.1–42.3 g/kg (Female)	–	↓ Body weight gain, body weights No mortality or treatment-related clinical signs were observed	Tasaki et al., 2008
Xanthotoxol	A549, NCI-H460 cell lines, *in vitro*	–	–	↑Toxicity, apoptosis ↓ DNA replication, cell cycle transition, migration, invasion, proliferation	Lin et al., 2022
Osthol	Daphnia magna, Danio rerio, *in vivo* (n=30)	2.5– 40.0 µM	–	↑ Morphological abnormalities, toxicity	Yim et al., 2014
Pinocembrin	Male Wistar rats, *in vivo*	1–100 mg/kg	–	↑Heme oxygenase activity	Punvittayagul et al., 2011
Trioxsalen	HaCaT keratinocytes cell line, *in vitro*	27 µg/l	–	↓TMP. TGF-α, IL-1R, IL-2Rα, IL-12β Non toxic	Sánchez Ruderisch et al., 2002
Senegenin	PC12 Cell line, *in vitro*	10–60 µM	–	No significant side effects, or toxicity observed.	Ren et al., 2022
Verbascoside	HepG2, NIH cell line, *in vitro*	–	–	Do not produce any toxic effects or deaths in animals.	Etemad et al., 2015
	Mice, *in vitro*	0–5 g/kg (i.p.)			
Cinnamic Acid	Phaseolus vulgaris, *in vitro*	10–20 ml	–	↓ Plant growth and development	Jităreanu et al., 2011
Salidroside	CAOV3, SKOV3, IOSE80 cell lines, *in vitro*	0–800 µM	–	↑Cytotoxicity ↓Clone formation, proliferation, cell migration, invasion ability, STAT3/c-Myc	Yu & Feng., 2024
Swertiamarin	Adult male and female zebrafish, *in vivo*	2.7 – 243 µM	–	↑Mortality, oxidative damage ↓SOD, CAT, GSH, GPx, GST Swertiamarin is a safe drug only at a low concentration (40 µM)	Perumal et al., 2021
	Wistar rats, *in vivo* (n=6)	5–2000 mg/ Kg (p.o.)	2000 mg/kg	No clinical signs of toxicity or mortality.	Dhanavathy & Jayakumar, 2017
Puerarin	Sprague–Dawley mice, *in vivo*	0–2000 mg/kg (p.o.)	–	No significant toxic effects observed.	Chung et al., 2009

Abbreviations: ↑:Increased; ↓:Decreased; p.o.: Per orally (oral administration); i.p.: Intraperitoneal (injection into the peritoneal cavity); MACO/R mice: Myocardial artery occlusion/reperfusion model mice; RA mice: Rheumatoid arthritis-induced mice; NAFLD mice: Non-alcoholic fatty liver disease mice; AMPK: AMP-activated protein kinase; Nrf2: Nuclear factor erythroid 2–related factor 2; HO-1: Heme oxygenase-1; GPx: Glutathione peroxidase; SOD: Superoxide dismutase; CAT: Catalase; GSH: Glutathione; GST: Glutathione S-transferase; TAC: Total antioxidant capacity; Glipr1a: Glioma pathogenesis-related protein 1a; Nox1: NADPH oxidase 1; TXNIP: Thioredoxin-interacting protein; ASC: Apoptosis-associated speck-like protein containing a CARD; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3 (inflammasome); STAT3: Signal transducer and activator of transcription 3; c-Myc: Myelocytomatosis oncogene (transcription factor); NF-κB : Nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1β: Interleukin-1 beta; IL-6, IL-8, IL-12β, IL-18 – Various interleukins (cytokines); TNF-α: Tumor necrosis factor alpha; TGF-α: Transforming growth factor alpha; IL-1R, IL-2Rα: Interleukin-1 and Interleukin-2 receptor alpha; TMP: Thymidine monophosphate; VKORC1: Vitamin K epoxide reductase complex subunit 1;

Conclusion

In conclusion, the toxicological assessment of natural bioactive compounds provides valuable insights into their safety profiles. The data indicate a broad range of toxicity levels, with some compounds, such as ellagic Acid and swertiamarin, exhibiting relatively high safety margins, while others, such as angelicin and xanthotoxol, demonstrate lower LD_{50} values, suggesting a higher toxic potential. Compounds such as ellagic acid, swertiamarin, and verbascoside were relatively safe, whereas angelicin and xanthotoxol showed higher toxic potential. Toxicity is significantly influenced by the route of administration, as observed with bakuchiol and osthol, where subcutaneous and intravenous routes yield different toxicity thresholds. Future studies should focus on chronic toxicity evaluations and mechanistic investigations to understand their safety profiles more comprehensively. Moreover, evaluating reproductive and developmental toxicity and using *in silico* QSAR models to forecast toxicity processes is also suggested. Additionally, integrating transcriptome and metabolomic profiling in animal models is recommended to understand cellular responses to prolonged exposure. However, this study is limited by its reliance on PubChem data and literature, focus on acute toxicity, and species differences, which may restrict the direct applicability of results to humans.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas, that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Data will be made available on request.

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Conflicts of Interest

The authors declare no conflict of interest.

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