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Gelsenicine as an emerging foodborne hazard: phytochemistry, pharmacokinetics, and mechanistic toxicology in a systems framework

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ABSTRACT: Gelsenicine is the most toxic indole alkaloid in *Gelsemium elegans* Benth. (*G. elegans*). Poisoning associated with this plant is frequent and poses a significant concern for food safety and public health. Human exposure occurs through accidental ingestion, plant misidentification during collection or purchase, contaminated foods, and indirect intake via honey. Different plant parts resemble commonly used medicinal or edible species, which increases the risk of unintentional consumption. Although low doses of gelsenicine exhibit pharmacological effects, its narrow therapeutic window and potent neurotoxicity make safe intake highly challenging. This review provides a food safety-focused summary of gelsenicine, covering its phytochemical origin, structural characteristics, and pharmacokinetics. Gelsenicine is rapidly absorbed, extensively distributed in the central nervous system, exhibits low oral bioavailability, and is metabolized predominantly via N-demethylation. Major exposure pathways related to plant misidentification, clinical features of poisoning, and toxicological evidence for risk classification are systematically reviewed. Mechanistically, we integrate *in vivo*, *in vitro*, and multi-omics data to propose a multi-target toxicity network model that includes calcium overload, excitotoxicity, neurotransmitter dysregulation, impaired energy metabolism, and respiratory center depression. This model provides a coherent link between molecular initiating events and systemic toxicity. Potential mitigation and detoxification strategies based on these mechanisms are also discussed. Future priorities include developing predictive, mechanism-based risk assessment frameworks using integrated systems toxicology, identifying early diagnostic biomarkers for rapid screening, and targeted interventions at key toxicity nodes. Collectively, these insights aim to support proactive prevention, rapid diagnosis, and risk-based management of gelsenicine poisoning, thereby enhancing food safety.

Keywords: Gelsenicine; *Gelsemium elegans* Benth.; Foodborne hazard; Phytochemistry; Pharmacology; Pharmacokinetics; Toxicology

1. Introduction

Gelsenicine, also known as humantenmine, is the most toxic alkaloid isolated from *Gelsemium elegans* (Gardner & Champ.) Benth. (*G. elegans*) [1, 2]. Repeated misidentification of *G. elegans* as edible or medicinal plants has led to accidental ingestion, making gelsenicine a serious concern for food safety and

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public health. While it shows potential pharmacological effects such as anti-inflammatory, analgesic, and antitumor activity, its extremely narrow therapeutic window and potent neurotoxicity severely restrict safe use and clinical development [3, 4]. *G. elegans* is an evergreen woody vine widely distributed in China and has a long history of folk use [5]. However, its high toxicity and frequent misidentification pose substantial public health risks [6, 7]. Accidental exposure can occur through miscollected plant materials used to prepare herbal teas or soups, misidentification as honeysuckle for tea, contamination of honey due to its poisonous nectar, or ingestion by livestock and poultry, which may introduce toxic residues into animal-derived foods [8, 9]. Together, these exposure pathways highlight the realistic possibility of gelsenicine entering the food chain and help explain the high fatality rate in recent *G. elegans* poisoning incidents [10, 11].

The medicinal and toxic effects of *G. elegans* are mainly due to its alkaloids [12]. Among them, gelsenicine is the most lethal component and represents the principal cause of poisoning. Despite increasing attention to *G. elegans*, a systematic integration of gelsenicine's chemistry, pharmacokinetics, and toxicological mechanisms remains limited. A clear and comprehensive understanding of this key toxic component is essential for effective risk assessment, prevention, and mitigation strategies [13]. This review focuses on gelsenicine from a food safety perspective. It summarizes its phytochemistry, pharmacokinetics, toxicological properties, and multi-target mechanisms of toxicity. By critically evaluating current evidence, we aim to identify knowledge gaps, propose mechanistic hypotheses, and outline strategies for toxicity reduction or detoxification. This work provides a scientific foundation for food safety risk assessment, as well as clinical, forensic, and regulatory management of gelsenicine as a foodborne toxicant.

2. Methodology

A comprehensive literature search was conducted to collect information on gelsenicine from multiple sources, including ScienceDirect, PubMed, Web of Science, CNKI, Google Scholar, Baidu Scholar, PubChem, and relevant books. The search focused on studies related to food safety, oral exposure, poisoning events, pharmacology, and toxicology. Keywords used for the search included "*Gelsemium*," "*G. elegans*," "gelsenicine," "humantenmine," "phytochemistry," "pharmacokinetics," "pharmacology," "toxicity," "toxicological mechanism," "food safety," "oral exposure," "foodborne poisoning," and "detection methods." Data extraction emphasized the phytochemistry and structural characteristics of *G. elegans* and its alkaloids, with particular attention to gelsenicine. Pharmacokinetic information, including absorption, distribution, metabolism, and excretion (ADME) and *in vivo* metabolic profiles, was summarized. Toxicity and mechanistic toxicology data were compiled, encompassing reported poisoning cases, LD_{50} values, and multi-target toxicity mechanisms. Detection methods and analytical approaches relevant to food safety and forensic assessment were also reviewed.

To visualize the research landscape more comprehensively, gelsenicine-related publications indexed in PubMed over the past three decades were analyzed using the Citexs platform (https://www.citexs.com/). This bibliometric analysis offered insights into publication trends, thematic distributions, and evolving research hotspots (Fig. 1A–D), highlighting the current status and potential future directions of gelsenicine research.

Collectively, these approaches provide a systematic foundation for understanding gelsenicine's chemistry, pharmacokinetics, and toxicity, and offer guidance for future research, food safety risk assessment, and potential mitigation or detoxification strategies.

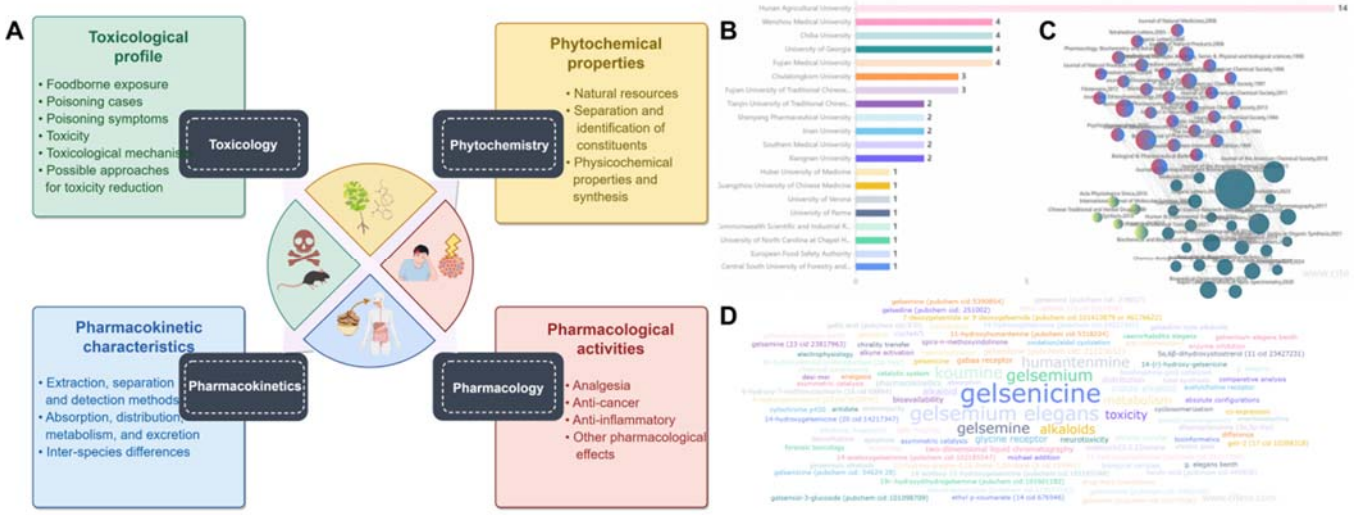


Fig. 1 Schematic overview of this review and research landscape of gelsenicine based on PubMed. (A) Conceptual framework highlighting the main topics covered in this review, including phytochemical properties, pharmacological activities, pharmacokinetic characteristics, and toxicological profile of gelsenicine. (B) Institutions contributing to gelsenicine-related publications. (C) Annual publication trends over the past three decades. (D) Frequency analysis of key research terms, illustrating the evolution of research hotspots. Created with Figdraw.

3. Phytochemical properties

3.1 Natural resources

Gelsenicine is isolated from *G. elegans*, which is commonly known in Chinese folk medicine as Gouwen, Hu Man Teng, Da Cha Yao, or Duan Chang Cao. It is currently recognized as the most toxic alkaloid identified from this species. *G. elegans* is native to East and Southeast Asia. In China, it is primarily distributed in Zhejiang, Fujian, Guangdong, Guangxi, Hunan, Guizhou, and Yunnan [14]. Although it has been used in traditional Chinese medicine, mainly for external application or in carefully controlled doses to treat certain ailments, its high toxicity and frequent misidentification pose a significant food safety risk. *G. elegans* belongs to the genus *Gelsemium* within the family *Gelsemiaceae*. The genus comprises three species: the Asian *Gelsemium elegans* (Gardner & Champ.) Benth. and two North American species, *Gelsemium sempervirens* (L.) J.St.-Hil. and *Gelsemium rankinii* Small [14, 15, 16]. All three species are well known for their potent toxicity and long-standing ethnomedical relevance. Importantly, gelsenicine is distributed across the entire plant, with the root bark containing the highest concentrations, thereby presenting a potential risk of oral exposure and underscoring the importance of evaluating its toxicological implications in food safety contexts [16, 17]. Phytochemical investigations have further demonstrated that species within this genus are particularly rich in alkaloids, especially indole alkaloids, which are critical contributors to both pharmacological activity and neurotoxicity relevant to food safety. Over the years, extensive studies have resulted in the isolation of a wide variety of structurally diverse alkaloids. The global geographical

distribution, traditional uses, and major constituents along with their categories of *Gelsemium* were summarized in Fig. 2A-C (https://www.gbif.org/) and Fig. S1 [15, 18, 19, 20]. Taken together, these findings underscore that systematic characterization of these alkaloids provides the foundation for understanding their toxicological risk in potential oral exposures.

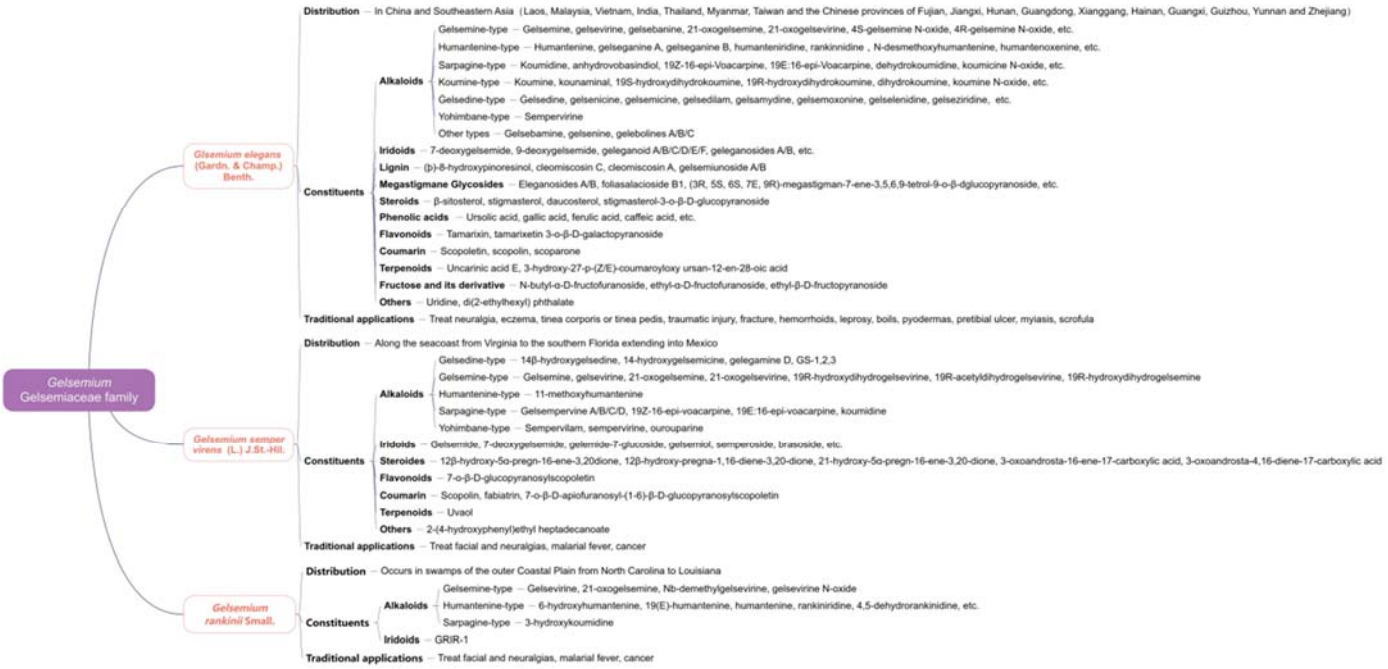


Fig. S1 Mind map of *Gelsemium*-related information: global classification, traditional applications, and bioactive components.

3.2 Separation and identification of constituents

In the study of phytochemical properties, significant progress has been made in the separation and identification of chemical constituents from *G. elegans*. To date, more than 190 compounds with complex structural features and diverse biological effects have been isolated, including over 120 indole or oxindole alkaloids [21]. Based on their structural characteristics, these alkaloids can be classified into six major groups: (1) Gelsemine, (2) Gelsedine, (3) Humantenine, (4) Koumine, (5) Sarpagine, and (6) Yohimbane-type (Fig. 2D) [18]. Among them, indole alkaloids such as gelsemine, koumine, gelsenicine, and gelsevirine represent the major active and toxic constituents relevant to food safety [4, 22, 23]. These alkaloids are present throughout the plant, but they are particularly concentrated in the roots. In *G. elegans*, koumine is the most abundant alkaloid. Structure–toxicity relationship (STR) studies indicate that the presence of a methoxy group at the N1 position and an ethyl group at the C20 position is crucial for gelsenicine's potent neurotoxicity. This provides a mechanistic basis for risk assessment in potential oral exposure scenarios (Fig. 2E) [24]. Alkaloids of the Gelsedine- and Humantenine-type that meet these structural criteria generally exhibit marked toxicity. Among them, Gelsedine-type alkaloids constitute the largest subfamily, with more than 80 members reported to date [25, 26]. They form the most prominent subgroup of *Gelsemium* monoterpenoid indole alkaloids. These compounds feature highly complex and diverse structures. Key characteristics include a distinctive spiro-N-methoxyindoleone chromophore, an oxabicyclo[3.2.2]nonane framework, and a highly

functionalized pyrrolidine ring integrated into the cage-like skeleton. The primary structural variations among individual Gelsedine-type alkaloids arise from differences in substituents (Rx) at key positions such as C11, C14, C15, and C20 (Fig. 2E) [26, 27]. These variations demonstrate the structural diversity of Gelsedine-type alkaloids resulting from modifications at critical positions. Within this subfamily, gelsenicine ((1R,2S,4S,7R,8S)-6-ethyl-1'-methoxyspiro[10-oxa-5-azatricyclo[5.3.1.$0^{4,8}$]undec-5-ene-2,3'-indole]-2'-one, CAS No. 82354-38-9) is the most representative and highly toxic compound. It serves as a reference for toxicological studies and food safety risk assessments (Fig. 2D) [28].

Research on the isolation and structural characterization of alkaloids has revealed their remarkable structural diversity. It has also underscored the pivotal roles of core scaffolds and key substituents in modulating pharmacological and toxicological activities. For gelsenicine, the Gelsedine-type scaffold provides a robust chemical basis for studying neurotoxicity and guiding STR analyses relevant to potential oral exposures. It also informs rational structural modifications aimed at enhancing safety. In particular, the N1 methoxy and C20 ethyl groups, together with systematic variations at C11, C14, C15, and C20 of the scaffold, offer a natural framework for structure–activity/toxicity (SAR)/STR analyses and informed structural optimization [29]. Table 1 summarizes the structural features of Gelsedine-type alkaloids that have been structurally characterized and are indexed in PubChem, with chemical structures drawn using ChemDraw. The table illustrates the diversity of core scaffolds and key substituent positions and visually presents the structural similarities and differences, providing readers with a clear comparison to better understand their structural diversity.

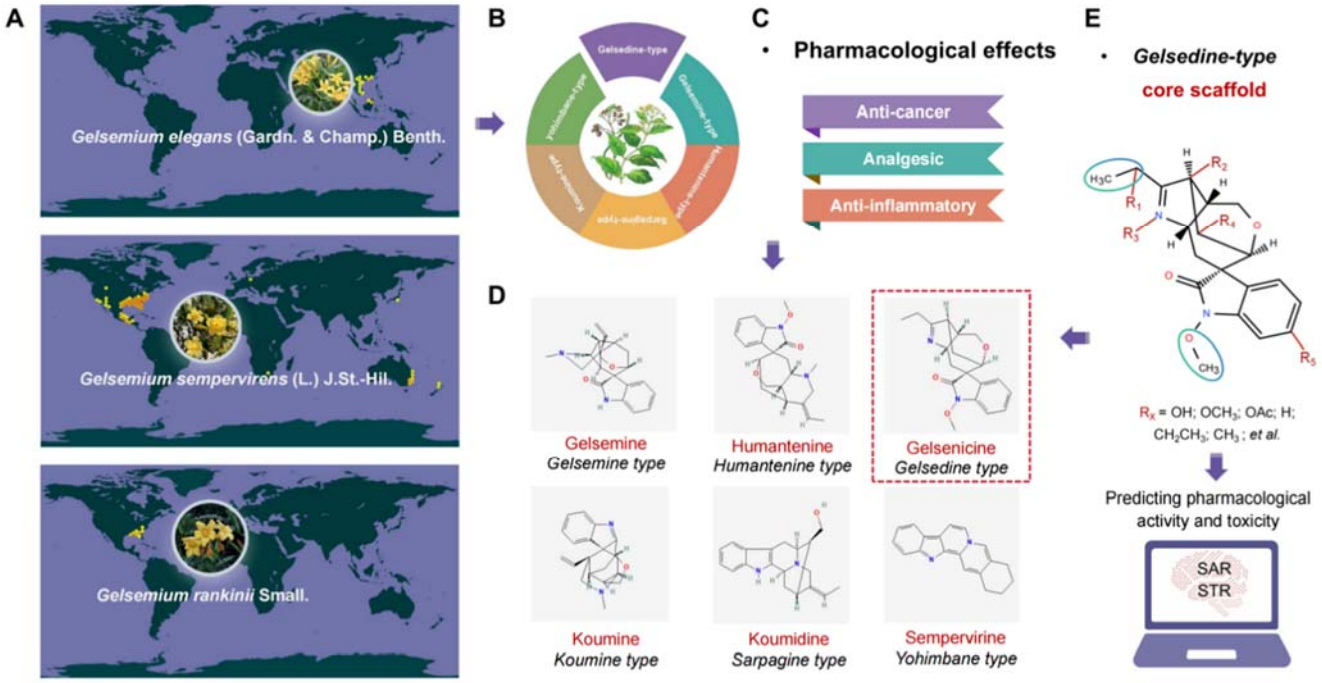
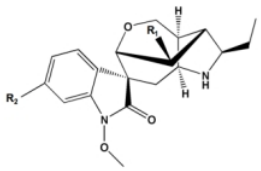
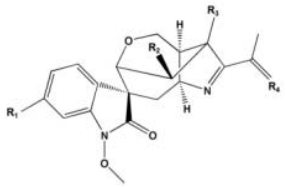
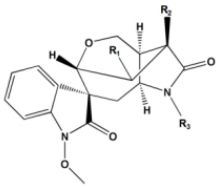
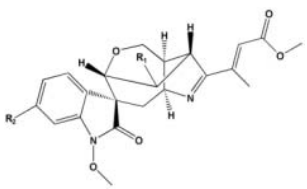
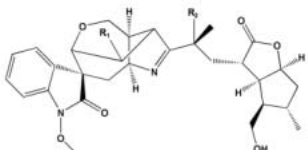
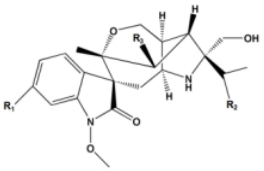
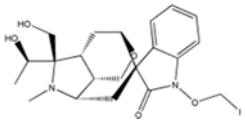
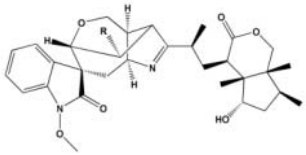
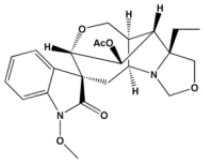
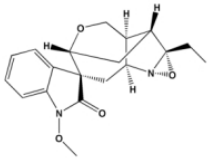
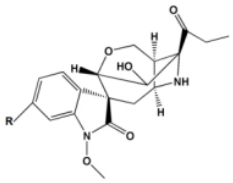
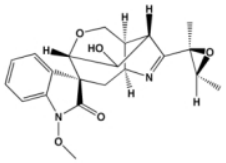
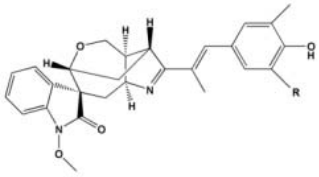
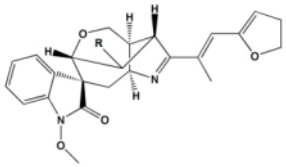
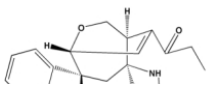
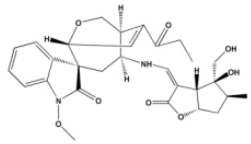
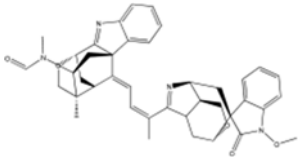
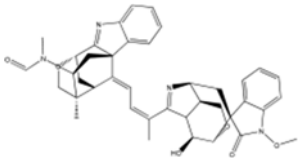
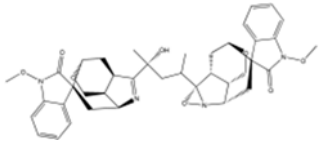
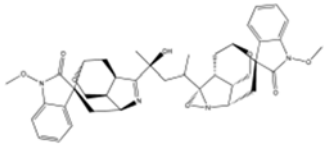
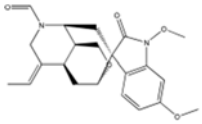
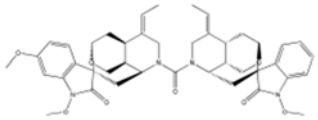


Fig. 2 Overview of *Gelsemium* species, its geographical distribution, and key bioactive ingredients. (A) Geographical distribution of *Gelsemium* species (data from the Global Biodiversity Information Facility). (B) Classification of major bioactive ingredients and their traditional medicinal applications. (C) Pharmacological properties of gelsenicine. (D) Representative members of different classifications of *Gelsemium* alkaloids in *G. elegans*. (E) Gelsedine-type core scaffold and potential substituent positions. Abbreviations: *Gelsemium elegans* Benth., *G. elegans*; STR, structure-toxicity relationship; SAR, structure-activity relationship. Images were sourced from https://www.iplant.cn/ and https://www.gbif.org/.

Table 1 Representative Gelsedine-type alkaloids and their structural characteristics[18, 26].

Compound	Substituent Configuration	Chemical Structure	Molecular Formula	Molecular Weight (g/mol)	PubChem CID
14β-Hydroxygelsedine	R_1=OH, R_2=H		$C_{19}H_{24}N_2O_4$	344.4	126023
14-Hydroxygelsemicine	R_1=OH, R_2=OCH_3		$C_{20}H_{26}N_2O_5$	374.4	597741
Gelsedine	R_1=H, R_2=H		$C_{19}H_{24}N_2O_3$	328.4	21589070
Gelsemicine	R_1=H, R_2=OCH_3		$C_{20}H_{26}N_2O_4$	358.4	5462428
Gelsenicine	R_1=H, R_2=H, R_3=H, R_4=H_2		$C_{19}H_{22}N_2O_3$	326.4	21123652
Gelegamine D	R_1=OCH_3, R_2=H, R_3=H, R_4=H_2		$C_{20}H_{24}N_2O_4$	356.4	101467880
Gelegamine E	R_1=OCH_3, R_2=H, R_3=H, R_4=O		$C_{20}H_{22}N_2O_5$	370.4	101467881
GS-1	R_1=OCH_3, R_2=OH, R_3=H, R_4=O		$C_{20}H_{22}N_2O_6$	386.4	12070887
11-Hydroxygelsenicine	R_1=OH, R_2=H, R_3=H, R_4=H_2		$C_{19}H_{22}N_2O_4$	342.4	102481549
11,14-Dihydroxygelsenicine	R_1=OH, R_2=OH, R_3=H, R_4=H_2		$C_{19}H_{22}N_2O_5$	358.4	101727430
Humantenidine/14-Hydroxygelsenicine	R_1=H, R_2=OH, R_3=H, R_4=H_2		$C_{19}H_{22}N_2O_4$	342.4	14217347
14-Acetoxygelsenicine	R_1=H, R_2=OAc, R_3=H, R_4=H_2		$C_{21}H_{24}N_2O_5$	384.4	11962104
14,15-Dihydroxygelsenicine	R_1=H, R_2=OH, R_3=OH, R_4=H_2		$C_{19}H_{22}N_2O_5$	358.4	44583829
14-Acetoxy-15-hydroxygelsenicine	R_1=H, R_2=OAc, R_3=OH, R_4=H_2		$C_{21}H_{24}N_2O_6$	400.4	177534303
Gelsedilam	R_1=H, R_2=H, R_3=H		$C_{17}H_{18}N_2O_4$	314.34	102254466
14-Hydroxygelsedilam	R_1=OH, R_2=H, R_3=H		$C_{17}H_{18}N_2O_5$	330.33	177571190
Gelsecrotonidine	R_1=H, R_2=H		$C_{22}H_{24}N_2O_5$	396.4	101449927
14-Hydroxygelsecrotonidine	R_1=OH, R_2=H		$C_{22}H_{24}N_2O_6$	412.4	177574141
11-Methoxygelsecrotonidine	R_1=H, R_2=CH_3		$C_{23}H_{26}N_2O_6$	426.5	101449930
Gelsamydine	R_1=H, R_2=H		$C_{29}H_{36}N_2O_6$	508.6	5317540
14α-Hydroxygelsamydine	R_1=OH, R_2=H		$C_{29}H_{36}N_2O_7$	524.6	44559138

19α-Hydroxygelsamydine	R_1=H, R_2=OH		$C_{29}H_{36}N_2O_7$	524.6	102003053
Gelselegine	R_1=H, R_2=H, R_3=H		$C_{21}H_{28}N_2O_4$	372.5	102061673
11-Methoxy-19-(R)-hydroxygelselegine	R_1=OCH_3, R_2=OH, R_3=H		$C_{21}H_{28}N_2O_6$	404.5	11090753
14-hydroxygelselegine	R_1=H, R_2=CH_3, R_3=OH		$C_{21}H_{28}N_2O_5$	388.5	102225867
14-Acetoxygelselegine	R_1=H, R_2=H, R_3=OAc		$C_{23}H_{30}N_2O_6$	430.5	101727431
Gelegamine C			$C_{21}H_{27}IN_2O5$	514.4	101467879
Elegansamine	R=H		$C_{29}H_{36}N_2O_6$	508.6	5317023
14α-Hydroxyelegansamine	R=OH		$C_{29}H_{36}N_2O_7$	524.6	44559137
Gelseoxazolidinine			$C_{23}H_{28}N_2O_6$	428.5	163031783
Gelseziridine			$C_{19}H_{22}N_2O_4$	342.4	101951238
Gelsemoxonine	R=H		$C_{19}H_{22}N_2O_5$	358.4	44583831
GS-3	R=OCH_3		$C_{20}H_{24}N_2O_6$	388.4	101751032
Gelselenidine			$C_{21}H_{24}N_2O_4$	368.4	101951237
Gelsesyringalidine	R=OCH_3		$C_{28}H_{30}N_2O_6$	490.5	136704418
Gelsevanillidine	R=H		$C_{27}H_{28}N_2O_5$	460.5	136811988
Gelsefuranidine	R=OH		$C_{24}H_{24}N_2O_5$	420.5	163192872
14-Dehydroxygelsefuranidine	R=H		$C_{24}H_{24}N_2O_4$	404.5	102417029
Gelsemolenine A	R=CH_3		$C_{21}H_{24}N_2O_5$	384.4	101951239

Gelsemolenine B	R=H		$C_{20}H_{22}N_2O_5$	370.4	101951240
Gelseiridone			$C_{29}H_{34}N_2O_8$	538.6	177548947
Gelsekoumidines A			$C_{40}H_{42}N_4O_5$	658.8	177588792
Gelsekoumidines B			$C_{40}H_{42}N_4O_6$	674.8	177465825
Geleganimine A			$C_{39}H_{44}N_4O_8$	696.8	102131190
Geleganimine B			$C_{39}H_{44}N_4O_8$	696.8	102131191
Geleganidine A			$C_{22}H_{26}N_2O_5$	398.5	122183789
Geleganidine C			$C_{42}H_{48}N_4O_8$	736.9	122183791

3.3 Physicochemical properties and Synthesis

The physicochemical properties of gelsenicine have been systematically characterized to better understand its chemical behavior and persistence in food matrices, which is critical for detection and risk assessment. Gelsenicine ($C_{19}H_{22}N_2O_3$) is an off-white to light yellow solid powder. It has a molecular weight of 326.39 Da and a flash point of 234.2 ± 31.5 °C. The compound is practically insoluble in water but dissolves readily in organic solvents such as methanol, ethanol, dimethyl sulfoxide, and chloroform. These properties reflect its low polarity, a typical feature of many indole alkaloids. Its density is 1.44 g/cm³. To ensure chemical stability, gelsenicine should be stored at low temperatures and protected from light during transportation and storage. Total synthesis of gelsenicine has been explored to overcome the limitations of natural extraction, thereby enabling reliable access for toxicological studies, analytical standard development, and mechanistic investigations related to food safety. Two representative total synthetic routes are summarized in Fig. 3. On the left side of Fig. 3, the efficient total synthesis reported by Eric M. Ferreira et al. (2016) constructs the bridged bicyclic core via a metal-catalyzed cycloisomerization followed by a Cope rearrangement, successfully achieving gelsenicine through a multistep sequence [30]. On the right side of Fig.

3, a divergent synthetic strategy for Gelsedine-type alkaloids developed by Dawei Ma and co-workers in 2018 is presented, which provides a versatile platform for systematic pharmacological and toxicological studies [25]. Final-stage functionalization, including α-acylation and selective reduction, enables access to multiple natural products, such as (–)-gelsenicine, (–)-gelsedine, and (–)-gelsemoxonine. This divergent approach allows efficient construction of complex polycyclic frameworks from common intermediates, facilitating the synthesis of structurally related analogues. Collectively, these advances provide a solid foundation for elucidating structure–function and structure–toxicity relationships, thereby supporting food safety risk assessment and the development of potential mitigation strategies for gelsenicine exposure.

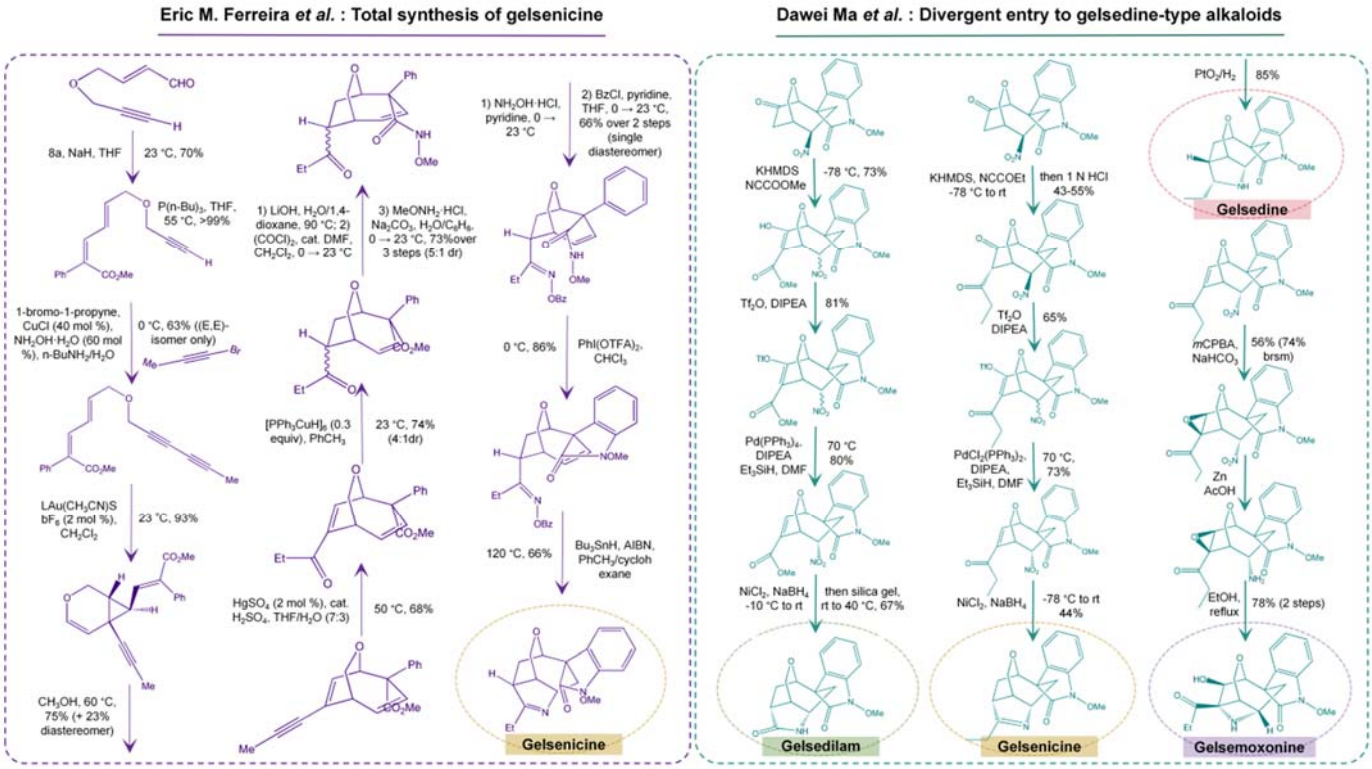


Fig. 3 Schematic representation of representative synthetic pathways for gelsenicine and Gelsedine-type alkaloids [25, 30].

4. Pharmacological activities

The traditional use of *G. elegans* in Chinese medicine highlights both its medicinal potential and its significant toxicological risk. While gelsenicine is best known for its neurotoxicity and role in poisoning incidents, accumulating evidence shows that it also possesses pharmacological activities, including analgesic, anti-inflammatory, and anticancer effects [31, 32]. Understanding these dual properties is critical for evaluating the benefit–risk profile of gelsenicine, particularly in the context of food safety and natural toxin exposure. Historical records indicate that *G. elegans* was primarily used for external applications, such as treating scabies, eczema, abscesses, and traumatic injuries, reflecting long-standing awareness of its high systemic toxicity [4, 18, 33]. Modern studies have further elucidated its mechanisms of action, revealing that the pharmacological effects of gelsenicine and related alkaloids partially overlap with pathways involved in their neurotoxic actions [12]. This duality underscores the importance of considering both therapeutic potential and toxicological hazards, and it motivates a systematic and cautious evaluation of gelsenicine's

pharmacology in parallel with its toxicity. To provide a structured overview of reported pharmacological studies, Table S1 summarizes available experimental evidence on gelsenicine and gelsenicine-containing *Gelsemium* alkaloids, including experimental models, dosing regimens, methodologies, key findings, and proposed mechanisms reported in the literature.

4.1 Analgesia

Gelsenicine exhibits significant, dose-dependent analgesic activity in both inflammatory and neuropathic pain models, with a non-addictive profile [3, 18, 34]. As summarized in Table S1, these effects have been consistently observed across different experimental pain models at doses below the LD_{50}. Mechanistically, gelsenicine alleviates inflammatory pain primarily through peripheral anti-inflammatory actions. Its effects on neuropathic pain may involve modulation of neuroinflammatory responses, inhibition of TNF-α, and promotion of neural repair [6, 35]. Based on these experimental findings, gelsenicine is proposed to act via molecular targets and signaling pathways distinct from conventional analgesics. This mechanism may confer advantages in overcoming tolerance and addiction, highlighting its potential as a novel candidate for the treatment of chronic pain, including inflammatory, neuropathic, and cancer-related pain. Notably, the estimated human equivalent doses, calculated using body surface area conversion, are lower than the alkaloid content reported in some traditional *G. elegans* preparations. This further underscores its potential for clinical development. Nevertheless, its narrow therapeutic window necessitates further mechanistic studies and rigorous safety evaluation before clinical application. Given that chronic pain often co-occurs with cancer, the anticancer potential of gelsenicine further enhances its pharmacological significance and warrants detailed investigation in tumor-related models.

4.2 Anti-cancer

Multiple alkaloids isolated from *G. elegans* have been shown to inhibit the proliferation of various tumor cell lines and induce apoptosis, demonstrating broad anticancer potential [14, 17, 36]. Among them, gelsenicine exhibits potent cytotoxicity against human epidermoid carcinoma A431 cells [37]. Studies focusing on liver cancer further demonstrate that *Gelsemium* alkaloids, particularly gelsenicine, suppress HepG2 cell proliferation by inducing S phase cell cycle arrest, promoting apoptosis, and activating the caspase-8/9-3 signaling cascade [38]. These representative in vitro findings, together with the corresponding experimental models and effective concentration ranges, are summarized in Table S1. Collectively, these results suggest that gelsenicine and other *Gelsemium* alkaloids possess measurable anticancer activity. However, their pronounced toxicity emphasizes the need for strict dose control and further research to clarify their mechanisms of action and potential applications. Moreover, given the well-established role of inflammation in cancer progression, the anti-inflammatory properties of *Gelsemium* alkaloids may further contribute to their pharmacological profile and provide a rationale for exploring these effects in subsequent research.

4.3 Anti-inflammatory

Several alkaloids from *G. elegans*, particularly koumine, display significant anti-inflammatory activity in diseases such as rheumatoid arthritis and inflammatory bowel disease, mainly by modulating immune responses and reducing inflammatory damage [19, 39, 40, 41]. For instance, studies by Yarong Lin et al. have shown that koumine can regulate macrophage polarization through the PI3K/AKT signaling pathway, which may be a key mechanism underlying its anti-rheumatoid arthritis effects [42]. Additionally, research by Ming Liu et al. confirmed that gelsenicine also has anti-inflammatory activity. In classic models of inflammatory pain, its efficacy is comparable to that of aspirin, yet at much lower effective doses, highlighting its high development potential and positioning it as a promising candidate for the treatment of inflammatory pain conditions such as rheumatoid arthritis [3]. Overall, the anti-inflammatory effects of gelsenicine should be studied further, as they may offer insights for treating autoimmune and chronic inflammatory diseases. Nevertheless, its high toxicity and narrow therapeutic window require careful evaluation before any practical or clinical use.

4.4 Other pharmacological effects

In addition to the pharmacological activities mentioned above, *G. elegans* and its alkaloids have also been reported to exhibit anxiolytic, immunomodulatory, neuroprotective, antiarrhythmic, and wound-healing effects [43, 44]. Traditional literature further records their topical use for treating abscesses, mastitis, wounds, ulcers, leprosy, and psoriasis. Regarding anxiolytic effects, both *in vivo* and *in vitro* studies indicate that several alkaloids, particularly koumine and gelsemine, exhibit significant anxiolytic activity through multiple targets and pathways, with a relatively wide safety margin. This suggests that these compounds could be developed as non-addictive anxiolytics [35, 45]. For gelsenicine, mechanistic and pharmacological studies remain relatively limited. Nevertheless, available experimental evidence from studies involving gelsenicine itself or gelsenicine-containing *Gelsemium* alkaloid extracts has been compiled as comprehensively as possible in Table S1. Overall, while gelsenicine is associated with multiple pharmacological effects, its narrow therapeutic window and pronounced neurotoxicity present major challenges for clinical translation. Future studies should combine molecular target identification, structural optimization, pharmacokinetic profiling, and careful toxicity assessment to evaluate whether safe therapeutic application is feasible.

From a translational perspective, it is noteworthy that among *Gelsemium* alkaloids, differential progress toward clinical application has been reported. Koumine, the main alkaloid in *G. elegans*, has shown more advanced translational potential. Its hydrochloride salt has been approved by the National Medical Products Administration of China to enter clinical trials as a Category 1 chemical drug (approval numbers 2023LP02123 and 2023LP02124), mainly for indications such as rheumatoid arthritis and neuropathic pain. In contrast, although gelsenicine has shown a variety of pharmacological activities in experimental models, it has not yet entered clinical trials. Research on gelsenicine remains focused on pharmacological characterization and mechanistic studies. Therefore, its activities should be considered as exploratory rather than an indicator of established clinical utility.

Table S1 Pharmacological studies of gelsenicine and gelsenicine-containing *Gelsemium* alkaloid extracts.

Pharmacological activity	Experimental model	Administration route	Dosage	Methodology	Key findings	Mechanism	Reference
Analgesia	PGE_2-induced mouse hyperalgesia	i.p.	**20 μg/kg**	Hot plate test; Western blot; HE staining; Antagonist validation	1. Significant increase in pain threshold, stronger analgesia than gelsemine and koumine. 2. Analgesia is strychnine-sensitive, mediated by GlyRa3 and Gephyrin upregulation.	Upregulation of GlyRa3 and Gephyrin activates glycine receptor pathway, reversing PGE_2-induced inhibition.	[35]
Analgesia	Neuropathic and inflammatory pain models	s.c.	0.8, 4, 20 μg/kg	**Acetic acid writhing test; Formalin test; CCI-induced hyperalgesia model**	1. Dose-dependent analgesia in all models. 2. Inhibition of second phase pain in formalin test (peripheral action). 3. Sustained analgesia post-withdrawal in CCI model.	Peripheral anti-inflammatory action, likely through suppression of inflammation and nerve repair.	[3]
Analgesia	Swiss albino mice	i.p.	1.0, 2.5 mg/kg	Formalin-induced pain tests (early/late phase)	1. Inhibited acetic acid-induced writhing. 2. No effect on thermal pain. 3. Stronger effects on late-phase pain in formalin test.	**Peripheral analgesic mechanism effective against chemical and late-phase pain.**	[46]
Analgesia	Chronic sciatic nerve compression injury (CCI) in rats	i.p. (daily for 9 days)	**0.28, 1.4, 7.0 mg/kg**	Thermal and mechanical hyperalgesia tests; Western blot	Dose- and time-dependent relief of hyperalgesia. 2. 7.0 mg/kg achieved optimal analgesia by day 10.	Modulates EGFR and JAK1 expression, reducing neuropathic pain.	[47]
Anti-cancer	BALB/c nude mouse subcutaneous xenograft tumor model (HCT116 cells)	i.p.	2 mg/kg (every 2 days for 3 weeks)	Network pharmacology, RNA-Seq, *in vitro* and *in vivo* validation	1. Induced dose-dependent apoptosis in HCT116/HT29 cells. 2. Reduced glucose uptake and ATP production.	Targets PDK1, inhibits Akt/mTOR/HK2 pathway, suppresses glycolysis, and induces apoptosis.	[14]
Anti-cancer	Human colon cancer cell line (HCT116)	Directly added to cell culture	Add 400 μM stock solution to culture medium for 48 hours	High-throughput sequencing, bioinformatics, molecular docking	Altered expression of 1,401 genes; affected pathways like tight junctions and actin regulation. 2. Reduced expression of m6A regulators.	Disrupts RNA m6A methylation, affecting gene expression and intestinal barrier function.	[36]
Anti-cancer	HepG2 liver cancer cells	Directly added to culture medium	100, 200, 400 μg/mL	MTT assay, flow cytometry, caspase activity assay	1. Inhibited cell proliferation in dose- and time-dependent manner. 2. Induced apoptosis.	Blocks cell cycle at S phase, activates caspase apoptosis pathway.	[38]
Anti-inflammatory	**Rat ear edema model**	Topical application	2.5 mg/ear	Ear thickness measurement at time points	Significant inhibition of edema, similar to betamethasone.	Peripheral anti-inflammatory effect.	[46]

Anti-inflammatory	Inflammatory pain model	s.c.	**0.8, 4, 20 μg/kg**	Acetic acid writhing, Formalin test, CCI model	Inhibited writhing in acetic acid model. 2. Inhibited second phase pain in formalin test.	Peripheral action through neuroinflammation regulation and nerve repair.	[3]
Anti-inflammatory	*In vitro* LPS-induced RAW 264.7 macrophages; *In vivo* zebrafish model	In vitro: Added to cell culture; In vivo: Exposed to water	*In vitro*: 1.25-50 μM; *In vivo*: 25 μM	Cytokine detection (ELISA); Neutrophil count (fluorescence); Macrophage observation	Inhibited TNF-α and IL-6 secretion. 2. Reduced neutrophil recruitment in zebrafish.	Inhibits neutrophil/macrophage recruitment, modulates inflammatory signaling.	[40]
Other pharmacological effects	Rabbit ($BaCl_2$ model); Mouse ($CHCl_3$ model)	Rabbit: i.v.; Mouse: i.p.	**Rabbit: 0.5 mg/kg; Mouse: 0.2 mg/kg**	Arrhythmia experiments (Rabbit and Mouse models)	Effective in counteracting arrhythmias.	Reduces phase 4 automatic depolarization in Purkinje fibers, inhibiting abnormal automaticity.	[44]
Other pharmacological effects	**Mouse chemotherapy-induced bone marrow suppression model; radiation-induced bone marrow injury model**	i.p., day 2 onwards, daily for 10 days	**1, 2, 3 mg/kg/d**	Blood profile, survival rate, stem cell function tests	Improved blood cell counts and survival. 2. Protected hematopoietic stem cells.	Promotes stem/progenitor cell proliferation and differentiation, counteracting myelotoxicity.	[48]
Other pharmacological effects	**NIH mouse**	i.m.	1.2–2.7 mg/kg (Analgesia); 1.3–2.4 mg/kg (Sedation)	Writhing test, hot plate, sleep test	**1. Inhibited writhing and enhanced heat pain threshold. 2. Enhanced sleep rate and inhibited spontaneous activity.**	Inhibits central nervous system transmission, enhancing pain inhibition and sedation.	[49]

*i.p., intraperitoneal injection; i.v., intravenous injection; i.m., intramuscular injection; s.c., subcutaneous injection.

5. Pharmacokinetic characteristics

Pharmacokinetics describes the ADME of compounds and is fundamental for understanding their biological effects. For gelsenicine, pharmacokinetic information is important for evaluating its behavior in the body, especially in the context of accidental oral exposure and food safety risk [50]. Several studies, including animal experiments and *in vitro* investigations, have provided insights into its ADME, although data remain somewhat limited [51]. These studies form the basis for summarizing gelsenicine's pharmacokinetic characteristics, which is essential for guiding toxicity assessment, risk management, and future research on potential mitigation strategies.

5.1 Extraction, separation and detection methods

The pharmacokinetic and toxicological investigation of gelsenicine critically depends on sensitive and reliable analytical methods suitable for diverse sample matrices. High-performance chromatographic and

mass spectrometric techniques have been widely applied to detect *Gelsemium* alkaloids in biological and plant-derived samples, establishing a robust methodological foundation for related research [52].

Extraction strategies are tailored to sample types. For biological matrices such as plasma or tissues, protein precipitation and liquid–liquid extraction are commonly employed. Plasma is often treated with acidified acetonitrile–methanol mixtures or extracted with dichloromethane to enrich and purify alkaloids [53, 54]. For plant materials, ultrasound- or microwave-assisted extraction is frequently used due to its efficiency and rapidity, significantly improving alkaloid recovery [55]. Separation aims to resolve multiple structurally similar alkaloids in complex matrices. Reverse-phase liquid chromatography with C_{18} columns and optimized gradient elution is standard [53, 54]. For more challenging matrices, two-dimensional liquid chromatography, combining ion-exchange and reverse-phase mechanisms, removes interferences online, enhancing selectivity and peak resolution for high-throughput applications [56].

Detection and quantification primarily rely on LC–MS/MS using positive-mode electrospray ionization and multiple reaction monitoring. This approach enables simultaneous ultra-trace measurement of multiple alkaloids with wide linear ranges, high specificity, and low detection limits (ng/mL to pg/mL) [53, 57]. These methods have been successfully applied to pharmacokinetics, absolute bioavailability, forensic toxicology, and comparative analysis of alkaloid content in different plant parts, providing essential data for evaluating *G. elegans* bioactivity and safety [54, 55]. Importantly, these sensitive analytical techniques also support food safety by enabling the monitoring of gelsenicine residues, assessing potential foodborne risks, and informing regulatory and preventive measures.

5.2 ADME Studies

The pharmacokinetic characteristics of gelsenicine have been extensively investigated in animal models and are summarized in Fig. 4. After oral administration, gelsenicine is rapidly absorbed from the gastrointestinal tract but exhibits low oral bioavailability, with peak plasma concentrations reached within a few minutes. Intravenous administration results in higher systemic exposure [54]. Gelsenicine primarily distributes to peripheral tissues, with the highest concentrations observed in the intestine, stomach, liver, and pancreas, while renal and fecal excretion remain minimal, indicating that the liver and pancreas serve as major peripheral target organs [58]. In the central nervous system (CNS), gelsenicine can efficiently cross the blood–brain barrier (BBB) due to its high lipophilicity. Peak concentrations in the CNS occur rapidly, within approximately 15 minutes, followed by a fast decline. Its CNS distribution is heterogeneous, with higher levels in the spinal cord, brainstem, hippocampus, and striatum compared to the cerebral cortex and cerebellum. Overall metabolism and clearance are completed within approximately 24 hours, with no detectable metabolites in the brain [12, 59, 60]. Metabolic studies confirm that gelsenicine undergoes rapid hepatic and intestinal metabolism, primarily via demethylation, hydroxylation, and conjugation reactions, with cytochrome P450 (CYP) enzymes, particularly CYP3A4 and CYP3A5, playing key roles. Table S2 compiles key pharmacokinetic parameters of gelsenicine reported in the literature, presenting detailed information on doses, routes of administration, and animal models across individual studies, thereby

providing quantitative support for Fig. 4. These ADME characteristics indicate that gelsenicine toxicity is driven by rapid CNS exposure combined with substantial hepatic metabolic burden, supporting its high acute toxicity following oral intake. Collectively, these data provide a mechanistic foundation for evaluating food safety risks and supporting forensic interpretation of *G. elegans* poisoning.

Table S2 Summary of reported pharmacokinetic parameters of gelsenicine from *in vivo* studies.

Dosage (mg/kg)	Administration Route	Animal Model	C_{max} (ng/mL or ng/g)	T_{max} (min)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	Vd (L/kg)	CL (L/h/kg)	Reference
0.1	i.v.	ICR mice	23.20 ± 6.35	~5 min	1.03 ± 0.42	16.64 ± 3.01	9.1 ± 4.6	6.2 ± 1.25	[52]
0.5	i.g.	ICR mice	1.08 ± 0.23	~30-60	1.72 ± 0.59	0.93 ± 0.15	1409.0 ± 602.3	561.6 ± 138.8	
1.0	i.g.	ICR mice	2.17 ± 0.83	~30-60	2.35 ± 1.03	2.09 ± 0.62	1849.0 ± 1167.2	508.7 ± 126.0	
0.04	i.p.	SD rat	4.28 ± 0.88	0.11 ± 0.07	2.30 ± 1.77	3.79 ± 1.58	38.47 ± 30.75	11.87 ± 4.03	[12]
0.06	i.g.	SD rat	3.97 ± 1.50	0.30 ± 0.07	2.95 ± 0.58	5.49 ± 2.62	53.10 ± 21.04	12.66 ± 4.65	
1000 (*G. elegans* extract)	i.g.	L×LW pig	104.82 ± 28.68	29.4 ± 25.8	11.15 ± 7.40	512.51 ± 123.76	-	-	[61]
100 (*G. elegans* extract)	i.g.	SD rat	8.97 ± 3.90	16.2 ± 10.2	5.09 ± 4.38	8.59 ± 5.46	-	-	
0.2	i.g.	SD rat	**9.29 ± 2.17**	**12.50 ± 2.74**	**1.37 ± 0.59**	**6.46 ± 1.11**	-	-	[54]
0.02	i.v. (tail vein)	SD rat	-	-	**1.10 ± 0.42**	**8.43 ± 1.10**	**0.633 ± 0.009**	0.79 ± 0.11	

***** i.g., intragastric administration; i.v. (tail vein), Intravenous injection (tail vein).

5.3 Inter-species differences

The pharmacokinetic characteristics of gelsenicine are influenced by its physicochemical properties, formulation, and individual genetic polymorphisms, with metabolic enzymes and transporters playing central roles in this process [62]. These factors vary across species, markedly affecting bioavailability, metabolic pathways, and toxicological outcomes. For instance, gelsenicine exhibits high toxicity in humans and mice, whereas it is non-toxic in pigs and goats, and may even promote growth and development in these species. Comparative analyses of gelsenicine metabolism across four species indicate that liver microsomal degradation occurs more rapidly in pigs and goats than in rats and humans. This is accompanied by increased levels of the demethylated metabolite M1, suggesting that demethylation is a primary detoxification pathway (Fig. 4) [63]. Gelsenicine is predominantly metabolized by CYP450 enzymes, especially CYP3A4 and CYP3A5. These enzymes are widely expressed in the liver, kidneys, gastrointestinal tract, lungs, and brain, mediating the majority of xenobiotic biotransformations and promoting excretion by increasing compound polarity and solubility [64, 65, 66]. Species-specific differences in CYP isoforms likely underlie interspecies variation in gelsenicine toxicity[67]. Overall, the toxicity of natural products is influenced not only by the

parent compound but also by metabolites formed during biotransformation [1, 63]. Clarifying these metabolic pathways is essential for understanding the mechanisms of toxicity and for establishing accurate analytical criteria for forensic identification. Collectively, these pharmacokinetic and metabolic characteristics highlight the potential hazards of gelsenicine in foodborne exposure scenarios and emphasize the need for systematic characterization of its metabolism to support accurate food safety evaluation and toxicological risk assessment.

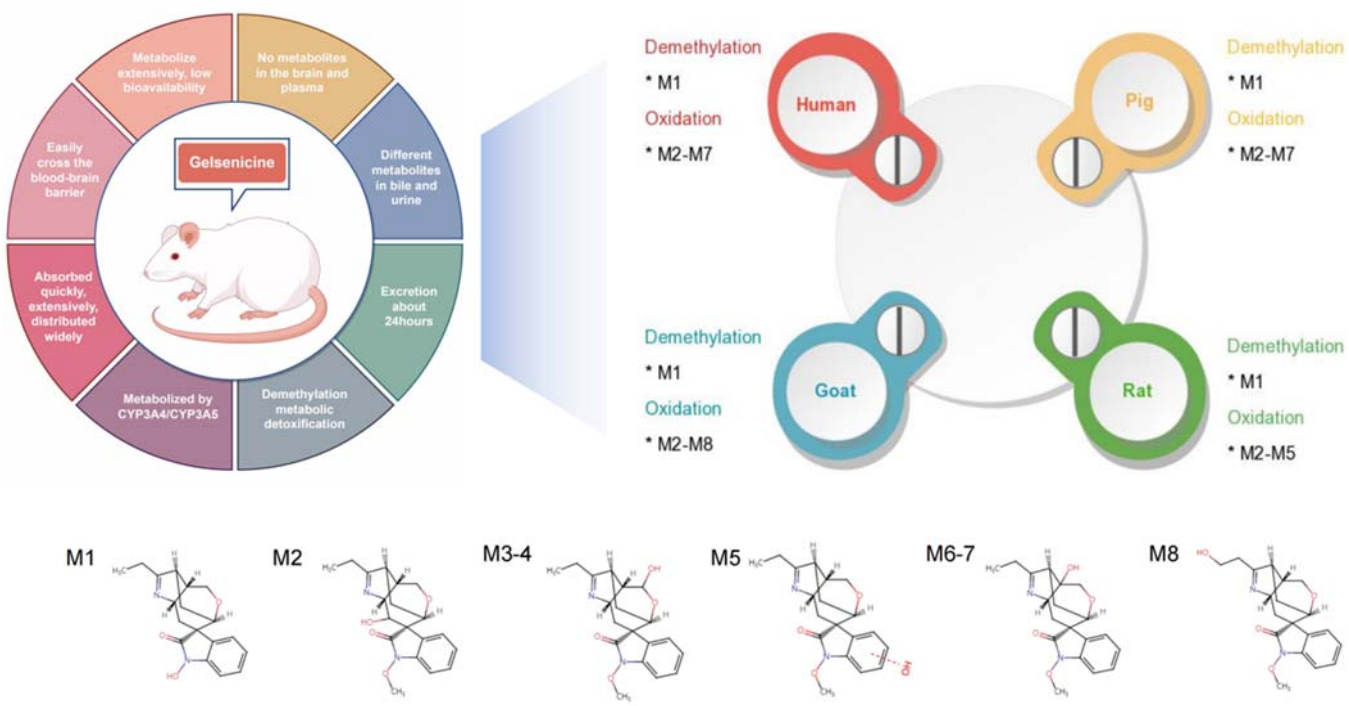


Fig. 4 Pharmacokinetic profile of gelsenicine in rats and comparative metabolism in liver microsomes from human, pig, goat, and rat. Differences among species are relevant for understanding toxicity and potential foodborne risk. Created with Figdraw.

6. Toxicological profile

To comprehensively characterize the toxicological attributes of gelsenicine within the context of food safety and public health, we synthesized current evidence on exposure pathways, reported poisoning incidents, clinical manifestations, and mechanistic toxicology. Available data show that gelsenicine can elicit rapid-onset, multi-system toxicity following inadvertent ingestion or foodborne exposure, driven by gelsenicine's high intrinsic potency, rapid absorption, efficient CNS penetration, and species-specific metabolic behavior. Drawing on these findings, this section integrates existing knowledge to delineate the toxic manifestations, underlying molecular mechanisms, and their implications for risk assessment and toxicity mitigation.

6.1 Foodborne exposure

Poisoning from *G. elegans* occurs relatively frequently and represents a notable public health concern. Human exposure arises through multiple pathways, including accidental ingestion, misidentified herbal preparations, contaminated food, honey produced by bees foraging on the plant, and, in some cases, intentional intake or suicide. Different parts of *G. elegans* closely resemble several commonly used medicinal

plants species, increasing the risk of accidental consumption (Fig. 5) (http://www.iplant.cn/, https://www.gbif.org/). Specifically, the flowers may be mistaken for *Lonicera japonica* Thunb. or *Polygala fallax* Hemsl., while the roots and vine-like middle stems resemble *Spatholobus suberectus* Dunn, *Ficus hirta* Vahl, or occasionally *Piper kadsura* (Choisy) Ohwi. Such confusion can occur during traditional herbal collection, in commercial herbal products, or in domestic culinary practices such as soups or teas. Bee products, particularly honey, can also serve as an indirect route of human exposure when colonies collect nectar or pollen from *G. elegans*. In addition, livestock including cattle and sheep may inadvertently consume the plant while grazing, potentially leading to animal-source contamination and associated foodborne risks. Taken together, these exposure routes illustrate the multiple ways in which *G. elegans* alkaloids can enter human and animal systems. They underscore the importance of accurate plant identification, careful handling, and monitoring to minimize accidental poisoning from both dietary and medicinal sources.

Fig. 5 *G. elegans* and plant species commonly misidentified as *G. elegans* across different plant parts. Images were obtained from iPlant (https://www.iplant.cn/) and PPBC (https://ppbc.iplant.cn/).

6.2 Poisoning cases

elegans poisoning occurs with notable frequency and can result from multiple exposure pathways. Over the years, the accumulation of such cases has increasingly raised concern as a public health issue. Several representative incidents illustrate the scope and severity of these poisonings. Zhou et al. reviewed 14 *G. elegans* poisoning incidents in Hong Kong between 2005 and 2017, involving 33 cases (55% female, median age 44). The primary cause was consumption of contaminated *Ficus hirta* soup (52%), followed by herbal misidentification (12%), ingestion of *Cassytha filiformis* (15%), and suicidal intake of *G. elegans* (3%). Similar cases continue to occur in southern China. In June 2024, a family of five in Shenzhen was poisoned after mistaking *G. elegans* for *Polygala fallax Hemsl.* and using it in chicken soup. In December 2024, another case in Shaoguan involved confusion with *Spatholobus suberectus* Dunn, while in the same month an elderly

individual in Guangdong died after consuming soup made from *G. elegans* sold as *Piper kadsura (Choisy)* Ohwi. Wen et al. also described an outbreak among migrant workers who drank self-prepared herbal liquor believed to contain *Ficus hirta* Vahl roots [68]. Symptoms developed within 0.5–1 h, severity increased with alcohol intake, and three fatalities occurred. Outside China, multiple cases were reported in Vietnam in 2022, with several deaths following the mistaken consumption of wild *G. elegans* leaves and flowers. In addition to herbal misidentification, *G. elegans* is recognized as a toxic melliferous plant. Bee colonies foraging on its nectar or pollen may produce honey containing *Gelsemium* alkaloids. Zhong et al. documented five poisoning cases in Guangxi (2015–2017), two of which were attributed to honey consumption [69]. Table 2 presents representative *G. elegans* poisoning cases, including the time and location of occurrence, affected individuals, clinical manifestations, and key forensic findings. Taken together, these incidents demonstrate that *G. elegans* can induce rapid-onset, multi-system toxicity involving the digestive, nervous, circulatory, and respiratory systems [46]. The diversity of exposure pathways, coupled with the potential for group poisonings, underscores the importance of elucidating its toxicological mechanisms and implementing preventive measures.

Table 2 Representative cases of *G. elegans* poisoning.

Year	Patient characteristics	Circumstances of poisoning	Clinical manifestations	Forensic/diagnostic findings	Reference
2022	Female, 73 Male, 81	Accidental ingestion of soup herbs (*Kadsura longipedunculata*) contaminated with *G. elegans*	Dizziness, limb weakness, followed by coma	Koumine, gelsemine, and gelsenicine in hair (6–7 cm segment) were detected. Blood and liver negative due to 240-day PMI. Herbal residue confirmed as *G. elegans*.	[70]
2016	Female, 26	Suicide by ingestion of *G. elegans* decoction	Acute: deep coma, severe hypoxia, acidosis, fixed pupils; Recovery: euphoria, childish behavior, cognitive deficits, depression; MRI: bilateral globus pallidus and asymmetric hippocampi (hypoxic brain injury)	Alkaloids detected in bedside decoction; poisoning confirmed based on clinical course and toxicological analysis.	[71]
2011	Male, 53/19 Female, 54	Accidental ingestion of parasitic plant (Wu Gen Teng)	Dizziness, blurred vision, nausea, vomiting, diplopia, and nystagmus	*Gelsemium* alkaloids detected in urine and plant. Mechanism: "compensated poisoning" due to toxin accumulation in Wu Gen Teng.	[72]
2007	Female, 65 Male, 69	Misidentification as *Adonis amurensis*	Dizziness, ocular symptoms, nausea, and vomiting	*Gelsemium* alkaloids detected in urine; toxicological screening positive; consistent with clinical features.	[72]
2020	Male, 41	Medicinal wine mistakenly prepared with *G. elegans* instead of *Lonicera japonica*	Dizziness, nausea, blurred vision, convulsions, progressing to respiratory failure and death (~6 h post-ingestion)	Gelsemine and koumine were detected in blood, gastric contents, and wine. Autopsy nonspecific; botanical ID confirmed *G. elegans*.	[11]

2011	Males, aged 28–56 years (10 poisoning cases)	Medicinal wine adulterated with *G. elegans* misidentified as *Mucuna macrophylla*.	Dizziness (82%), limb weakness (82%), dyspnea (91%), coma (91%), blurred vision (73%), convulsions (64%), dysarthria (55%), ptosis (36%), diplopia (27%), vomiting (18%)	Gelsemine detected in wine and plant residues; animal tests confirmed toxicity; common toxicants negative; plant ID confirmed *G. elegans*.	[73]
2012	Female, 37	Decoction of *Cassytha filiformis* parasitizing *G. elegans*.	Vertigo, vomiting	Gelsemine and humantenmine detected in decoction and urine; DNA and botanical analysis confirmed *Cassytha filiformis*.	[74]
2007	Female, 65	Self-prepared decoction: misidentified *Mussaenda pubescens* as *G. elegans*.	Dizziness, weakness, nausea, loss of consciousness, respiratory failure	Gelsemine detected in urine; gelsenicine in plant remnants; poisoning confirmed.	[75]

6.3 Poisoning symptoms

G. elegans is an extremely toxic plant, with ingestion of only 2–3 g of root or seven fresh shoots being potentially fatal [76]. Clinical symptoms typically appear within 10–30 minutes after ingestion, rarely exceeding 1 hour, and death can occur within 4–7 hours, or even within 1 hour following a large intake [23]. Once absorbed, toxic alkaloids rapidly distribute to the liver, gastrointestinal tract, and adipose tissue [52, 63]. In animal models, poisoning develops much faster, with symptoms appearing within 5 minutes and death occurring within 15 minutes after a lethal dose, reflecting significant species differences [59]. Currently, no specific antidote exists, and treatment primarily relies on symptomatic and supportive measures, including atropine for vagus nerve inhibition, neostigmine for muscle paralysis, and blood purification techniques to remove toxins.

The clinical manifestations of *G. elegans* poisoning involve multiple organ systems, with the nervous, respiratory, circulatory, and digestive systems being most severely affected. Symptoms commonly reported include burning sensations in the mouth and throat, nausea, vomiting, abdominal pain, and either diarrhea or constipation. Neurological symptoms include dizziness, slurred speech, dysphagia, muscle weakness, respiratory muscle paralysis [77], and, in severe cases, coma [72]. Respiratory and circulatory changes include tachypnea and bradycardia in the early stages, followed by tachycardia, shallow or irregular breathing, hypotension, and hypothermia, ultimately leading to respiratory failure in severe cases [15, 20]. Characteristic early signs such as dizziness, blurred vision, ptosis, and nystagmus serve as important diagnostic indicators. Most patients recover with conservative management and timely respiratory support; however, severe cases have been reported. For example, Zhou et al. described a 26-year-old woman who developed coma, hypoxia, and acidosis following ingestion. Mechanical ventilation successfully restored consciousness, although transient memory loss, disorientation, and childish behaviors were observed. MRI revealed hypoxic injury of the hippocampus and basal ganglia, which largely resolved within 8 months [71]. Overall, these observations underscore that *G. elegans* poisoning rapidly affects multiple organ systems and highlight the critical need to further elucidate the underlying toxicological mechanisms of gelsenicine.

6.4 Toxicity and risk assessment

Gelsenicine and other *Gelsemium* alkaloids pose significant risks to food safety and public health due to their high intrinsic toxicity. The risk of poisoning depends primarily on dosage and exposure route, emphasizing the need for systematic evaluation of their acute toxic effects [78, 79]. Quantitative studies, summarized in Table 3, reveal substantial variability in LD_{50} values among the major alkaloids, reflecting differences in their toxic potency. Gelsenicine is the most toxic compound, with an intraperitoneal LD_{50} of 0.165 mg/kg in mice, which is markedly lower than that of other alkaloids, underscoring its exceptionally narrow safety margin. Other constituents, including koumine, gelsemine, humantenine, and humantenidine, exhibit higher LD_{50} values, indicating comparatively lower toxicities. The dose-dependent nature of toxicity further emphasizes the importance of risk assessment for human exposure through food or contaminated products. LD_{50} data can be translated into estimated human exposure equivalents (mg/kg body weight), offering a practical reference for food safety assessment, clinical monitoring, and forensic investigation. Overall, these findings highlight that gelsenicine's high intrinsic potency, combined with its narrow safety margin, poses serious challenges for food safety management [25]. Systematic toxicological profiling, including comparative analysis of different alkaloids and consideration of exposure routes, is essential for guiding preventive measures, establishing safe handling practices, and informing public health and forensic strategies.

Table 3 LD_{50} of alkaloids isolated from *G. elegans.*

Compounds	Animals	Routes	LD_{50}/Dose range (mg/kg)	Reference
Gelsemine	Mice	i.p.	56.2	[80]
Koumine	Mice	i.p.	99	[19]
	Mice	i.p.	0.165/0.185	[80, 81]
	Rat	i.g.	0.520 (female), 0.996 (male)	[59]
Gelsenicine	Mice	s.c.	0.1–0.2	[3]
	Mice	i.p.	0.21	[82]
	Mice	i.v.	0.128	[82]
Kouminicine	Mice	i.p.	2.83	[80]
	Rat	i.v.	0.7	[80]
Gelsemicine	Frog	i.p.	20–30	[83]
	Rat	i.p. or i.v.	0.1–0.3	[83]
	Rabbit	i.v.	0.05–0.06	[83]
	Dog	i.v.	0.05–0.10	[83]
Humantendine	Mice	i.p.	0.21	[82]
	Mice	i.v.	0.128	[82]
	Rat	i.p.	0.26	[82]
	Rat	i.v.	0.15	[82]
Gelsevirine N-oxide	Mice	i.p.	63.1	[80]

6.5 Toxicological mechanism

Current research on *Gelsemium* alkaloids has primarily focused on structural identification and pharmacological activities, whereas mechanistic studies at the monomer level remain limited. Among these compounds, gelsenicine is the most toxic constituent, making the elucidation of its toxicological pathways essential for understanding *G. elegans* poisoning [24]. Accumulating evidence consistently points to its potent neurotoxicity, with central respiratory depression identified as the leading cause of death [82, 84]. Gelsenicine

inhibits the medullary respiratory center and motor neurons within the brain and spinal cord, resulting in respiratory muscle paralysis and subsequent respiratory failure. In addition, it may influence vagal activity, thus contributing to arrhythmias [82]. Early mechanistic hypotheses proposed that gelsenicine exerts its toxicity via peripheral neuromuscular blockade at the phrenic nerve–diaphragm junction [85]. However, subsequent studies disproved this notion, demonstrating that the CNS represents the major site of toxic action [82, 84].

Recent investigations highlight the central role of neurotransmitter imbalance and excitotoxicity in gelsenicine toxicity [86]. The balance between excitatory and inhibitory neurons in the CNS is crucial for maintaining brain function [87]. Phosphoproteomic and bioinformatic analyses indicate that gelsenicine disrupts synaptic signaling, particularly within glutamatergic and GABAergic pathways [88]. Molecular docking studies confirm its binding to N-methyl-D-aspartate receptors (NMDARs), triggering NMDAR-mediated excitotoxicity. This process involves excessive Ca^{2+} influx, mitochondrial dysfunction, and neuronal apoptosis or necrosis [89, 90]. The exacerbated or prolonged activation of glutamate (Glu) receptors triggers a cascade of neurotoxic events that ultimately lead to the loss of neuronal function and cell death [91]. Gelsenicine can cross the BBB, enhance gamma-aminobutyric acid (GABA)–GABAA receptor interactions, prolong chloride channel opening, and induce hypoxia. This hypoxia further promotes Glu release and exacerbates NMDAR overactivation [92, 93, 94]. Long-term exposure disrupts pyridoxal phosphate (PLP)-dependent metabolism, impairing GABA–Glu conversion and exacerbating excitotoxic injury [95, 96, 97]. Metabolomic and neurochemical studies support these findings. Zuo Mengting et al. reported that following *G. elegans* poisoning, Glu levels in multiple brain regions increased while glycine levels decreased. Long-term oral administration in rats reduced brain pyridoxal levels, indicating impaired PLP-related enzyme activity [96, 97]. Li Yujuan et al. identified dysregulation of serotonin, dopamine, GABA, adrenaline, and glycine in the brainstem, with whole-cell patch-clamp studies showing prolonged GABAA receptor channel opening [5]. Yang Shupeng's team demonstrated that 14-(R)-hydroxy-gelsenicine, a gelsenicine analog, similarly enhances GABA receptor binding, confirming a shared neurotoxic mechanism [24]. Calcium overload may be a key mediator of gelsenicine toxicity. Sustained Ca^{2+} influx activates degradative enzymes, nitric oxide synthase, and reactive oxygen species, leading to mitochondrial dysfunction, apoptosis, and necrosis [89, 98]. Phosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) amplifies excitotoxic damage. Meanwhile, endoplasmic reticulum calcium dysregulation can activate arrhythmogenic Na^{+}/Ca^{2+} exchange currents, increasing the risk of fatal ventricular arrhythmias [98, 99, 100, 101, 102]. Zhai Jinxiao et al. reported that gelsenicine also disrupts energy metabolism, particularly the malate–aspartate shuttle, resulting in mitochondrial dysfunction. Glu plays a key role in this process, and its dysregulation not only mediates excitotoxicity but also increases energy metabolic burden, making malate, Glu, and aspartate core biomarkers of neurotoxicity [103].

Collectively, gelsenicine toxicity can be summarized in three interconnected aspects: disruption of neurotransmitter signaling and excitatory–inhibitory (E/I) balance causing CNS toxicity, direct suppression of

the medullary respiratory center leading to respiratory depression, and interference with autonomic regulation causing cardiovascular effects such as arrhythmias and circulatory collapse. Overall, gelsenicine-induced poisoning is mediated through synaptic dysfunction, neurotransmitter imbalance, excitotoxic calcium overload, and metabolic perturbation, ultimately leading to respiratory failure and systemic toxicity. These findings provide a robust framework for targeted clinical interventions and precise forensic assessment of gelsenicine poisoning. Based on current research, gelsenicine appears to exhibit a dose-dependent biphasic effect. At low doses, it may provide neuromodulatory benefits, such as analgesia. At higher doses, it can induce neurotransmitter imbalance, excitotoxic calcium overload, and metabolic disturbances, ultimately resulting in neurotoxicity. In light of these mechanistic insights, we tentatively propose the neurotoxic mechanism of gelsenicine, as illustrated in Fig. 6. Specifically, gelsenicine enhances the interaction between GABA and GABAA receptors, prolongs channel opening times, and induces cellular hypoxia. Cellular hypoxia leads to a significant increase in Glu release at the presynaptic membrane, resulting in an imbalance in the GABA/Glu neurotransmitter conversion. Excessive Glu release results in the overactivation of NMDARs, causing a large influx of calcium ions and subsequent calcium overload in neurons. This overload triggers a series of pro-death signals, including calpain activation, reactive oxygen species generation, and mitochondrial damage. These events lead to disruptions in the TCA cycle, lipid and amino acid metabolism, and overall energy metabolism, ultimately culminating in cell necrosis or apoptosis. To date, multi-omics studies have provided initial insights into gelsenicine's neurotoxicity, though systematic investigations remain limited. Integrating these data within a systems toxicology framework could offer a comprehensive understanding of its mechanisms and support clinical monitoring, risk assessment, foodborne exposure management, and forensic evaluation.

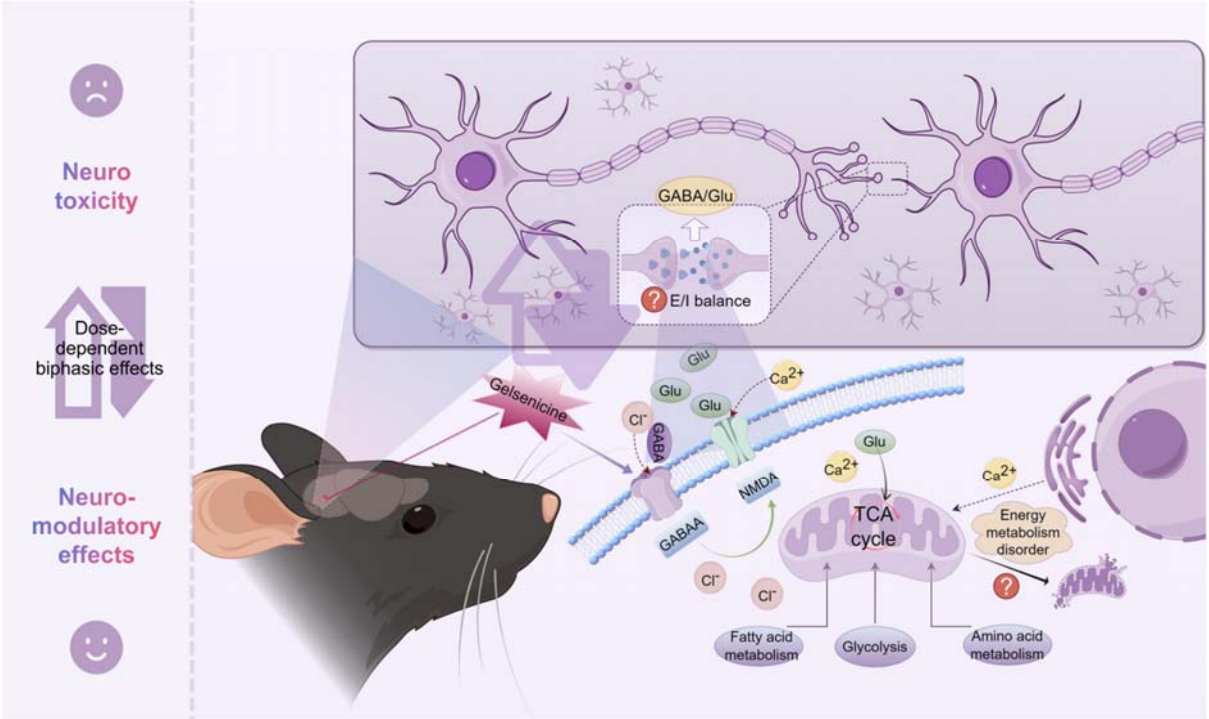


Fig. 6 Schematic representation of gelsenicine toxic mechanisms, based on reported findings and including potential hypothetical pathways. Abbreviations: E/I balance, excitation/inhibition balance; TCA cycle, tricarboxylic acid cycle. Created with Figdraw.

6.6 Possible approaches for toxicity reduction and detoxification

Natural product monomers possess diverse biological activities, yet their presence in food products may pose health risks due to the coexistence of efficacy and toxicity [104]. Systematic studies are therefore necessary to evaluate exposure, develop effective detoxification strategies, and mitigate potential foodborne risks, thereby improving consumer safety. *G. elegans* serves as a representative example, with its major toxic alkaloid gelsenicine warranting particular attention in food safety assessment.

One promising approach to reduce gelsenicine toxicity involves structural optimization and processing strategies [25]. Insights from SAR studies can guide selective modification, extraction, or processing approaches to lower toxicity while retaining bioactive properties. At the formulation level, approaches such as thermal treatment, enzymatic hydrolysis, and advanced delivery systems, including sustained-release preparations and nanocarriers, can help lower systemic exposure and peak concentrations. Another key strategy is monitoring and regulating dietary exposure. Although gelsenicine has low oral bioavailability, foods containing *G. elegans* or inadvertently contaminated ingredients may reach toxic levels, making early detection essential. Its pharmacokinetics are influenced by physicochemical properties, genetic polymorphisms, and gut microbiota. Advances in analytical techniques now enable trace-level detection, facilitating early identification of exposure and timely intervention. Gelsenicine undergoes extensive metabolism, including hydroxylation, demethylation, glucuronidation, sulfation, and methylation, and modulating these pathways may further mitigate toxicity. In addition, public education on proper plant identification and handling can reduce accidental ingestion and prevent poisoning events. Integrating structural optimization, processing and formulation strategies, pharmacokinetic insights, preventive monitoring, and educational measures provides a comprehensive framework to minimize gelsenicine toxicity and improve food safety.

Elucidating the toxic mechanisms of gelsenicine also informs risk mitigation strategies in the food chain. Experimental studies have shown that NMDA and baclofen, acting on NMDAR and GABA receptors, can regulate Glu clearance and calcium homeostasis, significantly improving survival in intoxicated mice. Similarly, flumazenil or diazepam combined with epinephrine can reverse toxicity, highlighting the relevance of mechanistic knowledge for managing accidental or foodborne exposure [59, 86, 105, 106]. From a systems toxicology perspective, modern bioinformatics-based approaches such as network toxicology, metabolomics, phosphoproteomics, and molecular docking have been applied to dissect gelsenicine-induced neurotoxicity [107, 108, 109], successfully identifying key targets [103]. This integrative strategy supports the development of multi-target detoxification approaches and early-stage biomarker systems for monitoring toxicity [86]. Incorporating machine-learning models into multi-omics analyses may further enhance target prediction, refine biomarker discovery, and accelerate the design of rational strategies to reduce foodborne risks.

Overall, integrating molecular optimization, processing and formulation strategies, dietary exposure monitoring, mechanistic studies, and multi-omics analyses provides a comprehensive framework for reducing gelsenicine toxicity (Fig. S2). This approach enhances understanding of its complex multi-target mechanisms,

supports the development of early biomarker systems, and informs risk management, food safety evaluation, and forensic investigation.

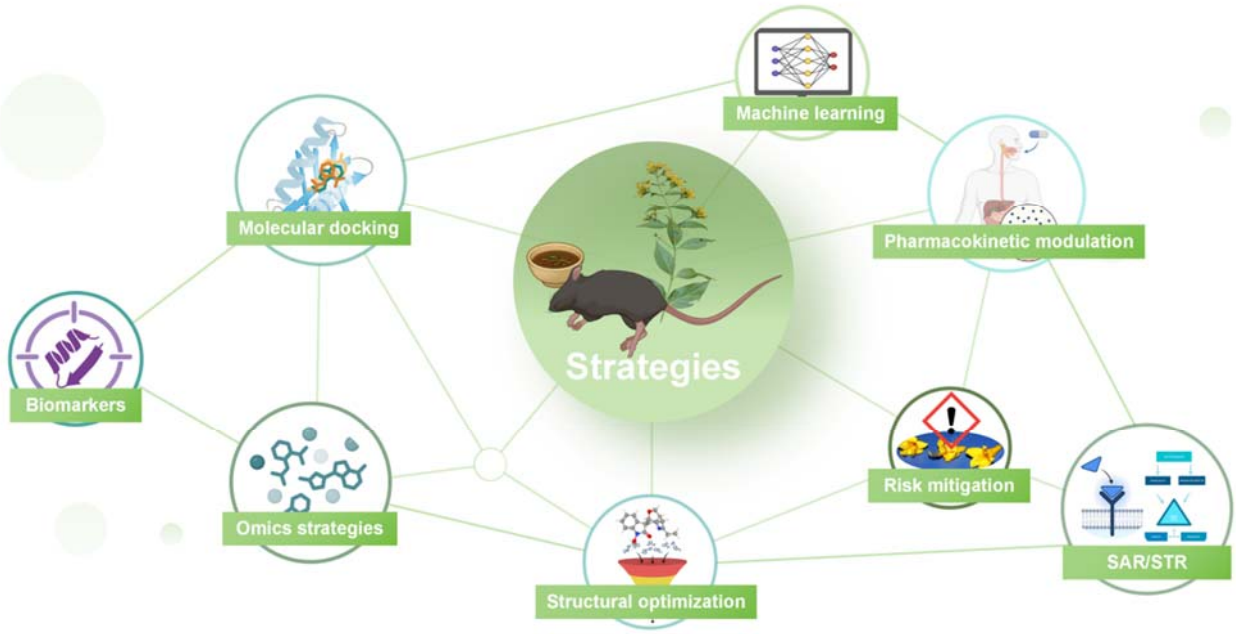


Fig. S2 Schematic illustration of integrated research strategies for gelsenicine detoxification.

7. Discussion and future perspectives

This review systematically summarizes current knowledge on gelsenicine, including its natural sources, structural features, detection methods, pharmacokinetics, and toxicology. As the most toxic alkaloid in *G. elegans*, gelsenicine poses significant health risks when present in food or herbal products. Although it exhibits diverse biological activities, its narrow therapeutic window and severe neurotoxicity make food safety a primary concern. From a food toxicology perspective, sensitive detection in both biological and food matrices is essential. LC-MS/MS remains the gold-standard method for trace-level quantification, enabling accurate risk assessment of contaminated foods and herbal preparations. Gelsenicine is rapidly absorbed, widely distributed, and exhibits low oral bioavailability, likely due to first-pass metabolism and efflux transporter activity, highlighting the need to evaluate dietary exposure, potential accumulation, and systemic toxicity. Its high lipophilicity and ability to cross the BBB further underscore the risk of central nervous system toxicity following ingestion. Metabolism predominantly occurs in the liver and small intestine, with demethylation representing a major detoxification pathway. Inter-individual variability arising from circadian rhythms, genetic polymorphisms, and gut microbiota may influence susceptibility, emphasizing the importance of personalized risk assessment in dietary exposure studies [110, 111]. Future research should prioritize strategies for toxicity mitigation in food and herbal products, including processing methods to reduce gelsenicine content, formulation adjustments to limit bioavailability, and systematic toxicokinetic studies. Integrating multi-omics approaches (metabolomics, transcriptomics, proteomics) with systems toxicology frameworks can provide insights into the toxicological pathways and facilitate the development of early warning biomarkers for foodborne gelsenicine exposure. Furthermore, identifying safe thresholds,

regulatory limits, and effective detoxification strategies will be essential for food safety management. Continued research on the toxicological mechanisms, ADME characteristics, and interaction with other dietary components will support risk assessment, regulatory decision-making, and the development of safe functional foods or herbal supplements. In conclusion, gelsenicine serves as a model compound for studying foodborne alkaloid toxicity, highlighting the need for comprehensive monitoring, mechanistic investigation, and intervention strategies to ensure consumer safety. *Gelsemium* alkaloids, due to their potent bioactivity and high toxicity, remain promising subjects for advancing food toxicology, risk assessment, and the safe application of bioactive plant-derived compounds.

8. Conclusion

This review provides a comprehensive overview of the phytochemistry, pharmacology, pharmacokinetics, detection methods, and toxicology of gelsenicine, with particular emphasis on its relevance to food safety. As the most toxic alkaloid in *G. elegans*, gelsenicine poses significant health risks when contaminating foods or herbal products due to its narrow therapeutic window, severe neurotoxicity, rapid absorption, wide tissue distribution, and effective BBB penetration. Demethylation in the liver and intestine represents the major detoxification pathway, although inter-individual metabolic variability may influence susceptibility. Sensitive analytical technologies, especially LC–MS/MS, remain essential for trace-level detection and early-warning monitoring in biological and food matrices. Gelsenicine's toxicity primarily arises from interference with neurotransmitter systems, disruption of excitatory/inhibitory balance, and modulation of receptor signaling pathways, leading to neurotoxicity and multi-organ effects. Nevertheless, pharmacokinetic and toxicological data, especially in humans, are still limited. Based on current evidence, this review highlights potential molecular toxic networks, proposes strategies for toxicity mitigation, and underscores the value of integrating metabolomics, transcriptomics, and proteomics within a systems toxicology framework. Such approaches are essential for balancing therapeutic efficacy with safety, evaluating dietary exposure risks, guiding regulatory standards, and supporting both clinical and forensic applications. In conclusion, gelsenicine serves as a model compound for studying foodborne plant toxins, and further systematic investigations are needed to inform safe consumption, mitigate toxicity, and support risk assessment in food and herbal supplement contexts.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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