

INVITED REVIEW

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The pharmacology, toxicology, and detoxification of *Aconitum kusnezoffii* Reichb., traditional and modern views

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Abstract

Aconitum kusnezoffii Reichb. is a medicinal plant widely used in traditional Asian medicine, especially in Korea, for its potent pharmacological effects. However, its toxic alkaloids pose significant risk, making careful processing essential to reduce its toxicity. This study reviewed the plant's processing methods, pharmacological activities, phytochemistry, toxicology, and detoxification techniques. Data from several databases, including Google scholar, PubMed, Scopus, Web science, peer-reviewed journal articles, classic herbal medicine books, and Allied and Complementary Medicine Database (AMED) were critically retrieved, organized and analyzed. The article's findings indicate that, various ethnic groups in Asia have utilized different techniques, involving fire, water, or a combination of both to maximize the plant's therapeutic potential and ensure safety. To date, more than 70 alkaloids, categorized into diterpenoids, nor-diterpenoids, and benzyloquinolines, have been isolated from different plant's parts (roots, leaves, stems, and flowers). These compounds exhibit various pharmacological activities including anti-inflammatory, analgesics, anti-cancer, anti-tumor, anti-arrhythmic and pain-relieving properties. Despite its therapeutic potential, *A. kusnezoffii* has narrow therapeutic window, meaning even small doses can be toxic. The study explored methods for reducing toxicity and detoxifying the herb emphasizing the importance of modern technologies such as propagation techniques, Systematic Evolution of Ligands by Exponential Enrichment (SELEX)-aptamer technology, and Chinmedomics in herbal medicine development. While research on this herb is extensive, gaps remain in clinical trials and efficacy studies. Further research is recommended to evaluate the quality of medicinal materials, understanding the herb's pharmacodynamic substances, and assess long-term toxicity and clinical efficacy.

Keywords *Aconitum kusnezoffii* Reichb., Detoxification, Aptamer, SELEX technology, Chinmedomics

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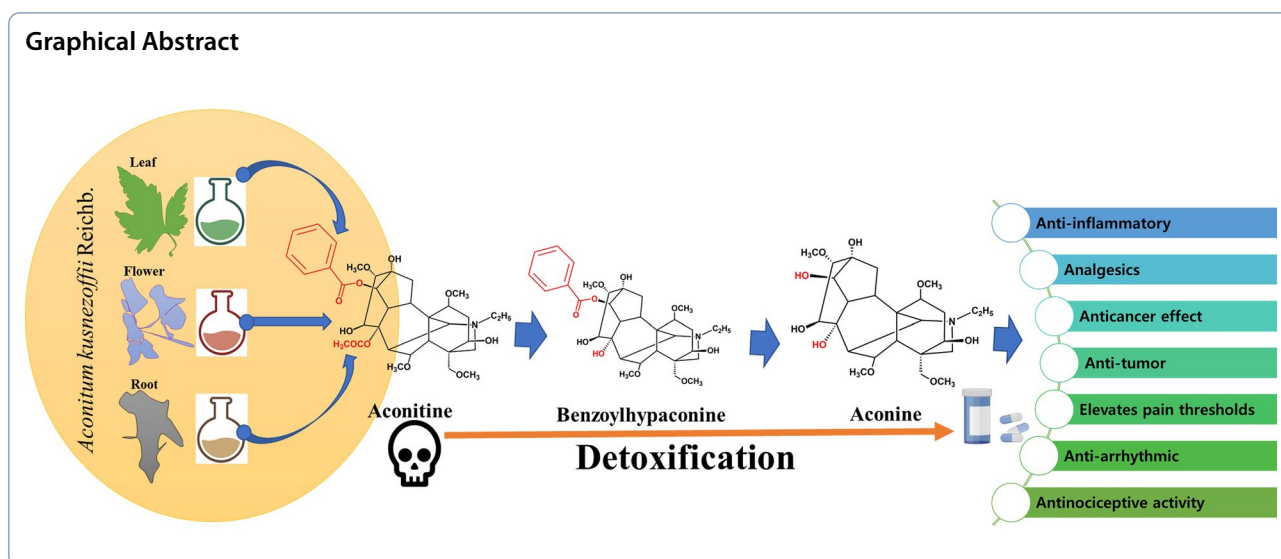
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Graphical Abstract



Introduction

The use of natural resources including plants, mineral animal, and microbes for medicinal purposes, dates back to the ancient times. In particular, medicinal plants (herbs) have been the cornerstone of traditional medicine systems across various cultures and generations worldwide. These practices have significantly increased the utilization of medicinal plants for the formulation of herbal remedies and the treatment of diseases, a trend that has persisted from antiquity to the present day [1]. According to Pan et.al. [2], approximately 80% of the global population relies on traditional medicine, predominantly herbal remedies, to manage or treat various conditions. The wide spread use of the herbal medicine is largely due to the accessibility of traditional knowledge and herbs, as well as the high cost of modern pharmaceuticals [3]. The formulation and processing methods of herbal medicine vary based on the local context of each society, and the importance of medicinal plants in the evolution and development of herbal medicine has been extensively documented [2]. Among the valuable medicinal plants used in traditional herbal medicine is the *Aconitum* genus, which belongs to the Ranunculaceae family. This genus comprises over 350 species, particularly flourishing in the biodiversity regions of Asia. Among the popularly used species are *Aconitum* plants from the Cho-o origin, these include *Aconitum kusnezoffii* Reichb., *Aconitum volubile* var. *pubescens*, and *Aconitum jaluense* var. *jaluense*. One of the most commonly used species within the genus is and Cho-o origin is *Aconitum kusnezoffii* Reichb. (*A. kusnezoffii*), which plays a significant role in Chinese patent medicine and Chinese folk remedies, accounting for over 90% of *Aconitum* products on the

Chinese market. The roots of *A. kusnezoffii*. (*Radix Aconitum kusnezoffii*) have been pivotal in traditional Asian medicine, particularly Traditional Chinese Medicine (TCM), due to their wide range of therapeutic effects, including anti-inflammatory, analgesic, antiepileptic properties. This herb has been applied in the treatment of various conditions such as rheumatic fever, paralysis following stroke, endocrinal disorders, carbuncle, painful joints, and furuncle [4]. As a result, *A. kusnezoffii* is used in both the traditional and modern medicine [5]. According to Ashraf et al. [6], *A. kusnezoffii*. (*Caowu*) are primarily used for their analgesic properties, while tincture made from roots are externally for their anti-rheumatic effects. The processed main root (*Zhi'cao'wu*), often used in decoction, serves as an anti-inflammatory and analgesic treatment for joint pain. The dried leaves (*Cao'wu'ye*) are typically formulated into round pills and used as anti-inflammatory, antipyretic, and analgesic remedies for conditions like abdominal pain, diarrhea, headache, and toothache. Importantly, roots of *A. kusnezoffii* must undergo processing before use, as the presence of diterpene-diester alkaloids in un processed roots render them highly toxic and unsuitable for therapeutical application. The pharmacological value of *Radix Aconitum kusnezoffii* is largely attributed to its secondary metabolites such as alkaloids, flavonoids, saponins, tannins, glycosides, terpenoids, free fatty acids and poly saccharides which have been shown to stimulate and catalyze healing processes in human [7]. *A. kusnezoffii* contains six key alkaloids: Aconitine (1), mesaconitine (2) Hypaconitine (3), Mesaconine (4), benzoylhypaconine (5), benzoylmesaconine (6) and benzoylaconine (7). These alkaloids serve as lead compounds for the discovery and

development of new pharmaceuticals [8]. According to Qiao et al. [9], *A. kusnezoffii* has been used for a variety of activities, including anesthesia, anti-inflammation [10], and treatments for vomiting, nausea and sweating [11]. Similar to other *Aconitum* species, it has also been used for analgesic effects [12]. However, despite its therapeutic potential, *Radix Aconitum kusnezoffii* pose serious poisoning risk due to its strong bioactive and toxic properties. According to Liu et al. [13], *A. kusnezoffii* is classified among the 10 most toxic plants in TCM. Its toxicity can cause adverse reactions, such as vomiting, hypotension, nausea, shock and dizziness. In more severe cases, toxic traditional medicine can damage the liver, kidneys, nervous, respiratory, and reproductive systems. *A. kusnezoffii* alkaloids have a narrow therapeutic index, which can lead to therapeutic failure if not carefully managed. Overdose of aconitine (1), mesaconitine (2), and lycaconitine [44] may induce arrhythmia and even result in death [14]. Additionally, direct contact *A. kusnezoffii* can cause skin irritation, including dermatitis and numbness, making the herb highly toxic to both human and animals [15]. The continued use of *Radix Aconitum kusnezoffii* in traditional medicine continues pose serious poisoning risk due to its cardiotoxic and neurotoxic effects, which can be fatal. As *A. kusnezoffii* herb becomes increasingly available globally, its toxic and medicinal properties present a worldwide concern if proper quality control and safety standards are not enforced during different value chain of the herb's development [16]. Despite the danger, toxic herbs like *A. kusnezoffii* have played a significant role in the development of traditional medicine. Over the years, numerous studies have focused on processing methods, phytochemical constituencies, pharmacological activities, toxicology and detoxification of toxic herbs like *A. kusnezoffii* to optimize their therapeutic value [4]. However, there remains a lack of consolidated information on the processing methods, phytochemical constituencies, pharmacological activities, toxicology and detoxification specific to *A. kusnezoffii*. The available data are dispersed across multiple publication platforms, including journals, posters, theses, and books making it difficult to assess the plant's properties in a comprehensive manner. Therefore, this review aims to explore the gap by exploring the traditional processing methods, phytochemical constituents, pharmacological activities, toxicology, detoxification and quality control of *A. kusnezoffii*, while detailing the alkaloids present in various part of the herb. Additionally, the review highlights emerging advances in herbal medicine that have the potential to improve and sustain the development of *A. kusnezoffii*. The insights from this review can offer a strong scientific foundation for future research, aiding

in the sustainable development of high-quality, safe, and effective products from *A. kusnezoffii*. for a range of diseases.

Methodological approaches

We conducted a literature review by gathering relevant data from peer-reviewed articles published in scientific journals, with a focus on the pharmacological activities, toxicology, and detoxification of *A. kusnezoffii*. Additionally, we collected information on herbal medicine from recently published articles related to these topics. The data was obtained through electronic searches on platforms such as Google Scholar, PubMed, Scopus, Web science, peer-reviewed journal articles, classic herbal medicine books, Allied and Complementary Medicine Database (AMED), and the Cochrane Library. We used specific keywords, including “botany and distribution,” “species,” “alkaloids,” “safety and toxicity,” “pharmacological activities,” “common formulation,” “treatment of intoxication,” “herb-herb combination,” “clinical symptoms,” and “effects on the cardiovascular system” in relation to *A. kusnezoffii*. Chemical structures were drawn using ChemDraw. The collected data was then summarized, analyzed, and conclusions were drawn based on the findings.

Results and discussion

Historical glimpse of *A. kusnezoffii*

A. kusnezoffii, commonly known as aconite, derives its name from the Greek word “Aconiton,” which was used by Theophrastus to describe a poisonous plant called “hemlock.” For centuries, various species of aconite, including *A. kusnezoffii*, have been integral to TCM, Korean medicine, and Ayurveda. The plant gained significance due to its diverse alkaloid content, ranging from non-toxic to highly toxic compounds. Among the many species of aconite, *A. kusnezoffii* was evaluated in ancient TCM for its quality and therapeutic efficacy based on morphological traits such as plant height, foliage, flowers, and tubers. The crude drug yield from *A. kusnezoffii* tubers typically ranged from 1.22 to 1.7 g per plant. Despite its potentially lethal toxicity, *A. kusnezoffii* has been used for centuries in TCM, Korean medicine, and Ayurveda to treat various ailments, including arthritis, diarrhea, cough, congestion, male infertility, gout, cancer, and inflammation [17]. The toxic nature of *A. kusnezoffii* has also been known since ancient times. Symptoms of poisoning, which manifest a few hours after ingestion, include nausea, vomiting, jaw and facial discomfort, muscular weakness, and restlessness [18]. To mitigate the toxicity of its alkaloid content, TCM literature highlights the importance of processing *A. kusnezoffii* roots, typically through boiling and soaking. This practice has long

been used to reduce toxicity, as improper processing or exceeding the recommended dose significantly increases the risk of aconite poisoning. Additionally, gargling with water and consuming large amounts of water to induce vomiting was considered one of the remedies for detoxification following aconite poisoning [4]. Historically referred to as the “queen mother of poisons” [19], *A. kusnezoffii* possesses unique characteristics, with a sharp, slightly bitter taste that causes a tingling or burning sensation in the tongue, mouth, and throat. This sensation intensifies, eventually affecting the entire mouth. The narrow safety margin between the therapeutic analgesic effects and the cardiotoxic risks of *A. kusnezoffii* makes accidental overdose particularly dangerous. In Ayurveda, aconite paste was historically used as an arrow poison for warfare and hunting [20]. According to Fraser et al. [21], arrow poisons made with *A. kusnezoffii* were especially lethal to warm-blooded animals, more so than those made with croton. However, a single arrow tipped with aconite generally contained insufficient quantities of poison to cause death in humans, even if the poison was rapidly absorbed. The dual nature of *A. kusnezoffii*, its poisoning and non-poisoning properties, has played a significant role throughout history, reflecting its importance in both medicine and ancient practices.

Botany and distribution of *A. kusnezoffii*

A. kusnezoffii, commonly known as “Caowu,” is a herbaceous perennial flowering dicotyledon belonging to the genus *Aconitum* in the Ranunculaceae family, which comprises over 400 species. This species is listed among endangered and rare plants in Mongolia [22]. *A.*

kusnezoffii is considered extremely toxic, as all parts of the plant contain high concentrations of potent alkaloids. Despite its toxicity, it holds significant economic value in several Asian countries, being a key component in TCM. It is also included in both the Chinese and Korean pharmacopoeias as part of Chinese patent medicine. The plant is primarily native to the mountainous regions of the Northern Hemisphere and is widely distributed across East Asia, including Korea, northern China, Russia, Mongolia, and Japan Fig. 1 [23, 24]. *A. kusnezoffii* typically grows to a height of approximately 1.5 m. It features a tall, erect, and usually branched stem with leaves arranged along its length, culminating in large, purple or white flowers. The dark green leaves are alternately arranged without stipules, and they are deeply palmately lobed, consisting of 5–7 segments, each further divided into three lobes with coarsely serrated edges. The flowers are zygomorphic (bilaterally symmetrical), bearing numerous stamens and 2–10 petals. The fruit of *A. kusnezoffii* consists of dry, multi-seeded follicles [23, 25].

Chemical compounds of *A. kusnezoffii*

Although *A. kusnezoffii* contains various secondary metabolites, such as alkaloids, flavonoids, saponins, tannins, glycosides, terpenoids, free fatty acids, and polysaccharides, modern Chinese research has identified alkaloids with C_{18} -, C_{19} -, or C_{20} - diterpenoid skeletons as the primary active medicinal constituents. These alkaloids range in toxicity from non-toxic to highly lethal [26]. The main alkaloids present in *A. kusnezoffii* include aconitine (1), mesaconitine (2), hypaconitine (3), benzoylhypaconine (5), benzoylmesaconine (6),



Fig. 1 Map of Asia showing the distribution of *A. kusnezoffii*

Table 1 Key chemical compounds derived from *A. kusnezoffii* that contribute to pharmacological effects and their natural origins within the plant

Group alkaloid	Alkaloids	Source (Plant part)	References
Diterpenoid alkaloids (DDA)	Aconitine (1)	Roots (Xylem, Phloem, Metaderm, Endodermis, Pith), Flowers, Stems, Leaves	[29, 30]
	Mesaconitine (2)	Roots (Metaderm, Xylem, Stone cell with endodermis, Stone cells, Pith), Flowers, Stem, Leaves	[29, 31]
	Hypaconitine (3)	Roots (Xylem, Stone cell with endodermis, Stone cells), Flowers	[32, 33]
	Mesaconine (4)	Roots (Xylem, Phloem, Cortex, Endodermis, Pith)	[34]
	Benzoylhypaconine (5)	Roots (Xylem, Phloem, Cortex, Endodermis, Pith)	[34]
	Benzoylmesaconine (6)	Roots	[34]
	Benzoylaconine (7)	Roots	[35]
	10-OH-mesaconitine (8)	Roots, Flowers	[36]
	3-acetylmesaconitine (9)	Flowers	[36]
	Deoxyaconitine (10)	Roots, Flowers	[36]
	10-OH-aconitine (11)	Flowers	[36]
	Neojiangyouaconitine (12)	Roots (Phloem, Xylem, Metaderm, Pith, Stone cells, Stone cell with endodermis)	[37]
	Isodelphinine (13)	Roots (Metaderm, Xylem, Stone cells, Stone cell with endodermis)	[37] [38]
	Bullatine B (14)	Roots (Metaderm, Xylem, Pith, Phloem, Stone cells, Pith, Stone cells)	[37]
	Kobusine (15)	Roots (Phloem, Xylem, Metaderm, Pith, Epidermis)	[39]
	Ignavine (16)	Roots	[39, 40]
	Jesaconitine (17)	Flowers, Roots	[39]
	Lepenine (18)	Leaves, Flowers, Stem	[41]
	Denudatine (19)	Leaves, Flowers, Stem	[42]
	Fuziline (20)	Roots	[43]
	Foresticine (21)	Roots	[37]
	Karacoline (22)	Roots	[41]
	Acetylaconitine (23)	Roots	[44]
	14-benzoylmesaconine (24)	Roots	[45]
	Lipo-14-O-anisoylbikhaconine (25)	Roots	[46]
	Chuanfumine (26)	Roots	[47]
	14-benzoyl-10-OHaconitine (27)	Roots	[47]
	1,15-Dimethoxy-3-hydroxy-14-benzoyl-16-ketoneoline (28)	Roots	[48, 49]
	3-acetyl-10-OHaconitine (29)	Roots, Flowers	[36]
	3-deoxyaconitine (30)	Roots (Pith, Stone cell with endodermis, Stone cells, Xylem, Metaderm)	[37]
	3-acetylaconitine (31)	Flowers	[36]
	Deoxymesaconitine (32)	Roots	[47]
	Napelline B (33)	Roots	[50]
	Napelline C (34)	Roots, Stem and Leaves	[50]
	Napelline B (35)	Roots	[50]

Table 1 (continued)

Group alkaloid	Alkaloids	Source (Plant part)	References
	Aconine (36)	Roots	[43, 51]
	Lycaconitine (37)	Roots	[44]
	14-O-veratoylneoline (38)	Roots	[46]
	Methyllycaconitine (39)	Roots	[44, 52]
	Atisine (40)	Roots (Metaderm, Xylem, Stone cells and stone cell with endodermis)	[37]
	Neoline (41)	Roots	[53]
	Bullatine (42)	Roots (Metaderm, Pith and Xylem)	[37]
	Talatisamine (43)	Roots	[39]
	Songorine (44)	Roots	[39]
	15 a-hydroxyneoline (45)	Roots	[54]
	Guan-Fu base A (46)	Roots	[54]
	Guan fu base Z (47)	Roots	[54]
	Guan fu base Y (48)	Roots	[54]
	Bulleyaconitine (49)	Roots	[54]
	Napilline (50)	Roots	[39]
	Senbusine B (51)	Roots (Metaderm, Xylem, Stone cells, Pith, Stone cells)	[37, 46]
	Senbusine C (52)	Roots (Phloem, Xylem, Metaderm, Stone cells)	[37, 46]
	14-O- 3-deoxyaconitine (53)	Roots (Metaderm, Xylem, Phloem, Stone cells)	[37]
	8-ole-benzoylaconine (54)	Flowers	[36]
	8-ole-benzoylmesaconine (55)	Flowers	[36]
	8-ole-benzoylhypaconine (56)	Flowers	[36]
	Septentrionaline (57)	Roots	[9]
	Anthranoyllycoclonine (58)	Roots	[9]
	Benzoyldeoxyaconitine (59)	Roots, Leaves and stem	[9]
	14-benzoyl-10-OH-mesaconine (60)	Roots	[47]
	14-benzoyl-10-OH-hypaconine (61)	Roots	[47]
	Benzoylaconine (62)	Roots	[34]

Table 1 (continued)

Group alkaloid	Alkaloids	Source (Plant part)	References
Norditerpenoid alkaloids (NDA)	Beiwutine (63)	Leaves	[55]
	Yunaconitine (64)	Roots (Phloem, Xylem, Metaderm, Pith, Stone cell, Pith, Stone cells)	[37]
	Beiwudine (65)	Roots	[54, 56]
	14-O-anisoylneoline (66)	Roots (Metaderm, Pith, Xylem, Stone cells, Pith, Stone cells)	[37]
	Anisoylneoline (67)	Roots (Phloem)	[37]
	Delphatine (68)	Roots (Metaderm, Xylem, Stone cells, Phloem, Stone cell with endodermis)	[37]
	Chasmanine (69)	Roots (Metaderm, Xylem, Stone cells, Stone cell with endodermis)	[37, 57]
	Delbrusine (70)	Roots (Metaderm)	[37],
	Vilmorrianine C (71)	Roots (Phloem, Xylem, Metaderm, Pith, Stone cells, Stone cell with endodermis)	[37]
	Bullatine C (72)	Roots (Phloem, Xylem, Metaderm, Pith, Stone cells, Stone cell with endodermis)	[37, 38]
	Lycotnine (73)	Roots, Leaves and stem	[46]
	Yunaconitine (74)	Roots (Metaderm, Pith, Xylem, Stone cells, Pith, Stone cells)	[37]
Benzylisoquinoline alkaloids (BIA)	Higenamine (75)	Roots	[58, 59]

and benzoylaconine (7), along with additional alkaloids listed in (Table 1), which are illustrated with their chemical structures in (Fig. 2). As shown in Table 1, different parts of the *Aconitum* plant yield various alkaloids upon extraction. The alkaloids of *A. kusnezoffii* are primarily classified into three major groups: diterpenoid alkaloids (DDAs), norditerpenoid alkaloids (NDAs), and benzylisoquinoline alkaloids (BIAs). These groups are distinguished by their core structures, which differ in the number and arrangement of carbon atoms, as well as their skeletal frameworks. DDAs are based on a diterpene skeleton containing 20 carbon atoms, such as aconitine (1), mesaconitine (2), and hyaconitine (3) [27]. NDAs have either an 18- or 19-carbon skeleton, with examples like bullatine C (72) and anisoylneoline (67) [6]. BIAs are known for their diverse structural variations, such as higenamine (75), found in *A. kusnezoffii* [28]. Figure 2 illustrates the chemical structures of these alkaloids.

In addition to the alkaloids, *A. kusnezoffii* also contains the non-alkaloid compound caryneine, which exhibits cardiotoxic effects [60].

Determination of DDA, NDA, and BIA

Sophisticated analytical techniques with high selectivity and sensitivity have been employed in various studies to identify, quantify, and determine the presence and concentration of different alkaloids in *A. kusnezoffii*.

Commonly used methods include High-Performance Liquid Chromatography (HPLC), Mass Spectrometry (MS), and the combination of HPLC with MS (HPLC–MS). Additionally, HPLC coupled with Diode Array Detection (HPLC–DAD) [33, 61], Gas Chromatography (GC) [62], high-performance capillary electrophoresis, capillary electrophoresis/LC–MS [27], and Ultra-High Performance Liquid Chromatography (UHPLC) with Quadrupole Time-of-Flight Mass Spectrometry (UHPLC–QTOF MS) have been utilized. Other methods include HPLC combined with Electrospray Ionization Mass Spectrometry (HPLC/ESI–MS) [63], Nuclear Magnetic Resonance (NMR) Spectroscopy [44], High-Resolution Mass Spectrometry, and HPLC/ESI–MS analysis [64]. Thin-Layer Chromatography (TLC) and Rapid Resolution Liquid Chromatographic methods have also been applied [9, 65]. The selection of an analytical method depends on several factors: the type of alkaloids being analyzed, their chemical properties, required sensitivity, and the availability of instruments [66]. For instance, DDAs, NDAs, and BIAs are detected at different wavelengths, exhibit varying retention times, and require distinct chromatographic conditions. Their peak shapes, resolution, molecular masses, and calibration procedures also differ. These analytical techniques are crucial for both the identification and quality control of *A. kusnezoffii* drugs.

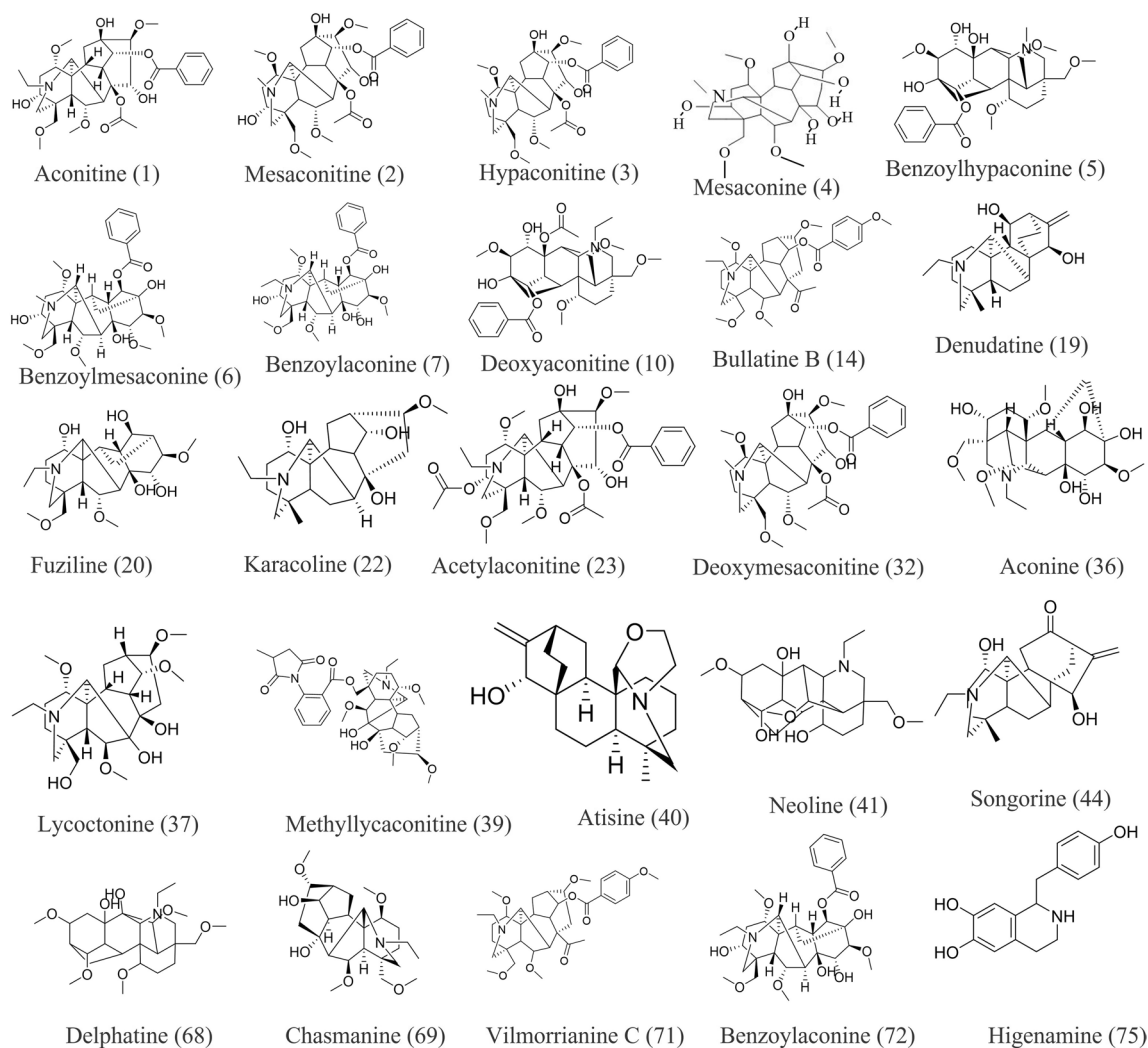


Fig. 2 Chemical structures of alkaloids in *A. kusnezoffii*. The structures include diterpenoid alkaloids (DDAs), norditerpenoid alkaloids (NDAs), and benzyloquinoline alkaloids (BIAs)

A. kusnezoffii plant parts used for medicinal purposes

Various parts of the *A. kusnezoffii* plant have been utilized for therapeutic purposes, with the roots being the most frequently employed in traditional medicine. This is largely due to the high concentration of alkaloids found in the roots. Additionally, other plant parts, such as the stems, leaves, and flowers, have been identified to contain alkaloids as well, though in lower quantities [67]. Figure 3 illustrates the percentage distribution of the different *A. kusnezoffii* plant parts used for medicinal applications.

History of processing *A. kusnezoffii*

The primary objectives of processing *A. kusnezoffii* medicinal materials can be summarized as

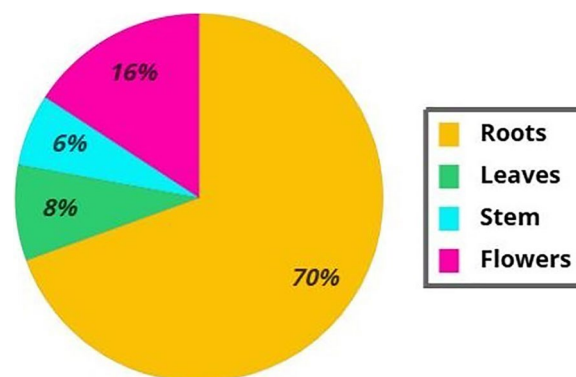


Fig. 3 *A. kusnezoffii* plant parts used for medicinal purposes

follows: (i) Reduce or eliminate the toxicity, concentration, and adverse aftereffects of *A. kusnezoffii* drugs to enhance user safety; (ii) Modify or alleviate the drug's performance; (iii) Improve medical efficacy; (iv) Alter the drug's target site of action or modify the course of its effectiveness; (v) Ensure suitability for administration and preparation; (vi) Purify therapeutic materials and improve storage; (vii) Enhance ease of use. However, the principal aim of processing *A. kusnezoffii* medicinal materials remains the elimination or reduction of toxicity, concentration, and adverse aftereffects to ensure the safety of the drug for users [68]. *A. kusnezoffii* is included in up to 600 formulations, as documented in historical texts and clinical reports [11]. Table 2 provides a summary of common processing methods for *A. kusnezoffii* over time and across different cultures in traditional medicine. Various methods have been employed to process *A. kusnezoffii* within Korean medicine and traditional Chinese medicine. These methods, along with associated prescriptions, were detailed in ancient texts with the aim of ensuring safe and effective clinical application. The first recorded mention of *A. kusnezoffii* appeared in *Shen Nong's Herbal Classic*, where it was classified as a toxic herb. The earliest records of its processing methods are found in the *Synopsis of Prescriptions from the Golden Chamber* [69]. Since then, numerous processing techniques have emerged across different dynasties. Over time, several new water and fire-based processing methods have evolved. Today, more than 70 methods for processing *A. kusnezoffii* have been developed. In general, the processing techniques for *A. kusnezoffii* can be classified into four main categories: (i) **Fire processing techniques**, which include methods such as baking, stir-frying, and roasting; (ii) **Water processing techniques**, such as soaking and washing; (iii) **Water and fire processing techniques**, including steaming and decocting, with or without adjuvants; (iv) **Mechanical processing techniques**, such as decortication [4, 70].

Processing methods of *A. kusnezoffii*

Fire processing method

The fire processing method involves heating herbal raw materials without the use of water or liquid adjuvants. Several factors are carefully controlled during this process, including the heating temperature, duration, and the specific technique employed [71]. Various techniques can be applied under the fire processing method, such as stir-frying, scalding, stir-frying with solid adjuvants, roasting, baking, calcining, and charring. The most common techniques for processing *A. kusnezoffii* are baking, stir-frying, roasting, and charring. Historically, the Han Dynasty first introduced the baking technique for

processing *A. kusnezoffii*, as recorded in the *Jinkui Yaolue Fang*: "bake and decorticate, then cut into eight pieces." This method was widely used through the Ming and Qing Dynasties [4, 72]. The subdivisions of the fire processing method for *A. kusnezoffii* are outlined below.

Stir-frying

Stir-frying has been one of the most commonly used methods for processing toxic herbs in traditional medicine since ancient times. Its popularity stems from its effectiveness in reducing the toxicity of raw medicinal materials [15]. This method has been passed down through various dynasties and continues to dominate the processing of key medicinal plants in the *Aconitum* genus, including *A. kusnezoffii*. During stir-frying, the cleaned and chopped raw material of *A. kusnezoffii* is fried in pots. This process can be done with or without excipients under low heat, reducing the water content of the raw material to about 10–13%, which helps to lower its hepatotoxic content [4]. While stir-frying can effectively detoxify *A. kusnezoffii*, improper handling may result in the loss of important compounds [5]. To maintain the desired compounds in the raw material, it is essential to avoid pre-soaking, use minimal water during cooking, minimize contact time with water, and carefully balance heat and moisture (i.e., high heat with minimal water or low heat with more water). Additionally, preserving the color of the raw material during stir-frying is crucial. The reduction of toxicity, modification of *A. kusnezoffii*'s harsh characteristics, and reinforcement or preservation of its efficacy can be enhanced by using various excipients, such as salt, ginger juice, sesame oil, wheat bran, croton, vinegar, or moistened paper. Depending on the excipient used, *A. kusnezoffii* may change color during stir-frying, turning yellow, brown, black, or dark. This color change is an important indicator of the degree of stir-frying [73]. When comparing the stir-frying process of *A. kusnezoffii* to other toxic root tubers, Pan et al. [15] highlights examples such as *Shanglu* (the roots of *Phytolacca acinosa* Roxb. or *P. americana* L.), which are commonly stir-fried with vinegar in Tujia medicine. In this process, the inflammatory toxic compound esculentoside H is transformed into the diuretic active ingredient esculentoside A, reducing toxicity while enhancing efficacy [74]. Additionally, stir-frying has a notable effect in reducing the hepatotoxic content of compounds like atractyloside and carboxyatractyloside, as well as toxic proteins [75].

Stir-frying with solid adjuvants

To significantly enhance the safety of alkaloid-rich herbs like *A. kusnezoffii*, it is essential to treat the herbs with solid adjuvants during the stir-frying process. Commonly

Table 2 Traditional methods used to process *A. kusnezoffii* in ancient medicinal practice [4, 67]

Dynasty	Origin	Processing method
Tang dynasty	Yinhai Jingwei CE 682	Baking without direct flames
Song dynasty	Fang CE 992	Charring
	Taiping Huiming Heji Jufang CE 992	Charring
	Lun CE 100	Stir-frying to brown
	Chuanxin Shiyong Fang CE 1180	Soaking in wine
		Decocting with black soybeans
	Puji Benshi Fang 1132 CE	Charring the roots
		Stir-frying until the roots darken in color
	Taiping Huiming Heji Jufang CE 1151	Baking and peeling
	Leibian Zhushi Jiyang Yitang CE 1253	Soaking in warm water
		Stir-frying
Jin Yuan dynasty	Nvke Baiwen CE 1279	Washing three times
	Huoyou Xinshu CE 1294	Fire crack and peeling
	Rumen Shiqin CE 1228	Water soaking
	Huoyou Xinshu CE 1294	Fire-crack and peeling
	Huoyou Xinshu CE 1294	Water soaking
	Zhuruitang Jingyan Fang CE 1326	Stir-frying with salt
	Danxi Xinfa CE 1347	Burning
Ming dynasty	Puji Fang CE 1406	Water immersion
		Soaking in rice
		Soaking in wine and peeling
		Ginger juice maceration
		Stir-frying with salt
		Stir-frying with vinegar
	Qixiao Liangfang CE 1470	Stir-fry with salt
		Stir-frying with sesame oil
	Yixue Gangmu CE 1565	Water soaking
	Yixue Gangmu CE 1565	Decocting with black soybeans
	Yixue Rumen CE 1575	Decocting with soybean curd
		Stir-frying with ginger juice
	Bencao Gangmu CE 1578	Decocting with black beans
	Waike Qixuan CE 1604	Stir-frying to yellow
		Quenching in vinegar
	Shoushi Baoyuan CE 1617	Soaking in rice water
		Stir-frying to brown
Qing dynasty	Shengji Zonglu CE 1117	Soaking in salt solutions
		Nature-preservative stir-frying
		Stir-frying with wheat bran and croton until black:
		Soaking in salt solution for 3 days, washing, and cutting into slices, then stir-frying to brown with wheat bran
	Puji Benshi Fang CE 1132	Bake-cracking after peeling
		Stir-frying with salt
		Decocting with soybeans until soft
	Zongwei Lunfang CE 1156	Soaking with mint and ginger juice for a day and drying by baking
	Sanyin Jiye Bingzheng Fanglun CA 1174	Soaking in rice water for three days and peeling
		Decocting with black soybeans
	Biji CE 1622	Processing with wine
	Yimen Falv CE 1658	Quenching in vinegar
	Waike Dacheng CE 1665	Soaking in warm water and peeling
		Soaking in ginger juice
	Waike Zhengzhi Quanshu Ji CE 1740	Decocting with mung beans
	Zengguang Yanfang Xinbian CE 1846	Roasting in flour wrap and stir-frying

Before the Tang Dynasty, *A. kusnezoffii* (Caowu) was referred to as aconitine. It was officially recorded under the name *A. kusnezoffii* after the Tang Dynasty, and its distinction as a medicinal herb was established during the Song Dynasty. As shown in Table 2, the traditional processing methods historically used for *A. kusnezoffii* include stir-frying, soaking, decocting, roasting, carrying, baking, and the use of adjuvants. Figure 4 illustrates the traditional techniques employed to

Table 2 (continued)process *A. kusnezoffii* in ancient medicinal practices

used adjuvants include rice, clam powder, and wheat bran, as indicated in different dynasties, shown in (Table 2). Wheat bran, when used in stir-frying, absorbs the oils from *A. kusnezoffii*, reducing its dryness and aiding in the breakdown of alkaloids. Meanwhile, rice helps to maintain moderate heat and prevent the charring of the herbal medicine during stir-frying [76]. Historically, stir-frying has been the most frequently used method for processing *A. kusnezoffii* (Table 2), particularly during the Song, Jin Yuan, Ming, and Qing dynasties. In the Jin Yuan dynasty, stir-frying was done with salt, while in the Ming dynasty, it was commonly combined with salt, vinegar, and sesame oil. During the Qing dynasty, wheat bran, croton, salt, and flour were used.

Charring

Charring of *A. kusnezoffii* plant materials has been practiced since ancient times and remains a common method in both Korean herbal medicine and TCM. The process, which partially carbonizes *A. kusnezoffii*, has been used to enhance its anti-inflammatory properties in these medicinal systems [14]. The primary objective of charring *A. kusnezoffii* is to produce traditional medicine with effective anti-arrhythmic and analgesic properties [67]. The predominant charring method is known as “nature-preservative burning,” which involves avoiding excessive heat to ensure the processed material retains its effectiveness [4]. Charring has also been applied to other herbs to boost their effectiveness in traditional medicine. For instance, the dried root tubers of *Mandragora caule-scens* are charred to treat sores and various dermatoses through external application. The sliced root tubers are heated in a pot until they turn black with a yellow hue. This process enables the charred root to be used orally for treating anthrax and other malignant diseases [76]. Charring of *A. kusnezoffii* originated in the Song dynasty and has been a staple of ancient processing methods.

Baking

Baking involves exposing medicinal herbal materials, whether soaked or not, to high temperatures for a prolonged period [77]. It is a straightforward, time-efficient, and energy-saving method that is stable and effective in reducing the alkaloid content of *Aconitum*. Trials have shown that baking *A. kusnezoffii* for extended periods results in only slight changes to its total alkaloid content. However, there is a consistent decrease in DDA throughout the first two hours of baking, after which the decline stabilizes. Through multi-factor, multi-intervention

(orthogonal) experiments, the most effective conditions were determined as follows: Soaking *A. kusnezoffii* until fully saturated, slicing the raw materials into 2 to 4 mm thick pieces, and baking the slices at 110 °C for four hours. Further research also explored the relationship between *A. kusnezoffii*'s texture and its effectiveness in detoxifying alkaloids through baking. The findings suggested a need to categorize the herb based on size and density before baking to optimize detoxification [4]. Historically, baking without the use of an open flame was common during the Tang dynasty.

Roasting

Roasting has been another method traditionally employed in herbal medicine, particularly for processing alkaloid-rich herbs such as *A. kusnezoffii*. In Traditional Chinese Medicine, the herb is wrapped in dough or wet paper and then buried in hot talcum powder or ash during roasting. This process significantly reduces the content of volatile and/or irritating toxins by inducing chemical reactions through heat, thereby lowering the toxicity of *A. kusnezoffii* [15].

Water processing method

The water processing method involves using water or other adjuvants (e.g., washing, soaking) on herbal raw materials without applying heat. This method is primarily used to soften the raw materials for easier cutting, slicing, and detoxification purposes [78]. The technique has been employed since ancient times. The water processing of *A. kusnezoffii* was first introduced by Zhouhou Beiji Fang during the Dongjin Dynasty, commonly referred to as vinegar-dipping. Subsequent dynasties, such as the Song and Ming, further developed the method. The Song Dynasty introduced the use of additional adjuvants like brine and wine, in addition to rice water, while the Ming Dynasty included ginger juice as an adjuvant. The *Puji Fang*, one of the most significant historical Chinese medicine texts, included a method for processing *A. kusnezoffii* with ginger juice, among 61,739 prescriptions from the Ming Dynasty [4]. Below are the main subdivisions of the water processing method for *A. kusnezoffii*.

Soaking

Soaking is a commonly used method for treating alkaloid-rich herbal medicines and has been practiced for processing *A. kusnezoffii* across many dynasties in traditional herbal medicine. Due to its high content of monoester aconitum alkaloids, which can be toxic, *A.*

kusnezoffii poses significant risks to cardiac function if the roots are used unprocessed [79]. Soaking in mediums such as water, rice water, wine, vinegar, or with additives like mint and ginger juice, renders *A. kusnezoffii* safer for medicinal use [4, 72]. Studies have shown that soaking reduces diterpene-diester alkaloids by 36.8% and monoester aconitum alkaloids by 25.5%, significantly reducing toxicity [80]. Soaking has been one of the most common methods for processing *A. kusnezoffii* since ancient times (Fig. 4), used during the Song, Jin Yuan, Ming, and Qing dynasties. In the Song Dynasty, *A. kusnezoffii* was mainly soaked in wine and water; during the Jin Yuan period, in water; in the Ming Dynasty, in rice water, water, and wine; and in the Qing Dynasty, soaking mediums included salt, mint, ginger juice, rice water, and warm water.

Washing (descaling)

Washing raw *A. kusnezoffii* materials, particularly roots, with clean water shortly after harvest aids in microbial fermentation, which enhances medicinal properties and reduces toxicity [81]. For effective washing, water should be changed frequently, and low concentrations of chlorine (e.g., sodium hypochlorite, bleach) are sometimes used [77]. While microbial fermentation is a well-established method for improving the medicinal properties of *Aconitum* species, additional washing agents such as children's urine, pomegranate water, and Qinke wine have been used, followed by repetitive rinsing with clean water. This process helps remove trace materials and elements, such as mercury (II) oxide (HgO), that are soluble

in weak acids or bases. However, this specific technique has not been commonly applied to the processing of *A. kusnezoffii* [76]. Historically, washing was commonly used during the Song and Qing dynasties.

Quenching

According to Koc et al. [82], Quenching is a heat treatment method that involves rapidly cooling materials from high to low temperatures using quenchants such as water, gas, oil, or a combination of fluids to achieve desired properties [83]. This method has been used for processing alkaloid-rich herbs, including *A. kusnezoffii*, for centuries due to its effectiveness in reducing toxicity while preserving therapeutic compounds [72]. The quenching process for *A. kusnezoffii* includes cleaning and slicing the raw materials (e.g., roots) into small pieces to increase surface area, soaking them in water for 6–12 h, and then boiling for 1–3 h. After boiling, rapid cooling is achieved by transferring the hot *A. kusnezoffii* radix into a cool water bath. This sudden temperature shift helps stabilize the beneficial compounds while further reducing toxicity [84]. In ancient processing, quenching emerged during the Ming and Qing dynasties, where vinegar was often used as an adjuvant in the quenching process.

Water immersion

Water immersion is a traditional herbal medicine processing method that extracts beneficial compounds while significantly reducing toxicity [85]. *A. kusnezoffii* is particularly potent and highly toxic due to the presence of alkaloids such as aconitine (1) and mesaconitine (2),

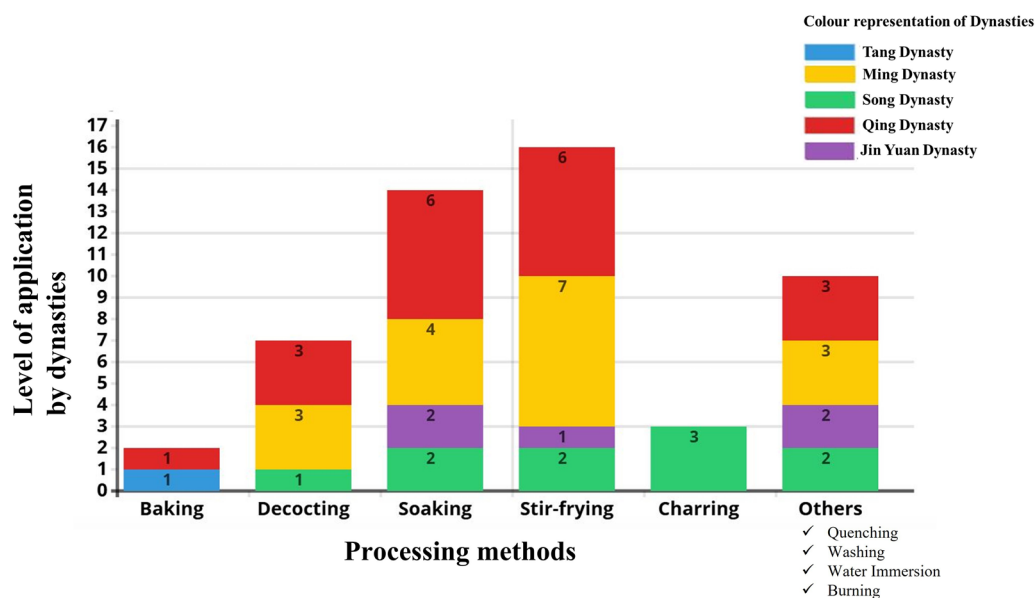


Fig. 4 Traditional methods used to process *A. kusnezoffii* in ancient medicinal practices

which can be harmful if not properly processed [86]. The water immersion method has long been recognized for processing alkaloid-rich herbs, from ancient times to the present. During this process, cleaned, pre-soaked, and sliced roots of *A. kusnezoffii* are placed in a sterilized container. A suitable solvent is selected and poured over the roots, and the container is tightly sealed to prevent contamination and solvent evaporation. Common solvents used in this method include alcohol or a water-alcohol mixture [87]. To avoid the degradation of active compounds, the mixture should be stored in a cool, dark place, away from light and heat [88]. The mixture is gently shaken at room temperature for about three hours to ensure thorough mixing and to aid in the extraction process. Afterward, it is filtered to separate the liquid extract from the solid herbal material [45]. Historically, water immersion for processing *A. kusnezoffii* first appeared during the Ming Dynasty.

Fire and water processing method

The fire and water method for processing herbal medicines primarily involves decocting, maceration, and stir-frying with liquid adjuvants. This method requires both water or another liquid and the application of heat [89]. The first recorded instance of fire and water processing for aconite dates back to the Han Dynasty [5], with detailed descriptions and formulas provided by Zhang Zhongjing [11]. In the Tang Dynasty, a new variation of the *A. kusnezoffii* processing method emerged, where raw materials were stir-fried and then decocted with ginger juice.

Decoction

Decoction is one of the most common methods used to process toxic, alkaloid-rich herbs in traditional Chinese medicine [86]. In this process, *A. kusnezoffii* materials are placed in a dolso-like pan (stone pot) along with lime, rapeseed oil, calcium, sesame oil, or other excipients. The mixture is heated with a warm fire for several hours, allowing the removal of impurities such as HgCl_2 , $\text{Hg}(\text{CN})_2$, and residual toxins from the initial washing [76]. Key factors to consider during decoction include the volume of water, the intensity of the heat (whether strong or slow), and the duration of the process. Excess water, improper cooking time, or incorrect temperature can reduce the effectiveness of the decoction [90]. Iron, copper, and aluminum utensils should be avoided, as these materials may react with the herbal compounds [91]. Sometimes, *A. kusnezoffii* is decocted two or three times to maximize its benefits and minimize waste [91]. Historically, decoction was widely used during the Song, Ming, and Qing Dynasties, with black soybean frequently employed as an adjuvant in the process.

Maceration

Maceration has been used in traditional medicine for centuries Chen et al. [92]. Studies have shown a direct relationship between the time of maceration and the yield of active herbal compounds. Maceration employs different solvents, with water being one of the most effective for processing herbs. In addition to water, methanol and water-alcohol mixtures are also commonly used to extract active compounds from *A. kusnezoffii* [52]. During maceration, water-soluble substances are dissolved and removed from the herbal material, increasing the availability of chemical markers that can later be extracted with a water-alcohol mixture [92]. *A. kusnezoffii* roots are typically macerated in an ethanol–water solution inside sealed extraction vessels at room temperature to prevent solvent evaporation. This process softens and breaks down the roots, facilitating the release of secondary metabolites. After a designated period, the mixture is filtered or decanted to separate the liquid extract from the solid materials [93]. Maceration enhances the dispersion of concentrated solution around the surface of the particles and allows fresh solvent to interact with the particles for further extraction [94]. This process leads to the formation of non-toxic compounds, such as benzoylaconine, through hydrolysis [46]. Additionally, maceration converts diester diterpenoid alkaloids in *A. kusnezoffii* to the less toxic monoester diterpenoid alkaloids [95]. In ancient times, maceration of *A. kusnezoffii* first appeared during the Ming Dynasty, where ginger juice was used as an adjuvant in the process.

Stir-frying with liquid adjuvants

Stir-frying with vinegar (Cuzhi in Chinese)

Vinegar is a widely used liquid adjuvant known for both its medicinal properties and its global use as a food condiment [96]. In TCM, vinegar is commonly used to process *A. kusnezoffii*, primarily for its pain-relieving effects [15]. The majority of *A. kusnezoffii* alkaloids, such as aconitine (1), mesaconitine (2), and hypaconitine (3), are either insoluble or only slightly soluble in water due to their complex, hydrophobic structures [97]. However, their solubility increases significantly when they form acetates with acetic acid [44]. Vinegar is also used in the preparation of other herbs in TCM. For instance, vinegar is used to process *Yahushua* (*Corydalis Rhizoma*), a herb known for its analgesic effects. In experiments on mice subjected to thermal stimulation to induce pain, *Corydalis* was found to significantly raise the pain threshold. Moreover, the analgesic effects of vinegar-processed products were markedly superior to those of raw products, suggesting that the dissolution of alkaloids was enhanced by stir-frying with vinegar [98].

Stir-frying with salt (Yanzhi in Chinese)

Highly concentrated salt solutions, or brine, are used to enhance the dissolution of *A. kusnezoffii* alkaloids by dissociating chloride ions in water, which then form salts with the alkaloids [4]. Beyond *A. kusnezoffii*, brine is also employed to improve the dissolution of alkaloids during the processing of other herbs, such as *Huang-bo*, by increasing the processing temperature [99].

Stir-frying with ginger juice

In this method, ginger juice is added to cleaned and cut crude *A. kusnezoffii*, which is then stir-fried to allow the ginger juice to gradually permeate the interior of the herb [5]. Other liquid adjuvants used in the stir-frying of *A. kusnezoffii* include sesame oil and honey. Sesame oil aids in binding and neutralizing certain toxic alkaloids, while honey acts as a binding agent. Additionally, both sesame oil and honey enhance the taste and texture of *A. kusnezoffii*, making the final product easier to consume [47].

Other methods of processing *A. kusnezoffii*

In addition to the methods mentioned above, *A. kusnezoffii* can also be processed through decorticating and burning. After being dried and ground, the herbal raw materials are stored under the same conditions before decorticating [100]. Decorticating methods for *A. kusnezoffii* date back to the Tang, Song, Jin Yuan, and Qing Dynasties. Burning is another traditional processing technique used for alkaloid-rich herbs, and its use in processing *A. kusnezoffii* emerged during the Jin Yuan Dynasty, originating from the *Danxi Xinfa* text in 1347 CE [76].

Use of adjuvants during processing

During the processing of *A. kusnezoffii*, various adjuvants are used, including water, wine, black beans (*Phaseolus vulgaris*), rice, vinegar, salt, ginger and ginger juice, lime, sesame oil, wheat bran, alum, soybeans, honey, licorice, brine, and others [101]. These adjuvants are believed to aid in detoxifying *A. kusnezoffii* and enhancing its medicinal properties. In certain cases, additional adjuvants such as milk, urine, black bean extracts, turmeric, and lemon juice are employed in the processing [87]. The use of cow milk, for example, during extraction significantly reduces the toxic alkaloids aconitine (1), mesaconitine (2), hypaconitine (3), and bewutine (63), which are found in unprocessed *A. kusnezoffii*. Specifically, processing with milk decreased the content of aconitine (1), mesaconitine (2), and hypaconitine (3) from 14.405, 14.150, and 18.135 mg/kg to 3.960, 4.389, and 1.720 mg/kg, respectively, representing a 4- to eightfold reduction in these toxic alkaloids. Additionally, several new compounds

were observed in the processed *A. kusnezoffii*, including benzoylaconine (7), 14-O-veratoylneoline (38), isodelphinine (13), bullatine B (14), lipo-14-O-anisoylbikhaconine (25), and lycoctonine (37). Other studies indicate that alkaloid-based herbs can be effectively extracted with milk [46], although they become unstable at high temperatures [11]. Milk's pH, which is approximately 6.5 (slightly acidic) compared to the more basic plasma pH of 7.38–7.42, facilitates the transfer of basic compounds, such as plant alkaloids, into the cow milk [102]. Thus, two key factors appear to support the compatibility of cow milk with alkaloid-based herbs: the pH difference and the instability of the mixture at elevated temperatures. This supports the hypothesis that cow milk can significantly detoxify *A. kusnezoffii* roots. Similarly, processing *A. kusnezoffii* with cow urine has shown a significant reduction in toxic alkaloids, with aconitine (1), mesaconitine (2), and hypaconitine (3) levels decreasing to 11.125, 4.865, and 3.08 mg/kg, respectively. New components, including delphatine (68), lipo-14-O-anisoylbikhaconine (25), and sembusine-C (52), were also observed after processing with cow urine. The use of water, cow urine, and cow milk as adjuvants or solvents can therefore be effectively applied in the detoxification of *A. kusnezoffii*. However, the quality of these adjuvants must be clearly defined and controlled according to pharmacopeial standards and relevant regulatory guidelines for herbal processing [46, 103]. Other processing excipients used in the detoxification of *A. kusnezoffii* include children's urine, *Baijiu* (a type of Chinese liquor), *huangjiu* (yellow rice wine), buttermilk, and *Hezi* decoction. These substances have been used therapeutically for purposes such as tranquilization, analgesia, and treatment of conditions like edema, paralysis, swelling, gastroenteralgia, stroke, and arthritis. Such practices are common among ethnic groups in China, including the Uyghur, Tujia, Miao, Zhuang, and Mongolian communities [46, 76].

Traditional medicine uses of *A. kusnezoffii*

For over 1900 years, *A. kusnezoffii*, commonly known as “Caowu”, has been a vital component in Korean herbal medicine and TCM, where it is used to treat a variety of ailments, particularly inflammatory conditions, pain, and arthritis. Its medicinal application spans multiple regions, including China, Korea, Japan, Europe, and India. Historically, it has also been utilized as a poison, owing to its chemical composition of C-19 (C-18) diterpenoid alkaloids, such as aconitine (1), mesaconitine (2), hypaconitine (3), bulletin (42), and songorine (44). These compounds contribute to the narrow safety margin of *A. kusnezoffii*, as its therapeutic dose is very close to its toxic dose. In Europe, *A. kusnezoffii* has also been used as a poison, specifically to kill lice and parasites [44]. The

toxicity of *A. kusnezoffii* was recognized in ancient times, with historical TCM records documenting its use in weaponry. It was noted that if pounded *A. kusnezoffii* was mixed with juice, dried, and applied to an arrow, it could kill a person or animal within a short distance, often described as less than ten steps [104]. To reduce the herb's toxicity, traditional processing techniques have been employed to convert the more toxic DDA into less toxic monoester diterpene alkaloids (MDA). These methods, which include steaming, boiling, and other mechanisms, effectively lower the DDA content, making *A. kusnezoffii* safer for medicinal use. As many alkaloids are water-soluble, processing techniques that incorporate steaming and boiling have been traditionally favored to reduce toxicity while preserving therapeutic efficacy.

Pharmacological activities of *A. kusnezoffii*

A. kusnezoffii has been used in various traditional medicine systems, including Traditional Chinese Medicine (TCM), Traditional Korean Medicine (TKM), Ayurveda, and other indigenous healing practices, particularly in Asian countries. The plant is associated with a wide range of pharmacological activities, providing treatments for numerous health conditions, as illustrated in Fig. 5.

Anti-inflammatory effect

Inflammation, characterized by redness, swelling, heat, and pain, is the body's defense mechanism in response to injury or external stimuli. It plays a crucial role in the

healing process by recruiting inflammatory cells, including macrophages, neutrophils, and lymphocytes, which release a range of chemical mediators at the site of injury or infection [105]. However, prolonged inflammation can lead to the destruction of normal tissues and organs, resulting in chronic inflammation [106]. Recent studies have demonstrated that the inhibition of the cyclooxygenase-2 (COX-2) enzyme, a key player in the inflammatory response, can be achieved by treating inflammatory diseases with neoline (41), a compound extracted from *A. kusnezoffii* (43). Additionally, songorine (44) has been shown to have both preventive and therapeutic effects on carrageenan-induced acute inflammation. In mouse models, songorine inhibited acute inflammatory responses induced by arachidonic acid and acetic acid [43]. Moreover, traditional processing techniques of *A. kusnezoffii* drugs have been found to enhance the amount of lipo-alkaloids, further contributing to their anti-inflammatory properties.

Analgesics

In traditional Chinese medicine, *A. kusnezoffii* (roots and leaves) has been commonly used to manage analgesic and cardiotonic conditions. The therapeutic effects of this plant are attributed to diterpenoids and polysaccharides isolated from its roots. Some aminoalcohol-diterpenoid alkaloids (ADAs) present in *A. kusnezoffii*, such as neoline (41) and songorine (44), have shown significant effectiveness in animal models

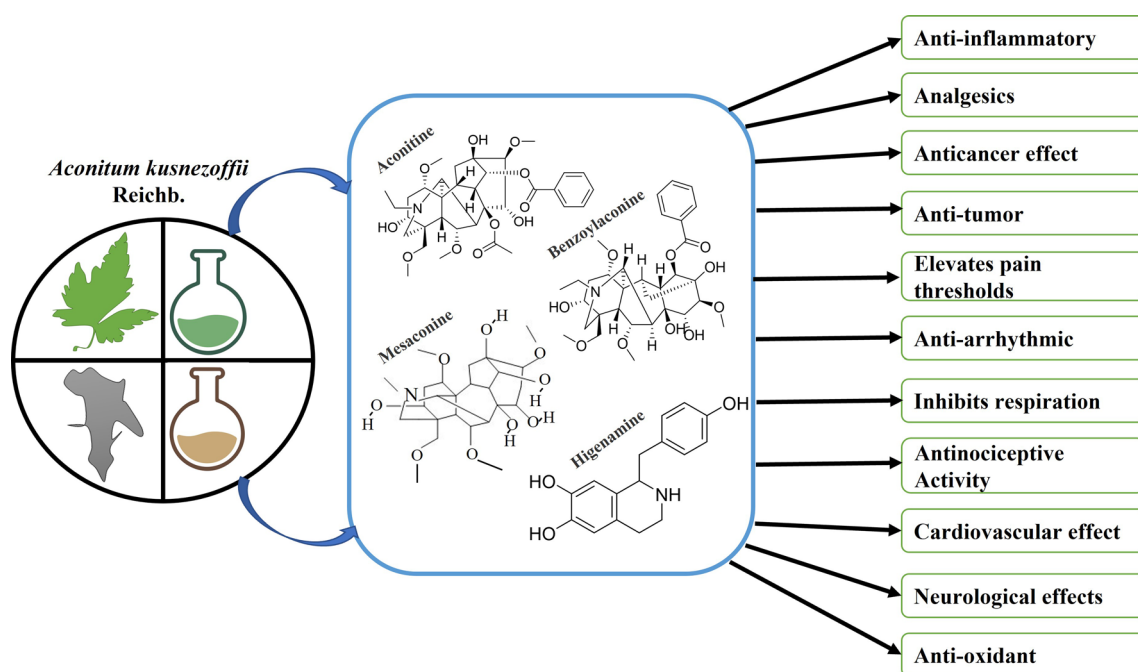


Fig. 5 Pharmacological activities of *A. kusnezoffii*

of pain, particularly neuropathic pain. Songorine (44) has demonstrated opioid receptor-dependent analgesic effects in acute pain models by increasing pain latency and reducing the number of writhing episodes in mice [107]. Neuropathic pain, which can arise from nerve damage or the side effects of anticancer drugs like oxaliplatin, as well as diabetic neuropathy, are common conditions where these alkaloids have shown promise [108]. Studies have found that in diabetic neuropathy, neoline (41) significantly increases the mechanical nociception threshold by alleviating mechanical hyperalgesia. This occurs through the inhibition of Nav1.7 voltage-gated sodium channels, which play a key role in pain signaling [109]. This inhibition process contributes to the relief of diabetic neuropathy. Additionally, research has shown that neoline (41) extracted from processed aconite roots can reduce neuropathic pain caused by anticancer drugs such as oxaliplatin and paclitaxel [110]. Further studies by Jin et al. [111] have indicated that neoline (41) increases the mechanical pain threshold, reduces mechanical hypersensitivity, and alleviates cold-induced hyperalgesia.

Results in tachyarrhythmia

Tachyarrhythmia, characterized by abnormal heart rhythms with a ventricular rate of 100 or more beats per minute, can impair cardiac output, disrupt normal heart function, and lead to severe complications such as heart failure, stroke, sudden cardiac arrest, or death [112]. In a case reported by Yeih et al. [113], a patient with tachyarrhythmia was treated with a concoction of processed *A. kusnezoffii* roots. Despite treatment, the patient continued to exhibit symptoms of tachyarrhythmia, including cold sweats, a blood pressure reading of 90/65 mmHg, and a pulse rate of 108 beats/min. A 12-lead electrocardiogram (ECG) revealed intermittent polymorphic ventricular tachyarrhythmia, along with bidirectional alterations in QRS configuration. Serum creatine kinase levels remained within normal limits. The patient was administered a 100 mg intravenous bolus of lidocaine, followed by continuous infusion at a rate of 2 mg/min for the ventricular tachyarrhythmia. Unfortunately, episodes of polymorphic ventricular tachycardia with hemodynamic compromise persisted. Consequently, 150 mg of amiodarone was infused slowly over 15 min, followed by a continuous infusion of 1300 mg over the next 36 h. The ventricular tachyarrhythmia ceased, and the patient regained sinus rhythm one hour after amiodarone administration. A total of 1450 mg of amiodarone was given without further need for oral administration. Pre-discharge evaluations, including ECG, echocardiography, and coronary angiography, were all normal.

Anti-arrhythmic

Arrhythmias can result from abnormal cellular conditions such as injury or hypoxia. For instance, during injury, an influx of Na^+ leads to intracellular calcium overload via the $\text{Na}^+-\text{Ca}^{2+}$ exchange, which can trigger arrhythmias [114]. *A. kusnezoffii* contains bioactive compounds, including diterpenoid alkaloids such as aconitine (1), mesaconine (2), and hypaconine (3). These alkaloids inhibit the activation of voltage-dependent Na^+ channels (5). The inhibition of these Na^+ channels, along with the blocking of delayed rectifier K^+ currents, plays a critical role in anti-arrhythmic activity [115]. Diterpene compounds from *A. kusnezoffii* act as competitive inhibitors of arrhythmia-inducing Na^+ channel activators. Thus, these bioactive compounds function by blocking sodium, potassium, and calcium ion channels, providing a therapeutic approach to arrhythmias [44]. Furthermore, anti-arrhythmic treatments derived from *A. kusnezoffii* target both ion channels and non-channel components, stabilizing cardiac action potentials and preventing abnormal heart rhythms [114].

Antinociceptive activity

Nociceptive pain, one of the most common types of pain, is characterized by sharp, aching, gnawing, or throbbing sensations, often caused by tissue damage from physical or chemical agents such as trauma, surgery, or burns [116]. This type of pain is triggered by acute noxious stimuli, including heat, cold, or mechanical force [117]. Over the past few decades, several plants, including *A. kusnezoffii*, have been identified as playing an antinociceptive role [27]. The pharmacological use of *A. kusnezoffii* for the treatment and management of nociceptive pain has been documented in TCM [118]. In an in vivo study by [119], the antinociceptive effects of Radix *A. kusnezoffii* extracts were tested on mice using an acetic acid-induced writhing model. After induction, a double-blind observation method was employed, and the number of writhes or stretches was recorded for each mouse over a five-minute period within a 15-min window. The effectiveness of Radix *A. kusnezoffii* was determined by calculating the mean reduction in the number of abdominal constrictions in mice treated with the extract, compared to vehicle-treated controls. The antinociceptive activity was assessed based on the decrease or inhibition of total abdominal writhes. In this study, different treatments were administered: Vehicle, Indomethacin (10 mg/kg), and Radix *Aconiti kusnezoffii* at doses of 20 mg/kg, 40 mg/kg, and 60 mg/kg. A 70% reduction in nociceptive responses was observed in the group treated with Radix *Aconiti kusnezoffii* at the highest dose (60 mg/kg). This demonstrated the antinociceptive activity of

Radix *Aconiti kusnezoffii*, as it significantly reduced acetic acid-induced abdominal writhes in a dose-dependent manner ($r=0.997$). If used at appropriate doses, Radix *Aconiti kusnezoffii* can effectively exhibit antinociceptive activity [120].

Anticancer effect

Several studies have investigated the anticancer effects of *A. kusnezoffii*, focusing on various cancer types, including breast, prostate, lung, kidney, and hepatocellular cancers. The mechanisms explored in these studies include increased immunological response, induction of apoptosis, and regulation of oncogene pathways [121]. Lycaconitine, a compound derived from *A. kusnezoffii*, has shown efficacy in combating multidrug-resistant cancer in chemotherapy, acting through mechanisms such as apoptosis induction, inhibition of cell proliferation, and anti-inflammatory activities [95]. Additionally, Zhao et al. [122] found that a water decoction of Radix *Aconiti kusnezoffii* improves intratumor hypoxia, capillary permeability, and gap-junction intracellular communication in tumor-bearing patients, which helps inhibit tumor growth and metastasis. Other *A. kusnezoffii* alkaloids with potential anticancer properties include aconitine, which demonstrates cytotoxic effects on cancer cell lines, mesaconitine (2), which inhibits cancer cell growth, hyaconitine (3), which induces apoptosis, and deoxyaconitine (10), which inhibits cancer cell proliferation [123].

Anti-tumor

Malignant tumors are among the most common forms of cancer, characterized by rapid growth, the ability to metastasize to distant tissues, lack of differentiation (anaplasia), loss of normal cellular regulation, and the tendency to invade surrounding tissues [124]. Malignant tumors pose a significant threat to human health, as they can spread throughout the body by entering blood vessels or the lymphatic system via metastasis [125]. According to Ines et al. [126], neoline (41), an alkaloid extracted from *A. kusnezoffii*, has been found to inhibit the growth of malignant tumor cells in murine colon, cervical adenocarcinoma, human melanoma, and human colon adenocarcinoma. Malignant tumors interfere with normal bodily functions by compressing, invading, and destroying normal tissues, and by producing substances that circulate in the bloodstream [127–129]. These tumors can develop regardless of age or organ [130]. Chemotherapy using medicinal compounds from *A. kusnezoffii* has been recognized as an effective treatment for malignant tumors and has been utilized in traditional medical systems, including Korean, Chinese, Mongolian, and Tibetan medicine, for decades [10]. Additionally, various

studies have demonstrated that herbs from the *Aconitum* genus, including *A. kusnezoffii*, are commonly used to treat tumors, painful joints, and rheumatic arthritis [131]. Aconitine ($C_{34}H_{47}NO_{11}$), a C_{19} -diterpenoid alkaloid present in *A. kusnezoffii*, exhibits strong anti-tumor, anti-inflammatory, and analgesic properties [132]. The primary mechanisms of *A. kusnezoffii* in anticancer therapy include inducing apoptosis, inhibiting cancer cell proliferation, and preventing cancer cell migration. A study by Yang et al. [133] confirmed the efficacy of *A. kusnezoffii* alkaloids in inhibiting malignant tumor growth in animal and cellular models. Through chemotherapy, *A. kusnezoffii* exerts significant anti-tumor effects by inhibiting the proliferation and migration of tumor cells, regulating the protein expression of cancer cells, and activating pathways such as the Bcl-2 family, Bax family, and inhibiting Caspase-3, Caspase-8, and Cleaved Caspase during intrinsic apoptosis [43, 134]. Furthermore, Gao et al. [135] suggests that non-starch polysaccharide (NSP) fractions found in *A. kusnezoffii* may enhance anti-tumor activity by boosting the immune system, inducing apoptosis in tumor cells, and inhibiting tumor growth.

Blocking Na^+ channel activity

A. kusnezoffii exerts pharmacological effects through its alkaloids, such as aconitine, which are potent blockers of voltage-gated sodium (Na^+) channels in nerve cells. The mechanism involves aconitine binding to these voltage-gated channels, located on the cell membranes of neurons [136]. Normally, these sodium channels open in response to changes in the cell's membrane potential (depolarization), allowing sodium ions to flow into the cell, a process essential for generating nerve impulses. Aconitine alters the conformation of sodium channels, preventing them from opening in response to depolarization. This action blocks the influx of sodium ions into neurons, thereby impairing their ability to depolarize properly, leading to a loss of nerve signal transmission [137].

Cardiovascular effects

Cardiovascular diseases encompass a broad spectrum of conditions affecting the heart and blood vessels. These diseases, which continue to have a significant impact on low- and middle-income countries, manifest in various forms, including heart failure (e.g., coronary artery disease and heart failure), hypertension, heart attack, stroke, and atherosclerosis. The consequences of cardiovascular disease are multifaceted, leading to complications such as impaired blood flow, reduced oxygen delivery (resulting in tissue damage), and increased risk of blood clots (which may cause pulmonary embolism), all of which can impair immune function and contribute to organ dysfunction [138, 139]. *A. kusnezoffii* plays

a significant role in the management and recovery from cardiovascular disease complications [140]. Its cardiovascular effects include: (a) Anti-arrhythmic properties: *A. kusnezoffii* stabilizes cardiac rhythm by acting on ion channels crucial to the initiation and propagation of action potentials in cardiac cells. This anti-arrhythmic action helps normalize heart rate and prevent arrhythmias (irregular heartbeats). Key alkaloids contributing to these effects include aconitine (1), mesaconitine (2), hyaconitine (3), and lycoctonine [11, 69]. (b) Vasodilation: *A. kusnezoffii* induces vasodilation, which widens blood vessels, improving blood flow and enhancing the body's ability to respond to infections and repair tissue damage. This mechanism is particularly beneficial in managing hypertension and other cardiovascular conditions. Alkaloids such as aconitine (1), mesaconitine (2), and hyaconitine (3) are involved in promoting vasodilation [141, 142]. (c) Anti-inflammatory properties: Alkaloids like aconitine (1), mesaconitine (2), hyaconitine (3), and benzoylaconine (7) in *A. kusnezoffii* help reduce inflammation in the endothelium and myocardium, stabilize plaques, and lower the risk of cardiovascular complications. (d) Analgesic properties: The analgesic effects of *A. kusnezoffii* help control cardiovascular-related pain, reducing stress on the heart and contributing to overall cardiovascular health through its anti-inflammatory and pain-relieving properties [143]. (e) Antioxidant properties: Oxidative stress, caused by the excessive production of oxidants—highly reactive molecules containing oxygen—can contribute to the pathophysiology of cardiovascular diseases. These oxidants damage lipids, proteins, DNA, and cells in the cardiovascular system, leading to endothelial dysfunction and inflammation [144, 145]. Antioxidant-rich herbs, such as *A. kusnezoffii*, play a key role in preventing cardiovascular diseases by protecting endothelial function, reducing inflammation, and supporting overall cardiovascular health. The antioxidant properties of *A. kusnezoffii* contribute to mitigating oxidative stress and promoting heart health [95, 146].

Elevates pain thresholds

Several diseases are known to lower pain thresholds, causing significant discomfort. Conditions such as inflammatory diseases, cancer, autoimmune disorders, central nervous system disorders, neuropathic pain, and chronic pain conditions like fibromyalgia and arthritis are among the most common culprits [147]. However, numerous medicinal plants, including *A. kusnezoffii*, have been reported to increase pain thresholds. The dry roots of *A. kusnezoffii* contain aconitine alkaloids that interact with sodium channels in nerve cells. This interaction inhibits the transmission of pain signals, ultimately increasing pain thresholds. The analgesic and

anti-inflammatory properties of *A. kusnezoffii* are linked to its effects on both the peripheral and central nervous systems, reducing the sensitivity of neurons to pain stimuli and influencing pain perception in the central nervous system [148]. Additionally, treatment with processed Radix *A. kusnezoffii* has been shown to increase the activity of key antioxidant enzymes such as glutathione peroxidase, glutathione reductase, and superoxide dismutase in the liver. This increase potentially mitigates pain, as these enzymes play a crucial role in the liver's antioxidant defense system and help reduce oxidative stress. These effects are associated with decreased inflammation, protection of nerve cells, modulation of pain pathways, and overall improvement of health. However, due to the high toxicity risk associated with improper use of *A. kusnezoffii*, its safe application must be carefully managed [149, 150].

Gastroenteritis (Stomach Flu)

Gastroenteritis is an inflammation of the gastrointestinal tract, affecting both the stomach and intestines. Symptoms typically include cramps, abdominal pain, vomiting, and diarrhea. The antimicrobial, anti-inflammatory, and pain-relief properties of *A. kusnezoffii* contribute to reducing bacterial load in gastroenteritis, alleviating inflammation of the gastrointestinal tract, and managing abdominal pain and cramps [151]. Other pharmacological uses of *A. kusnezoffii* include the treatment and prevention of cough, asthma, gouty arthritis, edema, and certain gynecological disorders such as irregular menstruation and dysmenorrhea, as well as the management of rheumatic fever and joint pain [151, 152]. While *A. kusnezoffii* is known for its therapeutic benefits, it also possesses bioactivities that can be harmful and toxic to the body. Some of the negative pharmacological effects are outlined below.

Inhibits respiration

Diterpenoid alkaloids from *A. kusnezoffii* are potent inhibitors of cellular respiration. This is due to their ability to block voltage-gated sodium channels in tissues such as nerve and muscle cells, thereby preventing the normal influx of sodium ions during action potentials [5].

Neurological effects

The diterpenoid alkaloids found in *A. kusnezoffii*, such as aconitine, can have potentially lethal effects on the central nervous system and cardiovascular system. These alkaloids act as neurotoxins by binding to and altering the function of voltage-gated sodium channels (Na^+) in neurons. This results in the prolonged opening of sodium channels, leading to sustained depolarization of the cells and excessive stimulation of nerves [42, 153].

Common formulations and products of *A. kusnezoffii*.

A. kusnezoffii has been incorporated into numerous formulations and herbal combinations over centuries in both Korean herbal medicine and TCM. Some of the common formulations involving *A. kusnezoffii* include: **Single herb decoctions:** *A. kusnezoffii* is used alone to treat specific conditions, such as pain [154]; **Herbal combinations:** Due to its toxicity, *A. kusnezoffii* is often included in various herbal formulations where it plays different roles, such as the primary, secondary, or complementary herb. This approach is reported to enhance its therapeutic efficacy while reducing its potential toxicity [5]; **TCM classical formulas:** For centuries, *A. kusnezoffii* has been used in classical TCM formulas to address specific patterns of disharmony and various health conditions [155]. For instance, it is a key component in formulas like “Sini Tang,” “Guifu Dihuang,” and “Fuji Lizheng Won,” which are used to treat conditions such as rheumatism, rheumatoid arthritis, cold-related ailments, and pain [37]; **Topical applications:** *A. kusnezoffii* is also used in topical treatments, such as ointments and creams, for its analgesic properties [156]. Formulations containing *A. kusnezoffii* are designed to address issues related to processability, stability, absorption, and therapeutic efficacy.

Toxicology, toxicity reduction, and detoxification

Despite its therapeutic benefits in treating pain, gout, cancer, and inflammation, *A. kusnezoffii* is highly toxic, necessitating careful detoxification to minimize health risks [5]. The primary toxic compounds in *A. kusnezoffii* are C₁₉-norditerpenoid ester alkaloids, such as

aconitine (1), mesaconitine (2), and hyaconitine (3) [157]. These alkaloids activate sodium channels, causing widespread membrane excitation in both the cardiovascular and nervous systems, leading to symptoms such as chest pain, cardiac arrhythmias, palpitations, hypotension, numbness, heart failure, and, in severe cases, death [86], [158]. Additionally, the toxic alkaloids can be absorbed through the skin during topical application, making it potentially dangerous even when applied externally. No specific antidote for *A. kusnezoffii* poisoning has been identified, but supportive treatments aimed at restoring normal bodily functions are employed in cases of poisoning [52]. Figure 6 presents the toxicology and detoxification of *A. kusnezoffii*.

Toxicology of *A. kusnezoffii*.

While traditional medicine is often assumed to be safe, numerous studies have shown that many medicinal plants can be highly toxic. Due to its toxic alkaloids, *Aconitum* is famously known as the “Queen of Poisons,” highlighting the notorious toxicity of *A. kusnezoffii*. Shakespeare even referenced the potency of the *Aconitum* herb in his play *Romeo and Juliet*, in which Romeo uses *Aconitum* poison to commit suicide [159]. According to Chan et al. [5], as little as 2 mg of *Aconitum* can be lethal to an average human, emphasizing the need for extreme caution when using *A. kusnezoffii* in herbal medicine. Research by Nyirimigabo et al. [44] confirms that the entire *A. kusnezoffii* plant is toxic, with higher concentrations of toxic compounds found in the roots and flowers compared to the leaves and stems, as shown in (Fig. 3).

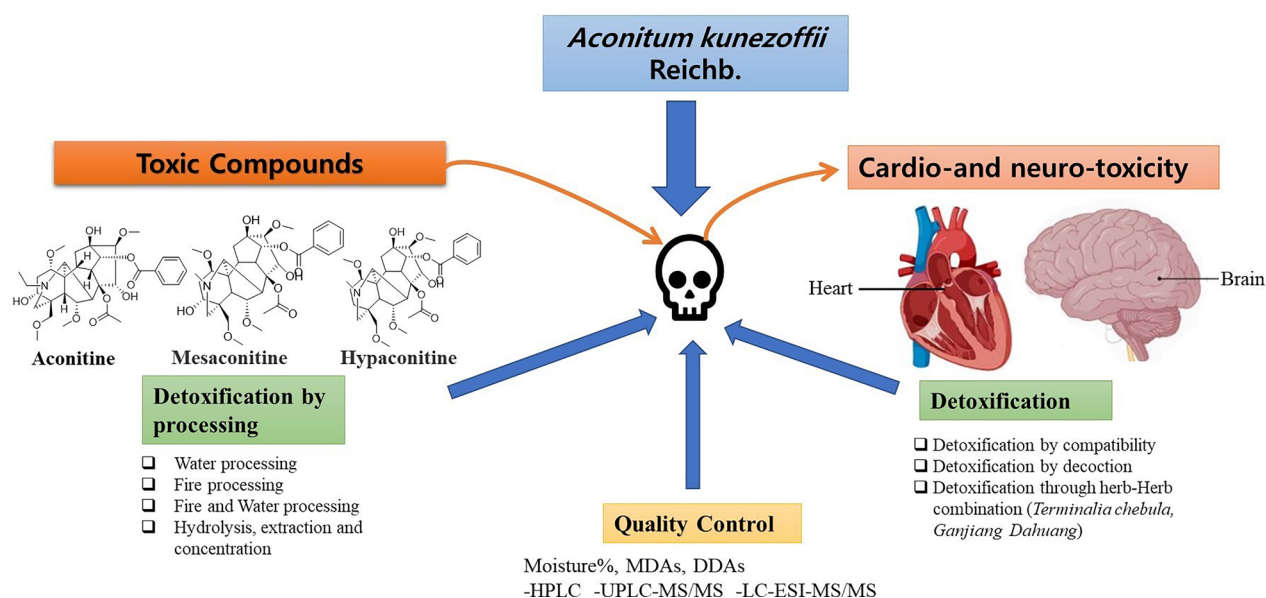


Fig. 6 Toxicology and detoxification of *A. kusnezoffii*

At low doses, *A. kusnezoffii* can be medicinal, but at higher doses, it becomes toxic, potentially causing death through ventricular tachyarrhythmia and cardiac arrest. The toxicity is primarily due to DDAs, such as aconitine (1), mesaconitine (2), hyaconitine (3), and talatisamine (43) in the aconitine category, and kobusine (15), ignavine (16), atisine (40), songorine (44), and napelline (50) in the atisine category. These alkaloids, particularly mesaconitine (2) and hyaconitine (3), can cause respiratory muscle paralysis. The main components responsible for the toxicity of *A. kusnezoffii* are diester diterpene alkaloids containing acetyl groups. However, through hydrolysis or traditional Chinese processing methods like “Paozhi,” these alkaloids can be transformed into less toxic forms [86]. The toxic effects of DDAs occur by acting on voltage-sensitive sodium channels in the cell membranes of cardiac and skeletal muscles, leading to cardiovascular toxicity and resulting in arrhythmias [52]. In addition, the toxic alkaloids affect the heart, digestive system, respiratory system, and central nervous system, leading to both cardiotoxicity and neurotoxicity, which manifest in a variety of symptoms [24]. The primary symptoms of *A. kusnezoffii* toxicity affect the central nervous system and the heart, with gastrointestinal symptoms also commonly observed. To ensure the safe use of *A. kusnezoffii*, careful dose management is critical. In a 14-day study conducted by Kim et al. [39], *A. kusnezoffii* pharmacopuncture was used to determine the lethal dose (LD₅₀) in 6 week-old Sprague–Dawley rats. This non-clinical study involved 40 rats (20 male and 20 female), divided into four groups of 10 (5 male and 5 female per group). Three experimental groups received *Aconitum kusnezoffii* Reichb. pharmacopuncture (AKRP) injections of 0.1, 0.2, or 0.3 ml, while the control group was injected with 0.3 ml of normal saline solution. General symptoms, mortality rates, and weight changes were observed from day 1 to day 14. After 14 days, the rats underwent further evaluation, including weight measurements, terminal necropsy of principal organs, and paraffin embedding. The study found that the LD₅₀ of AKRP administered via IV was greater than 1.77 ml/kg. No deaths occurred in any group, and while some changes in the weight of male rats were noted, there were no significant weight changes in female rats. Additionally, no abnormalities were found in the organs or tissues during terminal necropsy. These findings suggest that the LD₅₀ of AKRP is higher than 1.77 ml/kg in both male and female rats, indicating that AKRP is safer than previously reported [160]. However, despite these findings, *A. kusnezoffii* remains highly toxic and must be handled with extreme caution. As Lai et al. [161] reports, symptoms of acute toxicity from *A. kusnezoffii* can occur rapidly after ingestion.

A. kusnezoffii was originally classified as toxic in *Shen Nong's Herbal Classic* due to its potential for severe toxicity. Improper dosing can cause damage to vital organs, including the liver, kidneys, and heart. The primary toxic effects are cardiovascular toxicity and neurotoxicity [63]. Despite its toxicity, the final processed product of *A. kusnezoffii* is used to treat various conditions, often administered orally. However, the absorption of *A. kusnezoffii* into the bloodstream is complex, involving a double-absorption peak phenomenon for its main alkaloids. This complexity is due to delayed gastric emptying caused by low stomach pH and variability in absorption across different regions of the gastrointestinal tract [34]. Traditionally, processed *Aconitum* roots were considered safe and ready for use when the decoction no longer caused numbness on the tongue upon tasting [162]. Over the centuries, different Chinese dynasties contributed significantly to advancing medicinal practices related to *A. kusnezoffii*. These dynasties developed meticulous, multi-step procedures to reduce the toxicity of *A. kusnezoffii* roots while preserving their therapeutic properties, ensuring the herb could be safely and effectively used [77].

Toxicity reduction

A. kusnezoffii is widely recognized for its medicinal value in both Korean Traditional Medicine and TCM. However, it is also known for its highly toxic properties, which can adversely affect the heart, liver, kidneys, and nervous system [163]. While there is no clear literature defining the exact correlation between dosage and toxicity of *A. kusnezoffii*, it is well-documented in TCM that unprocessed aconite roots are extremely toxic due to the presence of DDAs. This explains why aconitine can only be safely used medicinally after undergoing proper processing. Processing aconitine transforms the toxic alkaloids from the highly toxic DDA form to the less toxic MDAs. Ancient TCM texts have long highlighted the critical role of processing methods in detoxifying toxic herbs like *A. kusnezoffii* to ensure safe clinical use. The most common traditional detoxification methods for *A. kusnezoffii* include heat processing, stir-frying, water processing, and decoction with various adjuvants such as black soybeans, mint, ginger, rice, wine, and salt solutions. These methods play a key role in reducing the herb's toxicity. With advancements in technology, over 70 detoxification techniques have been developed, including methods involving hydrolysis and compatibility with other substances. As shown in (Fig. 7), the toxicity reduction strategies for *A. kusnezoffii* can be categorized into five main groups: water processing, fire processing, combined fire and water processing, detoxification by

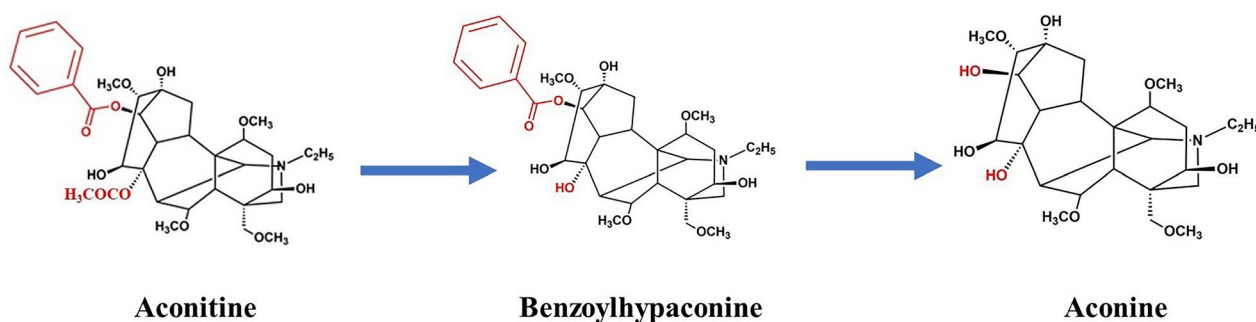


Fig. 7 An example of the two-step hydrolysis process of *A. kusnezoffii*

compatibility, and chemical detoxification through alkaloid hydrolysis [5, 11].

Water processing

Water processing is one of the most documented methods for reducing the toxicity of *A. kusnezoffii* in TCM. Repeated soaking of the raw materials in water and boiling them can reduce diterpene-diester alkaloid content by 36.8% and monoester alkaloid content by 25.5%. This reduction in toxic alkaloid concentrations, including aconitine (1), mesaconitine (2), and hypaconitine (3), makes the herb safer for consumption [77]. Additionally, various adjuvants are commonly used to balance therapeutic efficacy with safety. Some of the most commonly used adjuvants to neutralize toxic alkaloids in *A. kusnezoffii* include saltwater, ginger juice, rice water, vinegar, wine, and brine [5]. Furthermore, *Puji Fang*, the largest TCM prescription book in history, recorded the use of ginger juice maceration as an effective method for neutralizing toxic alkaloids [4].

Fire processing

Fire processing methods are also employed to reduce the toxicity of *A. kusnezoffii* by decomposing toxic alkaloids, such as aconitine (1), mesaconitine (2), and hypaconitine (3), through exposure to high temperatures [77]. This process involves heating the raw herb without adding water or other liquid adjuvants. Different fire processing techniques used to detoxify *A. kusnezoffii* include roasting, burning, baking, charring, scalding, calcining, and stir-frying with solid adjuvants [72]. These methods vary depending on the temperature, duration, and technique employed. To preserve the quality and efficacy of the processed products, the heating process, especially during charring, is carefully controlled to prevent excessive heat exposure, a practice known as "nature-preservative burning" [76].

Fire and water processing

The combination of fire (heat) and water (solvent) processing transforms highly toxic *A. kusnezoffii* alkaloids into less toxic derivatives. This method includes boiling, decocting, steaming, and stir-frying with liquid adjuvants. Besides water, various liquid adjuvants, such as wine, salt, ginger juice, rice water, and vinegar, are used in conjunction with heating methods like baking, stir-frying, or decoction to detoxify the herb. These adjuvants can be used independently or mixed to enhance detoxification [15, 44]. According to Wang et al. [164], pressure-steaming provides an ideal environment for transforming toxic aconitine alkaloids from the more poisonous DDA form to the less toxic MDA form, which can then be used for their anti-inflammatory and analgesic effects. This process involves placing crude herbs and pure water in an autoclave, where the mixture is steamed at 127 °C under pressurized conditions (0.15 MPa) for 60 to 90 min [11]. Under normal atmospheric pressure, steaming takes about 6 to 8 h [4].

Hydrolysis, extraction, and concentration

According to Cui et al. [65], DDAs, primarily aconitine in *A. kusnezoffii*, contain ester groups that significantly contribute to the herb's high toxicity. However, hydrolysis provides a safe and effective method for breaking down these toxic ester groups, converting DDAs into less toxic MDAs and, subsequently, into NDAs. The hydrolysis of *A. kusnezoffii* involves the cleavage of ester bonds under acidic or basic conditions in the presence of water, eliminating one of the ester groups in the DDA molecules. This promotes the formation of MDA and NDA molecules. During this two-step hydrolysis process, as depicted in Fig. 7, DDAs are converted to MDAs and eventually to NDAs by reducing the number of ester groups attached to the diterpenoid alkaloids. This effectively decreases toxicity without compromising the herb's bioactive properties [165, 166]. The primary goal

of the hydrolysis process in *A. kusnezoffii* is to reduce the toxicity of alkaloids such as aconitine (1), mesaconitine (2), and hypaconitine (3), converting them into less toxic compounds like benzoylaconine (7) and aconine (36). According to Shaw et al. [167], the hydrolysis process reduces aconitine content by approximately 90%. Initially, *A. kusnezoffii* contains around 0.199% aconitine alkaloid. After processing and hydrolysis, the aconitine percentage drops to 0.0084% and then to 0.034%. To maximize the therapeutic potential of *A. kusnezoffii*, extraction and concentration are performed following hydrolysis. Extraction is carried out using deep eutectic solvents (DESs) and a gas bath thermostat oscillator. DESs play a crucial role in detoxifying toxic alkaloids, while the gas bath thermostat oscillator facilitates the extraction process. Several factors influence the extraction of hydrolysates, including temperature, pH, extraction time, liquid-to-solid ratio, and the water content of the DESs. Concentration of the *A. kusnezoffii* extract is achieved through rotary evaporation, which efficiently removes solvents while enhancing the stability and efficacy of the bioactive compounds [168]. The hydrolysates of *A. kusnezoffii* include aconitine (1), mesaconitine (2), hypaconitine (3), benzoylaconitine (7), among others. During the hydrolysis, extraction, and concentration processes used to detoxify *A. kusnezoffii*, DESs demonstrate notable efficiency in DDA hydrolysis, while increased pH levels improve the extraction efficiency of MDAs, as the hydrolysis of ester bonds is pH-dependent [169]. Thus, detoxification via hydrolysis facilitates the transformation of highly toxic aconitine into lower-toxicity compounds

like benzoylaconine (7) and aconine (36), as shown in Fig. 8 [170]. These processes are verified using advanced analytical techniques, such as capillary liquid chromatography (LC) combined with fast atom bombardment mass spectrometry (FAB-MS), which offer high selectivity and sensitivity in detecting hydrolysis products [51].

DDAs are sensitive to heat and water, undergoing hydrolysis or decomposition, which results in the loss of acetic acid and their transformation into MDAs and NDAs [69].

Clinical symptoms of *A. kusnezoffii* toxicity

Symptoms of *A. kusnezoffii* poisoning include neurological issues, arrhythmia, chest pain, cardiovascular complications, gastrointestinal distress, bradycardia, chest tightness, dizziness, generalized muscle dysfunction, nausea, vomiting, palpitations, convulsions, hypotension (characterized by a decrease in systolic blood pressure), shock, and coma. In severe cases, ventricular tachycardia and ventricular arrhythmia can occur, potentially leading to death due to ventricular tachyarrhythmia and cardiac arrest, usually within 24 h of poisoning. There is no specific antidote for *A. kusnezoffii* poisoning; however, supportive treatment is typically applied to mitigate the symptoms and alleviate the condition [4, 171].

Detoxification

Detoxification of *A. kusnezoffii* is critical in herbal medicine due to its potential to cause poisoning in individuals who consume it [136]. While *A. kusnezoffii* is used to treat various conditions, improper handling (even at low

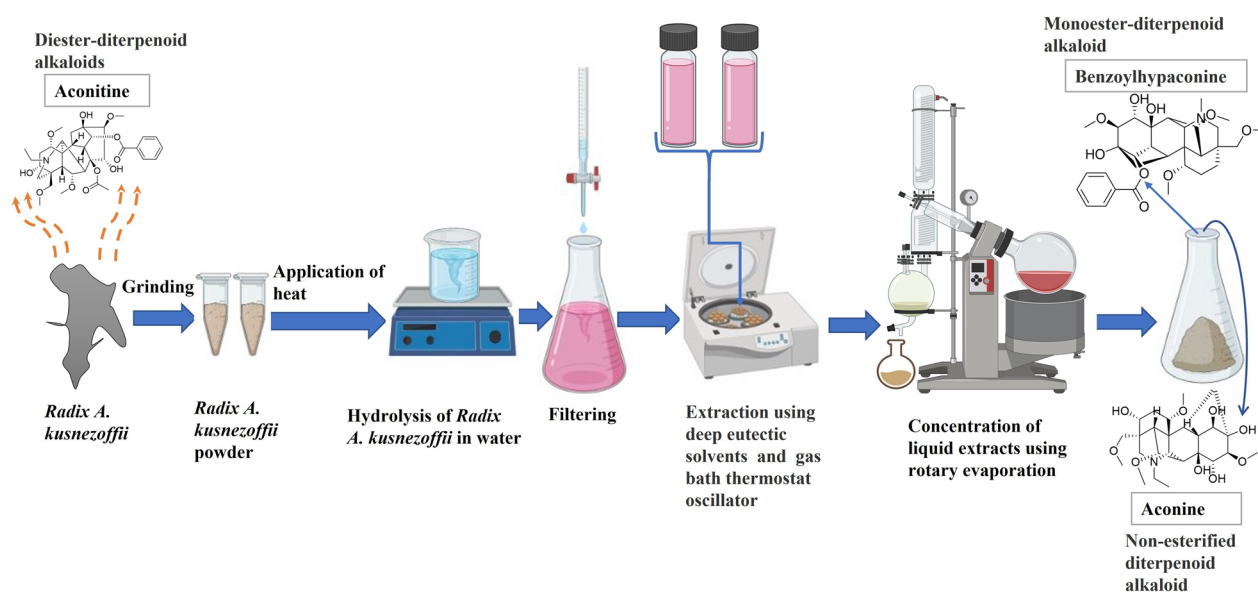


Fig. 8 Detoxification of *A. kusnezoffii* through hydrolysis, extraction, and concentration

doses) can lead to adverse effects. To reduce the risks associated with its toxicity while preserving its therapeutic properties, several detoxification processes have been implemented [4].

Detoxification by compatibility

According to Liu et al. [172], the combination of raw *A. kusnezoffii* with *Terminalia chebula* in a mass ratio of 3:1 significantly reduces the toxicity of aconitine (1), mesaconitine (2), and hyaconitine (3). In vivo experiments conducted on rats investigated the detoxification effects of *T. chebula* on *A. kusnezoffii*-induced cardiotoxicity. Rats were divided into three groups, each exposed to different mass ratios of raw *A. kusnezoffii*-*T. chebula* (1:3, 1:1, 3:1). The relevant mixture was administered intragastrically once a day for three consecutive weeks. The study found that the 3:1 ratio of *A. kusnezoffii*-*T. chebula* effectively decomposed the toxic components causing cardiotoxicity. The group treated with the 3:1 ratio showed myocardial tissue structure comparable to the control group, while the other ratios (1:3 and 1:1) exhibited signs of cell shrinkage and cytoplasmic staining. This confirms that the 3:1 ratio is the most effective herb-to-herb combination for detoxifying *A. kusnezoffii*.

Detoxification by decoction

Decoction plays an essential role in detoxifying poisonous herbs like *A. kusnezoffii*, enhancing their safety during use [173]. Decoction helps stabilize ester-diterpenoid alkaloids present in *A. kusnezoffii* during the process. The acute toxicity of detoxified *A. kusnezoffii* decreases with prolonged decoction time, improving its safety and efficacy. As the decoction time increases, the alkaloids (DDAs) are hydrolyzed into less toxic metabolites (MDAs and NDAs), reducing the herb's toxicity without affecting its pharmacological activity [4]. It is recommended to add water at the beginning of the decoction process. Insufficient decoction may result in poisoning [69].

Treatment and management of intoxication

In TCM, decoctions or unrefined tablets of *A. kusnezoffii* are commonly used for disease treatment. However, due to the herb's low safety margin, improper use of *A. kusnezoffii*, such as inadequately processed roots or large doses, can lead to poisoning and, in some cases, fatalities. Patients experiencing *A. kusnezoffii* poisoning require immediate medical attention due to the high risk of arrhythmia. Treatment should begin with continuous electrogastrogram (EGG) and blood pressure monitoring for at least 24 h, followed by laboratory tests and cardiac rhythm management to reduce the risk of heart failure and mortality [174]. According to Jeon et al. [175], gastric lavage and activated charcoal should be administered

to minimize gastrointestinal absorption in cases of *Aconitum* poisoning. If the patient exhibits low blood pressure, intravenous blood pressure stabilizers and preload augmentation should be provided. Additionally, charcoal hemoperfusion may be used to remove aconite compounds from the bloodstream in suspected poisoning cases [176]. Recovery times vary: mildly intoxicated patients typically recover within 1.5 to 2 days, while those with cardiovascular complications may require 7 to 9 days. Other treatments for *Aconitum* poisoning include intravenous dopamine infusion for hypertension, interventions for ventricular tachycardia, and treatment for ventricular ectopic beats [177].

Herb-Herb combination for therapeutic enhancement

The use of multiple herbs in combination can mitigate *A. kusnezoffii* poisoning [4]. In TCM, herb combinations have been reported to yield positive outcomes in treating poisoning cases [171]. A notable example is the combination of aconite and licorice, which has been effectively used for the detoxification of processed *Aconitum* roots [178]. However, Coulson et al. [179] emphasizes the need for caution in combining certain herbs, outlining various taboos in herbal formulations and providing guidelines for scientifically validated herb combinations. In multi-herb formulations, different herbs play distinct roles, as depicted in Fig. 9.

In the hierarchical structure of herb-to-herb interactions, *A. kusnezoffii* assumes the role of the “Emperor Herb,” which is the most important herb in the formulation. It addresses the primary disease or symptoms, plays the leading role, and induces perspiration. Licorice serves as the “Minister Herb,” reinforcing and supporting

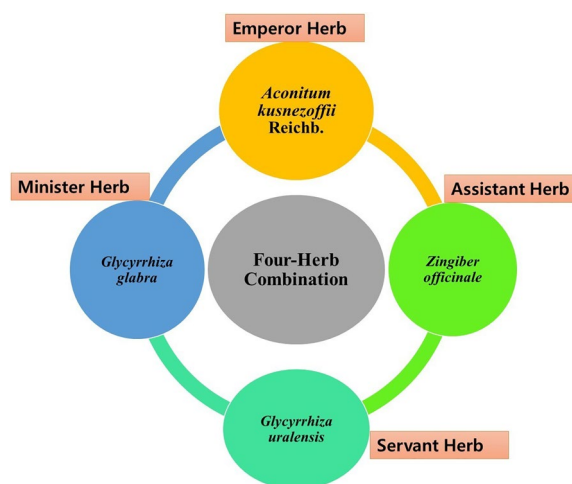


Fig. 9 The Four-Herb Combination with *A. kusnezoffii* as the Main (Emperor) Herb [180, 181]

the Emperor Herb, either as an adjunct or by addressing minor symptoms. It also warms the channels, dispels excessive coldness from the body, and expels pathogenic factors from muscles and skin. The “Assistant/Adjuvant Herb,” typically fresh ginger (*Zingiber officinale*), optimizes the therapeutic effects of both the Emperor and Minister Herbs, reduces their toxicity, minimizes side effects, and maintains a balance (such as the warm-cold effect). Finally, the “Servant/Dispatcher Herb,” commonly *Glycyrrhiza uralensis* (Gan Cao), harmonizes the entire formulation, ensuring that the herbs work together effectively and moderates the overall prescription [11, 182–184]. Beyond traditional medicine, herbs can also be combined with Western medicine. According to Zhang et al. [185], a combination of *A. kusnezoffii* and Western medicine has proven effective in treating joint swelling. This conclusion is based on a meta-analysis evaluating the efficacy and safety of using both *A. kusnezoffii* and Western medicine to treat rheumatoid arthritis (RA). Additionally, the combination of *Radix Aconiti kusnezoffii* with *Chebulae Fructus* and *Glycyrrhizae Radix Rhizoma* has been shown to reduce the toxicity of *Radix Aconiti kusnezoffii*. Studies indicate that this combination helps mitigate liver damage caused by the toxic effects of *Radix Aconitum kusnezoffii* [186]. Moreover, herb combination therapy has been successfully applied to treat diseases such as COVID-19, AIDS, and cancer, among others [187]. Such combinations have been shown to increase the efficacy of drugs while simultaneously reducing the side effects and toxicity of the formulations.

Herbs incompatible with *A. kusnezoffii*.

While the combination of certain herbs has been shown to reduce the toxicity of *Aconitum*, some herbs are known to be incompatible with species from this genus. These incompatible herbs are traditionally grouped under the “18 incompatible medicaments,” which include *Bailian* (*Ampelopsis radix*), *Gualou* (*Trichosanthis fructus*), *Baiji* (*Bletillae rhizome*), *Beimu* (*Fritillaria cirrhosa* bulb), *Pinellia ternata* (*Thunb*), and *Banxia* (*Pinelliae rhizome*). According to Zhou et al. [188], the combination of these herbs with *Heishunpian* significantly increases cardiotoxicity. In cases of herb incompatibility, overdose, or acute poisoning resulting from the misuse of *A. kusnezoffii* herbal medicine, it is essential to initiate immediate treatment and closely monitor the patient’s vital signs. Symptoms to watch for include gastrointestinal symptoms (nausea, diarrhea, vomiting), neurological symptoms (dizziness, paresthesia, weakness), and cardiovascular symptoms (arrhythmia, hypotension, bradycardia, and palpitations). Within 24 h of an *A. kusnezoffii* overdose or acute poisoning, a patient’s condition can deteriorate rapidly. This deterioration is often related to

prolonged depolarization, which can complicate management. While cardiopulmonary bypass can aid in control, treatment is generally supportive due to the lack of a specific antidote [189].

Several treatment strategies are recommended as follows:

- a. Ventricular arrhythmias: The first-line treatment involves intravenous (i.v.) administration of amiodarone, an anti-arrhythmic medication [189].
- b. Bradycardia and conduction blockage: Atropine (1–2 mg i.v. for an adult) is administered to correct bradycardia and conduction blocks caused by over-excitation of the autonomic nervous system [189].
- c. Alternative treatment for ventricular arrhythmias: Flecainide (i.v.) is also used as a first-line treatment for ventricular arrhythmias [189].
- d. Lidocaine: Subcutaneous injection of 1 mg of lidocaine can help manage primary symptoms of *A. kusnezoffii* poisoning, such as tachycardia, premature pulse, facial flushing, and irritation due to ectopic rhythm [11].
- e. Herbal formulas: In emergency cases of *A. kusnezoffii* overdose, herbal formulas containing *Flos Lonicerae* (Jinyinhua), crude *Radix Glycyrrhizae* (Gancao), and *Semen Phaseoli* (Ludou), each in a 30 g decoction, are commonly applied [11].
- f. Oral detoxification: The roots of *Dipsacus asperoides* (Xuduan), taken orally in juice form, can significantly detoxify *A. kusnezoffii* intoxication when administered within 30 min of acute poisoning [190].
- g. Chronic intoxication symptoms: Chronic symptoms such as irritation, dizziness, anxiety, and tachycardia can be managed with repeated administration of crude *Radix Glycyrrhizae* (Gancao) or “Shengmai Yin Decoction,” which contains *Radix Ginseng*, *Radix Ophiopogonis*, and *Fructus Schisandrae* [190].

In all cases of suspected *A. kusnezoffii* poisoning, heightened vigilance and care are essential. Patients should be treated in an emergency care unit, and their gradual symptom improvement should be closely monitored for at least two days [191].

Side effects of using *A. kusnezoffii*

Although *A. kusnezoffii* is renowned for its potent pharmacological effects, its therapeutic potential is significantly limited by the presence of hypertoxic alkaloids such as aconitine, mesaconitine, and hypaconitine, which can make its use dangerous [192]. Several studies have highlighted the potential side effects associated with the use of *A. kusnezoffii*. Richa et al. [153] indicates that *A. kusnezoffii* can cause serious side effects or even death

if used improperly. Aconitine, mesaconitine, and hypaconitine alkaloids, derived from *A. kusnezoffii*, are particularly known for their potent neurotoxic, cardiotoxic effects, along with other pharmacological effects [189], their toxic effects are associated with severe side effects, which can vary in severity depending on factors such as the dose, method of administration, and the individual's sensitivity to these alkaloids. These side effects include dizziness, tingling or numbness around the mouth and limbs, headache, arrhythmia, convulsions, loss of consciousness, rapid heartbeat, low blood pressure, slow heart rhythm, and cardiac failure, nausea, vomiting, and abdominal pain, drooling, difficulty breathing or suffocation and even death [5, 11, 43]. A study on body weight using *Aconiti* tuber in normal rats indicated that *Aconiti* tuber may be effective in treating obesity. However, notable side effects, including elevated liver enzymes such as alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, were observed in the groups treated with *Aconiti* tuber [193]. According to Romaiah et al. [194], increased ALT and AST levels typically indicate liver damage or inflammation, such as hepatitis, fatty liver, or drug toxicity. Elevated levels can also signal muscle injury or biliary obstruction. Therefore, *A. kusnezoffii* should be cautiously to avoid toxicity and its effects. To ensure its safe use, process before use, reduce the dosage, monitor for signs of toxicity, discontinue if adverse effects arise, and seek medical attention for severe neurotoxic or cardiotoxic reactions [5, 153].

Quality control of *A. kusnezoffii* products

A. kusnezoffii and its diterpenoid alkaloids are highly toxic, making it essential to ensure the safety and efficacy of its herbal products, particularly those used in Korean herbal medicine and TCM. Given the cardiotoxicity and neurotoxicity associated with *A. kusnezoffii* and its diterpenoids, accurately determining the qualitative and quantitative amounts of DDAs for disease treatment remains challenging [27]. Therefore, a robust quality control process is necessary to enhance the safety of *A. kusnezoffii* herbal products. This process may involve several key steps: (i) Botanical Identification: This includes the microscopic and macroscopic examination of plant parts and comparison with reference specimens. DNA analysis can also be performed to confirm the plant species' authenticity. (ii) Chemical Identification: HPLC or other analytical techniques can be employed to profile and quantify specific alkaloids present in *A. kusnezoffii*, such as aconitine (1), mesaconitine (2), and hypaconitine (3). (iii) Purity and Contamination Testing: It is crucial to test for heavy metals, such as lead, mercury, cadmium, and arsenic, which can be toxic to humans even in low concentrations and may accumulate in the plant from

environmental sources. Additionally, residual solvent testing (e.g., ethanol, methanol, acetone) must be conducted to ensure that no harmful solvent traces remain from the extraction process. Other tests include checking for foreign matter like dirt, dust, insects, or plant debris, as well as measuring moisture content to prevent microbial growth during storage [195]. Toxicological studies can be conducted using in-silico methods, mammalian and non-mammalian cell lines, or "omics" approaches, such as proteomics and transcriptomics, to further support quality control in herbal medicine [196]. Testing protocols and acceptance criteria for *A. kusnezoffii* are defined by pharmacopoeial standards, such as those found in the Korean, Chinese, and Japanese pharmacopoeias. To maintain consistency and safety, regulatory requirements are in place to govern the quality of *A. kusnezoffii* herbal products [167].

Recent advances and emerging perspectives in medicinal plants

Recent advances in herbal medicine emphasize the need for sustainable propagation and production methods, alongside innovative molecular techniques. Developments in plant propagation focus on optimizing tissue culture, cloning, and seedling production to ensure a reliable and continuous supply of high-quality medicinal plants. These advances not only support conservation efforts but also ensure the efficient availability of medicinal raw materials. One of the emerging techniques in this field is the use of Systematic Evolution of Ligands by Exponential Enrichment (SELEX)-aptamers, which are synthetic DNA or RNA molecules designed to bind specifically to target molecules. This cutting-edge technology is increasingly being used to identify and study bioactive compounds in medicinal plants. By employing aptamers to precisely target and evaluate plant metabolites, researchers can enhance the discovery of new therapeutic agents and improve the efficacy and safety of herbal treatments. In addition to propagation techniques and SELEX-aptamer technology, Chinmedomics is another emerging advancement in herbal medicine that warrants further exploration. It is a modern approach that integrates traditional medicine with advanced "omics" technologies such as metabolomics, genomics, and proteomics, to comprehensively study the effect of herbal medicine. Below is a detailed description of propagation, SELEX-aptamer and Chinmedomics advancements.

Application of propagation techniques

A. kusnezoffii, primarily found in East Asian countries such as Korea, China, Japan, Russia, and Mongolia (Fig. 1), has traditionally been harvested from the wild [5]. However, concerns about biodiversity loss and the

overharvesting of wild populations are raising serious questions about the sustainability of *A. kusnezoffii*. Additionally, climate change continues to threaten natural resources, including wild medicinal plants, exacerbating the risk to these species. The growing demand for *A. kusnezoffii* in China, driven by its therapeutic properties, has further intensified the pressure on wild populations [197]. To address these challenges, new propagation techniques for medicinal herbs have emerged. These methods integrate scientific research, conservation principles, and sustainable practices to ensure the long-term availability of herbal plants for both health and commercial purposes. The primary goals of these propagation techniques include: Cultivating and farming *A. kusnezoffii* under controlled conditions to guarantee consistent quality, quantity, and availability of herbal raw materials [198, 199]; Rapidly increasing the biomass of the plant to meet the growing demand for raw materials used in herbal medicine formulation [200]. Preserving the plant's genetic fidelity to maintain its desirable therapeutic properties [201]. These propagation strategies blend biotechnology advancements with traditional knowledge, modern science, and commercialization efforts. They involve both in vivo and in vitro techniques. In vivo propagation methods include advanced agricultural practices such as hydroponics, aeroponics [202], plant growth chambers [203], climatron [204], phytotron [205],

precision farming [206], smart farming systems agrochemomics (the growing of plants with the aim of extracting bioactive compounds and application of omics studies during the process) [207, 208], and vertical farming [209]. Meanwhile, in vitro propagation methods encompass a range of biotechnological approaches, including organogenesis, somatic embryogenesis, callus culture, protoplast culture and fusion, cell suspension culture, shoot tip culture, and microtuberization, as illustrated in (Fig. 10) [200, 210, 211]. These emerging propagation techniques as indicated in Fig. 10, not only support the sustainable production of *A. kusnezoffii* but also contribute to its conservation and economic viability. Moreover, they enhance the content of bioactive compounds, ensuring the herb's therapeutic efficacy in future applications.

Application of aptamers

In recent years, aptamers have garnered significant attention across various scientific disciplines. Aptamers are chemically synthesized oligonucleotides with high specificity and affinity for target molecules, including proteins, peptides, carbohydrates, small molecules, toxins, and even live cells. Developed through a process called Systematic Evolution of Ligands by Exponential Enrichment (SELEX), aptamers share many properties with antibodies but offer distinct advantages, as highlighted in clinical research [212]. Over the past three decades, aptamers

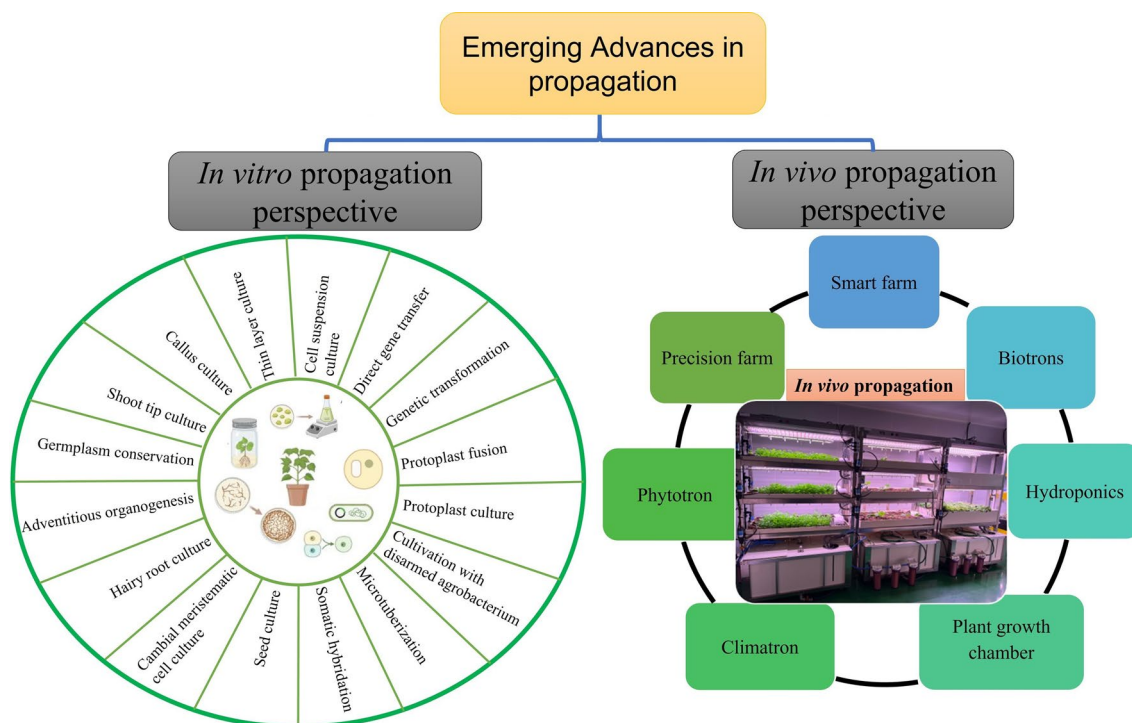
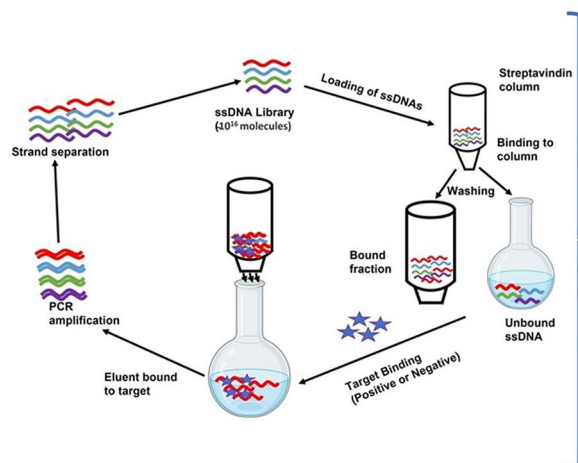


Fig. 10 Emerging advances in the propagation of medicinal plants

The schematic diagram for the SELEX(Systematic Evolution of Ligands by Exponential enrichment) process



SELEX-Aptamer applications

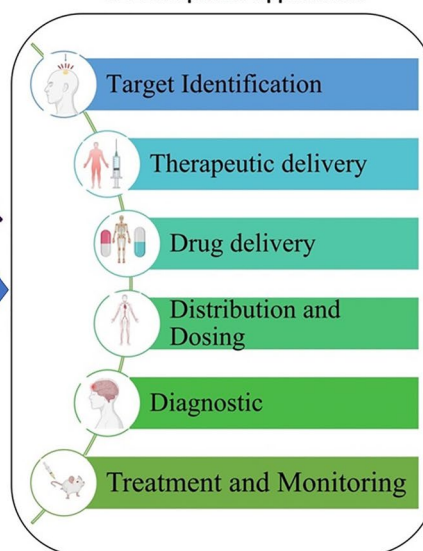


Fig. 11 Emerging advances in aptamer and SELEX technology in herbal medicine development

have gained prominence in therapeutic development due to their ability to mimic both antibodies and small molecule drugs [213]. From a therapeutic perspective, aptamers can function as stand-alone therapeutic agents, or they can be used for various purposes, such as target identification, drug delivery, diagnostics, and dosage and distribution control as indicated in Fig. 11. Aptamer-based therapeutics typically operate through one of three mechanisms: first, by obstructing disease-related target interactions (e.g., receptor-ligand binding); second, by triggering the activation of target receptors; and third, by serving as cell-type-specific carriers for the delivery of other therapeutic agents [214]. These mechanisms contribute to the broader goal of enhancing the therapeutic potential of herbs, while maintaining consistent standards of efficacy and safety [215]. In the context of *A. kusnezoffii*, aptamers can be developed through SELEX to target a wide variety of molecules produced by the herb. Their application in this area can provide a more detailed understanding of *A. kusnezoffii* and help ensure its safety and efficacy in herbal medicine. For example, aptamers can be used to target, detect, and qualify specific alkaloids, thereby improving the quality control process and enhancing the evaluation of *A. kusnezoffii* formulations. Aptamers present a broad range of applications in the therapeutic development of *A. kusnezoffii*, including targeting toxic alkaloids [216], ensuring quality control and batch consistency [217], conducting pharmacokinetic studies [218], enhancing bioavailability [219], elucidating pharmacological mechanisms [220], assessing the safety of herbal medicines [221], optimizing formulations [222],

exploring combination therapies [223], enabling targeted drug delivery [224], and serving as diagnostic tools [225], among other applications as indicated in Fig. 11. While aptamers are primarily used in biotechnology and modern medicine, their application to *A. kusnezoffii* would involve specialized approaches aimed at enhancing both safety and efficacy. The emerging role of aptamers in herbal medicine development offers a comprehensive and transformative approach to improving the safety, efficacy, and scientific credibility of *A. kusnezoffii*. By detecting, qualifying, and controlling toxic alkaloids, aptamers provide researchers and practitioners with new opportunities for the evidence-based use of *A. kusnezoffii* in herbal medicine and healthcare. This innovative approach holds great promise for optimizing health outcomes for patients.

Application of Chinmedomics

Chinmedomics is an emerging standardized strategy that integrates traditional medicines with modern omics technologies to systematically study the therapeutic efficacy and mechanisms of herbal medicines. It combines the theories and technologies of system biology and serum pharmacochimistry in traditional medicine to create a comprehensive methodology for identifying biomarkers of syndromes, assessing the efficacy of herbal medicine formulas, and uncovering the pharmacodynamic active compounds within herbal medicines and formulation [226]. By applying Chinmedomics to the development of *A. kusnezoffii*, researchers can gain deeper insight into its pharmacology, optimize its therapeutic use, reduce its

toxicity, and standardize its quality. This leads to safer, more effective and scientifically validated applications of *A. kusnezoffii* in traditional and modern medicine. Several mechanisms can be used in the application of Chinmedomics in the development of *A. kusnezoffii*. Since *A. kusnezoffii* contains both therapeutic alkaloids and toxic ones, it makes its use risky [11]. Given that Chinmedomics has been used to enhance a systematic analysis of the metabolic profile of several herbs [227], it can as well be applied in *A. kusnezoffii* to identify both bioactive compounds responsible for its therapeutic effects and toxic compounds. In addition, Chinmedomics has been used in comparing metabolites in biological samples (Example blood and urine) before and after treatment with different herbs in traditional medicine [228]. This helps to identify how the herb influences the body's biochemical pathways, highlighting on their mechanism of action at the molecular level. In addition, the comparison aids in identifying specific metabolites or compounds responsible for therapeutic effect. Therefore, Chinmedomics can help identify compounds from *A. kusnezoffii* that are linked to positive health outcomes and the ones that are associated with toxicity. Wan et al. [229] indicates how Chinmedomics has similarly been applied in the study of other herbal plants to identify active and toxic compounds. Furthermore, by studying changes in metabolite profiles after administering the herb, researchers can use Chinmedomics strategy to map out how the herb interacts with various biochemical system in the body [230]. Therefore, if applied to *A. kusnezoffii*, Chinmedomics will give room for a deeper understanding of how the herb exerts its medicinal effects, such as pain relief, anti-tumor, anti-inflammatory actions, and anticancer effects while tracking any unwanted toxic effects. Wang et al. [231] indicates how Chinmedomics has been applied in Understanding mechanism of action of herbal medicine. Apparently, one of the biggest challenges in using *A. kusnezoffii* is balancing the efficacy with safety [5], however, several studies have indicated the roles of Chinmedomics in establishing safe and effective dosages by studying the dose–response relationship between the herb's compounds and their effects on metabolic profiles [232]. By identifying biomarkers of toxicity, Chinmedomics aids in refining processing methods (for example decoction, steaming) that reduce the level of toxic alkaloids, ensuring safer user of the herb. Therefore, application of Chinmedomics in *A. kusnezoffii* development can enhance optimizing dosage and reducing toxicity of the herb. Furthermore, studies have indicated how Chinmedomics helps in standardizing herbal products by identifying specific metabolic biomarkers linked to both efficacy and toxicity [233]. This can help in ensuring consistence and quality control of the herbs, assuring safety of herbal

medicine use, enhancing effective dosage and improving patient outcome. Since the chemical composition of *A. kusnezoffii* can vary due to factors such as cultivation conditions, harvest time, and preparation methods [9], application of Chinmedomics in *A. kusnezoffii* helps in its products' standardization through identifying specific metabolic biomarkers linked to both efficacy and toxicity, which ensures that each batch of its product meets consistent quality standard. Besides, *A. kusnezoffii* is often used in multi-herb formulas/polyherbal formulations to balance the formulation. In the formula, some herbs neutralize *A. kusnezoffii* toxic compounds, providing a holistic treatment approach [167], however, studies have indicated challenges associated with polyherbal formulations that include: variable efficacy that may interfere with absorption and metabolism, inconsistency in outcome potency due to varied growing conditions, harvest time/procedure and preparation methods [234–236] complex pharmacokinetics that affects absorption, distribution, metabolism and excretion [237, 238], and the complexity in formulation design that requires balancing various properties such as potency compatibility, and toxicity to enhance pharmacokinetics and pharmacodynamics [226, 239]. However, studies have indicated how Chinmedomics have been used to evaluate how herbs interact with each other components in a polyherbal formulation, providing insight into synergistic effects. By tracking the metabolic changes in the patients treated with the herbal formula, Chinmedomics can determine the pharmacodynamics basis of the combined effect and help optimize the formular for both safety and therapeutic values [226]. Therefore, Chinmedomics has the potential of Evaluating herbal formulas containing *A. kusnezoffii* and enhance its efficacy while reducing its toxicity. Figure 12 presents the application of Chinmedomics in herbal medicine.

In Chinmedomics, metabolomics and serum pharmacochemistry work to provide a more precise and scientifically grounded understanding of TCM. Metabolomics helps to elucidate the metabolic pathways and mechanisms of action of TCM, while serum pharmacochemistry focuses on the absorption, distribution, and safety of the active ingredients in the body. Both approaches are essential for enhancing the efficacy, safety, and standardization of TCM treatments, ensuring they can be used effectively and safely in modern medicine [231]. Meanwhile, bioinformatics in Chinmedomics is essential for understanding how TCM works by identifying biomarkers, active ingredients, and their underlying therapeutic mechanism. By integrating omics data, bioinformatics uncovers how TCM compounds interact with biological pathways, revealing how they influence health diseases. This integration improves precision, efficacy, and safety

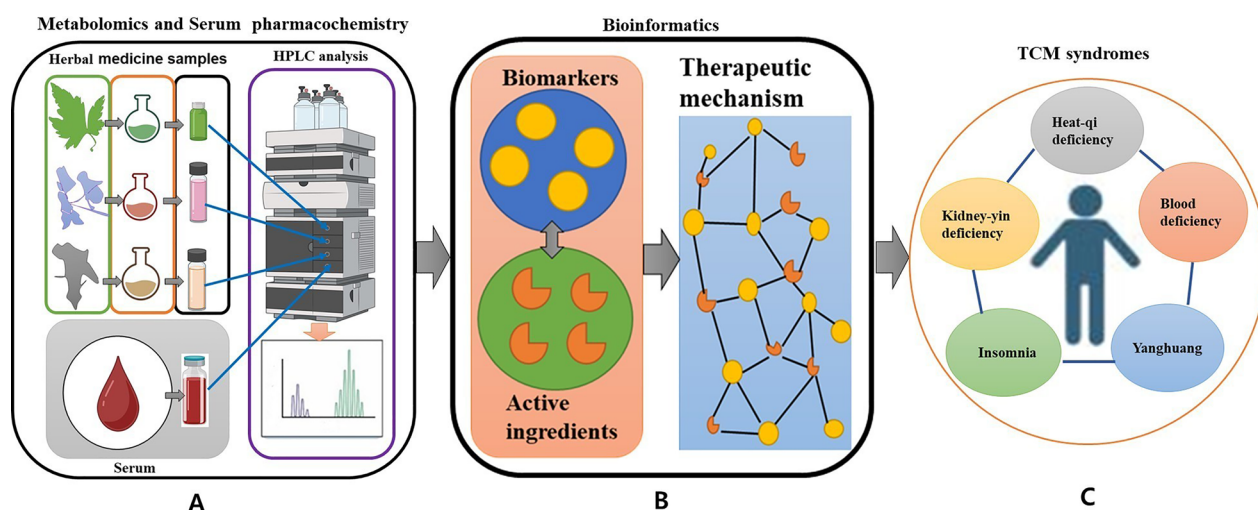


Fig. 12 Chinmedomics application in herbal medicine. **A** Metabolomics and Serum pharmacochemistry application in Chinmedomics, **B** Bioinformatics application in chinmedomics, **C** TCM syndromes (pattern of symptoms and signs that are used to diagnose and treat patients)

of TCM, making it more suitable for integration into modern healthcare practice [240]. In TCM, a syndrome refers to a pattern of symptoms and signs that are used to diagnose and treat patients. Each TCM syndrome reflects an imbalance in the body Qi, Yin, Yang, or blood, and can be linked to specific organ systems. By understanding how TCM syndrome manifest at the molecular level, chinmedomics uses modern tools to identify biological markers of these imbalances and how herbal remedies correct [241–243]. Based on Fig. 12, under Chinmedomics approach, the TCM syndromes of insomnia, Heat-Qi deficiency, Kidney Yin deficiency, Yanghuang, and blood deficiency are studied through a combination of metabolomics, bioinformatics and serum pharmacology. These technologies help identify biomarkers, track metabolic changes, and reveal the active compounds in herbal medicines that target the underlying therapeutic mechanisms of these syndromes. Integrating traditional knowledge with modern scientific tools enables a more precise and effective approach to herbal medicine use in TCM, enhancing the understanding of how herbal formulations can restore balance and promote health.

Meaning of specific words in TCM

- **Heat-qi:** This describes conditions where excessive heat or heat like symptoms arise due to an imbalance of Qi (vital energy that flows through the body). The imbalance can lead to a range of symptoms such as fever, redness of the eyes, dry mouth, red tongue, irritability, among others [244]. Therefore, *Heat-qi deficiency* refers to a condition in which the body is both energetically weak and unable to generate suf-

ficient internal warmth, leading to various symptoms [245].

- **Yin:** Represents the nourishing, cooling, and restorative aspect of life. It is essential for maintaining balance within the body, ensuring that organs are hydrated, energy is sustained, and the body's functions remain steady. A deficiency in Yin can lead to a range of symptoms, particularly associated with dryness and heat, and is treated by replenishing Yin through herbs, diet, and other TCM therapies [246]. Therefore, *Kidney Yin deficiency* refers to conditions where the nourishing, cooling, and restorative aspect of the kidney is insufficient. Its symptoms include night sweats, dry skin, constipation, dizziness, among others [244].
- **Yang:** Represents the active, warming, energizing, and expansive force that drives the body's vital activities and maintains circulation, movement and metabolism [244].
- **Yanghuang:** This refers to a type of jaundice caused by excess heat in the body, particularly affecting the liver and gall bladder. It is characterized by lighter tone of the skin [247].

A. kusnezoffii has been, and will continue to be, a highly significant herb in herbal medicine practices. Known for its diverse chemical components, pharmacological activities, and toxic effects, it presents a dual nature, much like Janus in Greek mythology—one side supporting healing, while the other poses lethal risks. Its major alkaloids, such as aconitine, mesaconitine, and hypaconitine, are recognized for their toxicity. Therefore, careful consideration is essential when using this herb, as even small

doses can be hazardous. Despite its toxicity, *A. kusnezoffii* has been a crucial part of traditional medicine since ancient times, with various Chinese dynasties utilizing it in different forms. Ongoing clinical trials continue to explore its therapeutic potential, with some studies suggesting its use in cancer treatment. However, in Ayurveda, *A. kusnezoffii* has been used for centuries without the need for such trials. Given its narrow margin of safety due to its well-documented toxicity, different dynasties have developed various processing methods to reduce its harmful effects, optimize its medicinal properties, and ensure its safe use. Common methods across different ethnic cultures and dynasties in China include stir-frying, soaking, decocting, and decorticating. Modern advancements in the processing of *A. kusnezoffii* are aimed at further reducing its toxicity. These developments are critical for health authorities to guide, regulate, and control the preparation and use of *A. kusnezoffii* for patient safety. This article not only highlights the rich traditional processing methods but also provides detailed information on the alkaloids found in different parts of the plant and their pharmacological activities, demonstrating the full healing potential of *A. kusnezoffii*. It also outlines various detoxification mechanisms, treatment and management of intoxication, and quality control measures for its products. Given the herb's narrow therapeutic range, careful attention is required. Nonetheless, its toxicity can be mitigated through various techniques, allowing it to harness its full pharmacological potential, including anti-inflammatory, analgesic, anti-arrhythmic, anti-cancer, and anti-tumor effects. To promote the sustainable use of *A. kusnezoffii* in herbal medicine development, the article emphasizes the importance of incorporating recent advancements in propagation aptamer and SELEX technology and Chinmedomics.

Abbreviations

AMED	Allied and complementary medicine database
BIAs	Benzylisoquinoline alkaloids
DDAs	Diterpenoid alkaloids
DEs	Deep eutectic solvents
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FAB-MS	Fast atom bombardment mass spectrometry
HPLC	High-performance liquid chromatography
HPLC/ESI-MS	High-performance liquid chromatography electrospray ionization mass spectrometry
HPLC-DAD	High-performance liquid chromatography-diode array detection
LC	Liquid chromatography
LD	Lethal dose
MS	Mass spectrometry
NDAs	Norditerpenoid alkaloids
NMR	Spectroscopy nuclear magnetic resonance
NSP	Non-starch polysaccharide
pH	Potential of hydrogen
QTOF MS	Quadrupole time-of-flight mass spectrometry
RA	Rheumatoid arthritis
RNA	Ribonucleic acid

SELEX	Systematic evolution of ligands by exponential enrichment
TCM	Traditional Chinese Medicine
TKM	Traditional Korean Medicine
TLC	Thin-layer chromatography

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Kenneth Happy: Writing-reviewing-editing original draft, visualization. Sungyu Yang: review and editing. Chang Ho Kang: visualization, validation, reviewing. Youngmin Kang: Supervision, Project administration, Funding acquisition.

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Availability of data materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

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Competing interests

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