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•Review•

A systematic review of pharmacological activities, toxicological mechanisms and pharmacokinetic studies on *Aconitum* alkaloids

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[ABSTRACT] The tubers and roots of *Aconitum* (Ranunculaceae) are widely used as heart medicine or analgesic agents for the treatment of coronary heart disease, chronic heart failure, rheumatoid arthritis and neuropathic pain since ancient times. As a type of natural products mainly extracted from *Aconitum* plants, *Aconitum* alkaloids have complex chemical structures and exert remarkable biological activity, which are mainly responsible for significant effects of *Aconitum* plants. The present review is to summarize the progress of the pharmacological, toxicological, and pharmacokinetic studies of *Aconitum* alkaloids, so as to provide evidence for better clinical application. Research data concerning pharmacological, toxicological and pharmacokinetic studies of *Aconitum* alkaloids were collected from different scientific databases (PubMed, CNKI, Google Scholar, Baidu Scholar, and Web of Science) using the phrase *Aconitum* alkaloids, as well as generic synonyms. *Aconitum* alkaloids are both bioactive compounds and toxic ingredients in *Aconitum* plants. They produce a wide range of pharmacological activities, including protecting the cardiovascular system, nervous system, and immune system and anti-cancer effects. Notably, *Aconitum* alkaloids also exert strong cardiac toxicity, neurotoxicity and liver toxicity, which are supported by clinical studies. Finally, pharmacokinetic studies indicated that cytochrome P450 proteins (CYPs) and efflux transporters (ETs) are closely related to the low bioavailability of *Aconitum* alkaloids and play an important role in their metabolism and detoxification *in vivo*.

[KEY WORDS] *Aconitum* alkaloids; Pharmacological activities; Toxicity; Pharmacokinetics
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Introduction

Aconitum alkaloids are bioactive components with complex chemical structures that mostly exist in plants of the two genera *Aconitum* and *Delphinium* [1, 2], including the characteristic active and toxic components of diterpene alkaloids. According to their chemical skeletons, diterpene alkaloids can be divided into C_{18}-, C_{19}-, and C_{20}-diterpene alkaloids, and their chemical structures are presented in Fig. 1. C_{19}-Diterpene alkaloids, the main types of *Aconitum* alkaloids, include aconitines [3], lycoctonines [4], pyro-types [5], rearranged-types [6], 7, 17-seco-types [7], and lactone types [8]. Based on the esterification of hydroxyl groups at C_8 and C_{14} sites in their structures, aconitines can be further classified into diester-diterpenoid alkaloids (DDAs), monoester-diterpenoid alkaloids (MDAs), and hydramine diterpenoid alkaloids (HDAs) [9-11]. With the sequential hydrolysis of ester bonds at C_8 and C_{14}, their toxicity was substantially reduced [12, 13]. In contrast, C_{18}-diterpene alkaloids are the least distributed *Aconitum* alkaloids, and classified into lappaconitines and ranaconitines [14-16]. Compared with lappaconitines, the hydrogen at C_7 site of ranaconitines was substituted by oxygen-containing groups. Furthermore, the chemical skeletons of C_{20}-type diterpene alkaloids are complex and diverse, with the common structural types of hetisines [17, 18], hetidines [19], atisines [20], denudatines [21], veatchines [22] and napellines [23]. For exmaple, songorine is a typical active napelline-type C_{20}-diterpene alkaloid extracted from *Aconitum carmichaeli* [24].

A large number of studies have confirmed that *Aconitum* alkaloids are the characteristic bioactive components of *Aconitum* species, which exhibit substantial analgesic, anti-inflammatory, antioxidant and anti-tumor activities [25, 26]. However, due to a narrow therapeutic window, they may cause toxicity to the heart, liver, muscle tissues and nervous system [27, 28]. Thus, the use of *Aconitum* in herbal prepara-

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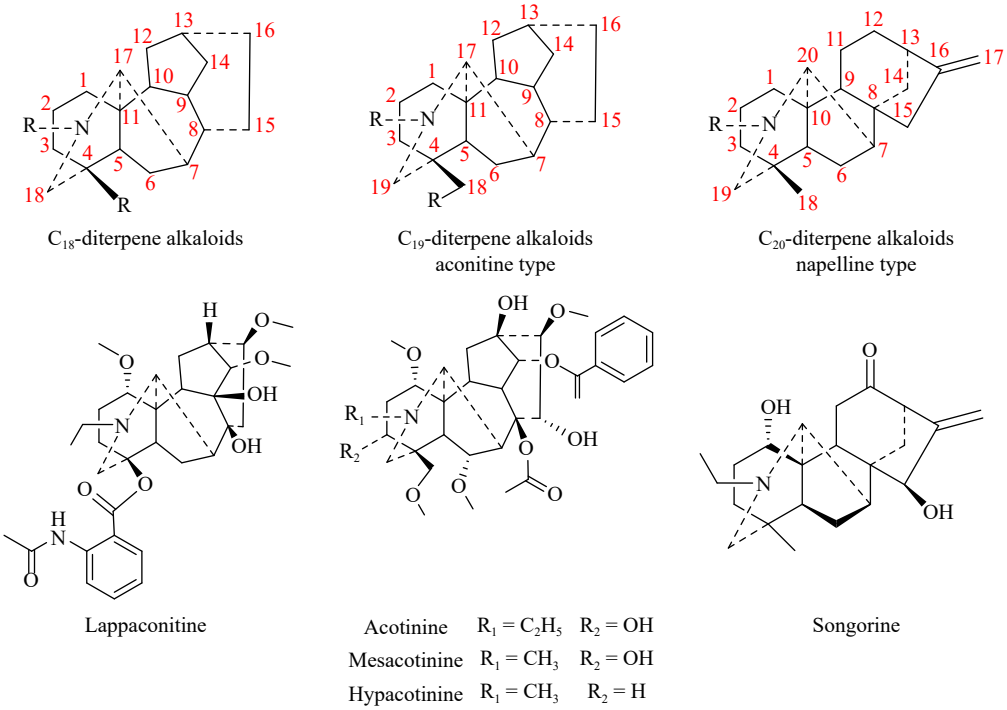

Fig. 1 Classification, general structures and numbering systems for C_{18}-, C_{19}- and C_{20}-diterpenen alkaloids and chemical structures of classical diterpene alkaloids

tions is limited in Europe and the United States [29]. In recent years, to elucidate the absorption and metabolism characteristics of active or toxic alkaloids in the body, pharmacokinetic studies have been widely performed, which indicate that *Aconitum* alkaloids can be quickly absorbed and widely distributed in the body [30]. But the bioavailability of *Aconitum* alkaloids is extremely low, while highly toxic alkaloids can be converted into less toxic metabolites and soluble derivatives [31, 32], playing an important role in their metabolism and detoxification *in vivo*.

Recently, many efforts have been devoted to reviewing the phytochemical characteristics of *Aconitum* and its active components as well as related pharmacological activity and analytical methods. For instance, Zhou *et al.* [26] presented an investigation concerning the safety application of *Aconitum* by summarizing the phytochemical and pharmacological activity and toxicity of *Aconitum*. Furthermore, Elshazly M *et al*. [33] focused on liquid chromatography/mass spectrometry analysis of *Aconitum* and its Chinese herbal medicine. Wu *et al*. [32] illuminated the application of *Fuzi* as personalized medicine from the respect of pharmacokinetics. So far, there has been no comprehensive and systematic review of *Aconitum* alkaloids. Therefore, in the current review, we summarize the up-dated, comprehensive, and systematic information about the pharmacological activity and toxicity of *Aconitum* alkaloids in the cardiovascular system, nervous system, liver, and other organs, as well as the absorption and metabolic characteristics of *Aconitum* alkaloids, and discuss the toxicity-efficacy relationship and pharmacokinetics of *Aconitum* alkaloids, so as to provide evidence for further development and clinical application of *Aconitum* drugs.

Pharmacological Activities of *Aconitum* Alkaloids

Effects on the cardiovascular system

Aconitum plants have long been used for the treatment of heart failure and poor circulation [29, 34], and *Aconitum* alkaloids are the main active ingredients for cardioprotective effects (Table 1). For instance, *Fuzi* total alkaloid (FTA) significantly decreased myocardial damage and infract size in rats with myocardial infraction, which stabilized the cardiomyocyte membrane structure through improving myocardial energy metabolic abnormalities, phospholipids levels and distribution patterns [35]. Moreover, fuziline and neoline showed pronounced activity against pentobarbital sodium induced damage in cardiomyocytes, which was characterized in restored beating rhythm and improved cell vitality [36]. C_{19}-Diterpenoid alkaloids such as mesaconine, hypaconine and beiwutinine showed remarkable cardiac effects on the isolated bullfrog hearts. Notably, the protective effects of mesaconine were achieved by improving the inotropic effect and left ventricular diastolic function in rats with myocardial ischemia-reperfusion injury [37]. Higenamine, a benzyltetrahydroisoquinoline alkaloid, showed inhibitory effects on both human and rat platelet aggregation, which was achieved by increasing the recovery rate in a mouse model of acute thrombosis, and lowering the weight of thrombus in an arterio-venous shunt (AV-shunt) rat model[38]. Meanwhile, higenamine was proved to increase the fibrinogen level, decrease fibrinogen/fibrin degradation product (FDP) level and prothrombin

Table 1 Effects of *Aconitum* alkaloids on the cardiovascular system

Component/Dose/Duration	Cell type/Animal model	Effects	Mechanisms	Ref.
Radix Aconiti Lateralis Preparata extract (RAE) and *Fuzi* total alkaloid (FTA) 1.6, 0.8, and 0.4 $g \cdot kg^{-1}$ for 14 d	Rats with myocardial infarction	Anti-myocardial infarction effect	Improve myocardial energy metabolic abnormalities, change phospholipids levels and distribution patterns, and stabilize the structure of cardiomyocyte membrane	[35]
Fuziline and neoline 10, 1, and 0.1 $\mu mol \cdot L^{-1}$ for 24 h	Neonatal rat cardiomyocytes	Against pentobarbital sodium induced damage in cardiomyocytes	Recover beating rhythm and increase cell viability	[36]
Mesaconine and hypaconine 5 $mg \cdot mL^{-1}$ for 30 s (isolated bullfrog hearts), 1 $nmol \cdot L^{-1}$ for 10 min (isolated rat hearts), and beiwutinine 5 $mg \cdot mL^{-1}$ for 30 s (isolated bullfrog hearts)	Isolated bullfrog hearts,and isolated rat hearts after ischemia-reperfusion	Optimal cardiac action on isolated bullfrog hearts and inhibiting myocardial ischemia-reperfusion injury in isolated rat hearts (measconine)	Increase the average rate of amplitude, and improve the inotropic effect and left ventricular diastolic function	[37]
Higenamine 50 and 100 $mg \cdot kg^{-1}$ for 3 d (mice)	ADP, collagen and epinephrine-induced human and rat platelet aggregation, and collagen and epinephrine induced acute thrombosis in mice	Antiplatelet aggregation and anti-thrombotic effects	Inhibit epinephrine-induced platelet aggregation, increase the recovery rates from acute thrombotic challenge in mice, and lower the weight of thrombus within the arteriovenous shunt (AV-shunt) tube of rats	[38]
Higenamine 10, and 50 $mg \cdot kg^{-1}$ for 10 d	A disseminated intravascular coagulation (DIC) model in rats	Therapeutic potential for DIC and/or accompanying multiple organ failure	Ameliorate the decrease of fibrinogen level in plasma, increase fibrinogen/fibrin degradation product (FDP) level and prolong prothrombin time (PT)	[39]
Mesaconitine 30 $mmol \cdot L^{-1}$ for 0−40 min	Rat aorta	Relaxation in the aorta	Stimulate Ca^{2+} influx *via* the Na^{+}/Ca^{2+} exchangers in endothelial cells	[40]
Hypaconitine 24, 48, and 90 $\mu mol \cdot L^{-1}$ for 21 h	Oxidized low-density lipoprotein (oxLDL) induced endothelial cells	Suppress the apoptosis of endothelial cells	The histone deacetylase-HMGB1 pathway	[41]
C_{19}-Diterpenoid alkaloids 2.5 or 5 $mg \cdot mL^{-1}$ for 30 s or 10 $mmol \cdot mL^{-1}$ for 30 s	Isolated bullfrog hearts	Structure-cardiac activity relationship	Increase the average rate of amplitude	[42, 43]

time (PT) in a model of disseminated intravascular coagulation (DIC) in rats[39]. Mesaconitine, as another active *Aconitum* alkaloid, induced vasorelaxation in the aorta of rats through promoting Ca^{2+} influx and activating nitric-oxide synthase [40]. Furthermore, hyaconitine targeted the histone deacetylase-high mobility group box-1 pathway to inhibit the oxidized low-density lipoprotein (ox-LDL)-induced apoptosis of endothelial cells [41]. According to the structure-activity relationship data, the structures of *Aconitum* alkaloids necessary for cardiac activity included an α-methoxyl or hydroxyl group at C-1, a hydroxyl group at C-8 and C-14, *α*-hydroxyl group at C-15, and a secondary amine or *N*-methyl group in ring A. Additionally, an *α*-hydroxyl group at C-3 also contributed to cardiac activity [42, 43].

Fuzi is the processed lateral roots of *Aconitum carmichaeli* Debx. (Ranunculaceae), and has been used in traditional Chinese medicine for the treatment of chronic heart failure, hypotension, coronary heart disease and acute myocardial infarction owing to its remarkable effects of restoring yang and saving adversity [29]. A large number of studies have shown that the cardiotonic effects of *Aconitum* alkaloids, the characteristic active components of *Fuzi*, are multi-targeted, which are achieved by restoring myocardial cells vitality, improving the inotropic effect and left ventricular diastolic function, and inhibiting platelet aggregation. Therefore, the clinical application of Fuzi and *Aconitum* drugs in the treatment of cardiovascular diseases is closely related to the cardiotonic bioactivity of *Aconitum* alkaloids.

Effects on the nervous system

The nervous system can monitor and respond to the changes in the internal and external environment, participate in critical physiological processes such as learning, memory, cognition and initiate all autonomous movements [44, 45]. A large number of studies have confirmed that *Aconitum* alkaloids exert remarkable protective effects on the nervous system (Table 2). Neuropathic pain is a highly debilitating chronic pain directly caused by various lesions or diseases affecting the somatosensory nervous system [46], which is characterized by spontaneous ongoing pain and hyperalgesia [47]. *Aconitum* plants have been widely used for analgesia since ancient time. C_{18}-Diterpenoid alkaloids (weisaconitines D) isolated from *Aconitum weixiense* and two sulfonated C_{20}-

Table 2 Effects of *Aconitum* alkaloids on the nervous system

Component/Dose/Duration	Cell type/Animal model	Effects	Mechanisms	Ref.
Weisaconitines D 50, 100 and 200 mg·kg^{-1}	A mouse model of CH_3COOH-induced writhing	Analgesic activity	Inhibit acetic acid-induced writhing in mice	[48]
Aconicatisulfonines A and B 0.1, 0.3 and 1.0 mg·kg^{-1}	Acetic acid-induced mice	Analgesic activity	Inhibit acetic acid-induced writhing in mice	[49]
Songorine, napelline, mesaconitine, hypaconitine and 12-epinapelline *N*-oxide 0.025 mg·kg^{-1} for 5 d	A mouse model of acetylcholine cramp and inflammatory hyperalgesia induced by naloxone Freund' s adjuvant	Analgesic activity	Prolong the time before manifestation of nociceptive reaction and reduce the number of cramps	[50]
Guiwuline 15 mg·kg^{-1}	Hot-plate method induced mice	Analgesic activity	Improve the results of the hot-plate test in mice (55 °C)	[51]
Neoline 6 mg·kg^{-1}·d^{-1} for 5 and 7 d	Dorsal root ganglion neurons isolated from normal mice	Alleviate neuropathic pain	Alleviate the oxaliplatin-induced reduction of neurite elongation and inhibit the induction of mechanical and cold hyperalgesia	[52]
Neoline 10 mg·kg^{-1}·d^{-1} for 7, 9 and 21 d	A mouse model of mechanical allodynia	Relieve neuropathic pain	Ameliorate the mechanical threshold of von Frey test and eural plasticity	[53]
Isotalatizidine 0.1, 0.3 and 1 mg·kg^{-1} for 30 min, 1, 2 and 4 h; isotalatizidine 25 μmol·L^{-1} for 1 h	A mouse model of CCI-induced neuropathic pain, and BV-2 and primary microglial cells	Attenuate the hypersensitivity of somatic pain	Stimulate the expression of microglial dynorphin A mediated by the ERK/CREB signaling pathway	[54]
Lappaconitine 0.3, 0.7, 2 and 7 mg·kg^{-1} for 1 h interval	A rat model of neuropathic pain and bone cancer pain, primary microglial cells and neurons	Antihypersensitivity in chronic pain	Stimulate the expression of spinal microglial dynorphin A	[55]
Bulleyaconitine A 10, 30, 100, 300 and 1000 ng for 1 h (rat) or 100 nmol·L^{-1} for 2 h (cell)	A rat model of neuropathic pain and bone cancer pain, primary neuron and glial cells	Block painful neuropathy caused by the spinal nerve	Activate spinal k-opioid receptors and stimulate the expression of dynorphin A in spinal microglia	[56]
Bulleyaconitine A 10 μmol·L^{-1} for 3 ms	HEK293t cells	Adjuvant for prolonged cutaneous analgesia	Inhibit Nav1.7 and Nav1.8 Na^+ currents	[57]
Bulleyaconitine A 5 nmol·L^{-1} for 15 min	Dorsal root ganglion neurons	Antineuropathic pain effect	Block tetrodotoxin-sensitive voltage-gated sodium (Nav1.7 and Nav1.3) in dorsal root ganglion neurons	[58]
Bulleyaconitine A 10 μmol·L^{-1} for 4 ms	Clonal GH3 cells	Treat chronic pain and rheumatoid arthritis	Reduce neuronal Na^+ currents	[59]
Pyroaconitine, ajacine, septentriodine, and delectinine 10 μmol·L^{-1} for 8 ms	CHO cells	Potential anti-epileptic activity	Inhibit Nav1.2 channel	[60]
Aconorine and lappaconitine 50, 75 and 100 μmol·L^{-1} for 15 min; heteratisine and hetisinone 50, 75, 100, and 125 μg·mL^{-1} for 30 min; heterophyllinine A and heterophyllinine B 0.2 mmol·L^{-1} for 15 min	ACh and BCh	Cholinesterase inhibitory effect	-	[64, 65, 67]
Hemsleyaline IC_{50} 471 ± 9 μmol·L^{-1} for 30 min; kirisine G, kirisine H, gigaconitine and aconicarmichinium C 10 μL for 30 min	ACh	Acetylcholinesterase inhibitory effects	-	[15, 66]

Continued

Component/Dose/Duration	Cell type/Animal model	Effects	Mechanisms	Ref.
Higenamine 10 μmol·L^{-1} and cnryneine 100 μmol·L^{-1}	Mouse phrenic nerve-diaphragm preparation	Higenamine augments the release of both nerve-evoked and spontaneous ACh, and muscle tension. Coryneine reducea the nerve-evoked release of ACh	Higenamine increases ACh release through activation of β-adrenoeptor and cnryneine and depresses ACh release by preferentially acting at the motor nerve terminal	[68]
Aconitine 3 × 10^{-6} mol·L^{-1} per 10 s	Mechanically dissociated ventromedial hypothalamic (VMH) neurons in rats	Modulate the membrane excitability of VMH neurons in rats	Activate voltage-dependent Na^+ channels, depolarize the presynaptic membrane, activate voltage-dependent Ca^{2+} channels and increase intraterminal Ca^{2+} concentration	[69]
Songorine 5, 25, and 100 μg·kg^{-1} for 5 d	Scopolamine-traumatized mice	Correct scopolamine-induced abnormalities of mnestic function	Improve conditioned passive avoidance response (CPAR) and normalize behavior activities	[70]
Napelline and songorine, 0.025 mg·kg^{-1} for 5 d	Albino outinbred mature female mice and a mouse model of serotonin-induced edema	Antidepressant and antiexudative effects	Reduce the time of immobilization in the tail suspension test and modulate the sensitivity to serotonin	[75]
Diterpenoid alkaloids from the roots of *Aconitum pendulum* Busch 25 μmol·L^{-1}	-	Neroprotective activity	With remarkable disaggregation potency on the Aβ_{1-42} aggregates	[76]
Bullatine A 1, 10, 20 and 50 μmol·L^{-1} for 24 h	ATP-induced BV-2 cells	Anti-rheumatic, anti-inflammatory and anti-nociceptive effects	Attenuate ATP-induced BV-2 microglia death/apoptosis *via* the P2X receptor pathway	[77]
Diterpenoid alkaloids from the Lateral Root of *Aconitum carmichaelii* 10 μmol·L^{-1}	Serum deprivation-induced PC12 cells	Treat neurodegenerative disorders	Increase cell viability	[78]
Songorine 0.1−300 mmol·L^{-1}	Triton-treated synaptic membranes of CA1 hippocampal neurons in rats	Enhance the excitatory synaptic transmission in rat hippocampus	Activate the D_2 receptor (for excitation) and block the postsynaptic $GABA_A$ receptor (for disinhibition)	[79]
Songorine 0.25 and 2.5 mg·kg^{-1} for 5 d	Vogel's conflict test	Anxiolytic activity	Increase the number of punished drinks and produce higher values of behavioral activity parameters	[80]
Talatisamine 300 μmol·L^{-1}	Dissociated CA1 pyramidal neurons	Alzheimer's disease	Delay rectifier K^+ channel in rat hippocampal neurons	[81]

diterpenoid alkaloid iminiums isolated from a water extract of the *Aconitum carmichaelii* lateral roots produced obvious analgesic activities against acetic acid-induced mice writhing [48, 49]. Diterpene alkaloids extracted from *Aconitum baikalensis* presented substantial analgesic effects on the naloxone-induced acetylcholine cramp model and rats with inflammatory hyperalgesia induced by Freund's adjuvant [50]. Furthremore, a novel franchetine type of norditerpenoid, which was isolated from the roots of *Aconitum carmichaeli* Debx, showed potential analgesic activity and less toxicity [51]. Neoline, the active ingredient in processed aconite root, alleviated oxaliplatin-induced murine peripheral neuropathy [52] and mechanical hyperalgesia induced by partial ligation of the sciatic nerve [53]. Isotalatizidine exerted analgesic effects by activating the ERK1/2-CREB pathway and mediating the expression of dynorphin A in microglia cells [54]. Another research proved that lappaconitine and bulleyaconitine A exerted anti-hypersensitivity in spinal nerve ligation-induced neuropathic rats through stimulating spinal microglia to express dynorphin A [55, 56]. In addition, bulleyaconitine A also played a role in anti-neuropathic pain *via* blocking Nav1.7 and Nav1.3 channels to reduce the hyper-excitability of dorsal root ganglion neurons caused by nerve injury [57, 58]. Bulleyaconitine A also displayed long-acting local anesthetic properties both *in vitro* and *in vivo*, and often used in the treatment of chronic pain [59]. Diterpene alkaloids isolated from the roots of *Aconitum moldavicum* showed significant inhibitory effects on the Nav 1.2 channel [60], suggesting po-

tential anti-epileptic activity.

The cholinergic system is a major constituent of the central nervous system, which is closely related to learning, memory and sensory information [61, 62]. Acetylcholine (ACh) is the neurotransmitter used by cholinergic neurons at the neuromuscular junctions and in the spinal cord, memory-related circuits in the brain and parasympathetic nerve terminals, which plays a crucial role in the peripheral and central nervous systems [62, 63]. Acetylcholinesterase can degrade acetylcholine, block the excitatory effect of neurotransmitters on the post-synaptic membrane, and ensure the normal transmission of nerve signals [62]. According to recent reports, diterpenoid alkaloids in *Aconitum* such as aconorine, lappaconitine, and heteratisine exerted significant anti-cholinesterase activity [64, 65]. In addition, the new diterpenoid alkaloids isolated from *Aconitum* also showed probable inhibitory effects against cholinesterase [66, 67]. Moreover, the four diterpenoid alkaloids extracted from the roots of *Aconitum kirinense* Nakai exhibited moderate anti-acetylcholinesterase activity and neuroprotective activity [15]. Interestingly, higenamine promoted the release of ACh *via* activating *β*-adrenoeptor, while cnryneine preferentially acted at motor nerve terminals to inhibit ACh release, exerting antagonistic effects on the release of ACh [68]. In addition, aconitine depolarized the presynaptic membrane *via* activating voltage-dependent Na^+ channels, and enhanced the spontaneous transmitter release of the presynaptic nerve terminals by activating voltage-dependent Ca^{2+} channels, which played an important role in modulating the membrane excitability of ventromedial hypothalamic (VMH) neurons in rats [69]. Repeated administration of songorine improved conditioned passive avoidance response (CPAR) conditioning and normalized behavioral activities throughout the entire observation period, thereby correcting scopolamine-induced abnormality of mnestic function [70].

Neuroinflammation, chronic oxidative stress and neuronal damage contribute to the onset of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophy lateral sclerosis as well as neuropsychiatric illnesses such as depression and autism spectrum disorder [71-74]. Current research confirmed that the diterpenoid alkaloids of *Aconitum* exhibited antidepressant properties through regulating the sensitivity to serotonin [75], and they also showed significant disaggregation potency on the $A\beta_{1-42}$ aggregates, indicating probable inhibitory effects against Alzheimer's disease [76]. Bullatine A, a diterpenoid alkaloid of the genus *Aconitum*, attenuated ATP-induced BV2 microglia death/apoptosis *via* the P2X receptor pathway, thereby exerting neuroprotective effects [77]. Some other diterpene alkaloids extracted from the lateral root of *Aconitum carmichaelii* also exerted neuroprotective effects [78]. For instance, songorine was proved to be a non-competitive antagonist at the $GABA_A$ receptor in the brain of rat, which resulted in potential therapeutic effects on amyotrophy lateral sclerosis [79]. Moreover, songorine also exhibited significant anxiolytic activity [80]. In addition, talatisamine was a potent blocker of delayed rectifier K^+ channels in rat hippocampal neurons, which was beneficial for Alzheimer's treatment [81].

Aconitum has also been widely used as analgesic and antispasmodic drugs since ancient times, and *Aconitum* alkaloids exert prominent central analgesic effects without addiction, which are considered as the potential active ingredients of new analgesics. At present, Wutou decoction and Shenfu injection show significant therapeutic effects on angina pectoris and pain of joints [29, 82]. In addition, *Aconitum* alkaloids, as a type of naturally active ingredients with significant anti-cholinesterase activity and neuroprotective effect, have shown potential therapeutic effects on a variety of nervous system diseases, and their clinical therapeutic effects remains to be further studied.

Effect on the immune system

The immune system, consisting of immune organs, immune cells and immune factors, is a major defense mechanism to protect host homeostasis against the invasion of pathogens, toxins, and allergens. However, if the immune system cannot distinguish between itself and non-self, it will cause excessive damage to own tissues [83, 84], resulting in autoimmune diseases such as systemic lupus erythematosus [85], rheumatoid arthritis [86], and cold agglutinin disease [87]. The protective effect of *Aconitum* alkaloids on the immune system has been extensively studied (Table 3).

A large volume of studies indicated that *Aconitum* diterpene alkaloids partly inhibited the proliferation and NO production in LPS-induced RAW264.7 cells [88-92]. Aconitine inhibited RANKL-induced osteoclast differentiation and the expression of osteoclast-specific genes *via* suppressing NF-*κ*B and NFATc1 activation in RAW264.7 cells [93]. What's more, total alkaloids of *Aconitum tanguticum* improved the pathological changes in the lungs, and reduced inflammatory cell infiltration and pro-inflammatory cytokine release *via* inhibiting the NF-*κ*B activation in LPS-induced acute lung injury in rats [94]. 14-*O*-acetylneoline, isolated from *Aconitum laciniatum*, showed anti-inflammatory effect on colitis mice characterized by decreasing weight loss, inhibiting macroscopic pathology and histological inflammation and reducing the colonic IFN-*γ* mRNA levels [95]. Moreover, *Aconitum* alkaloid suppressed the proliferation and migration of SW982 cells through inhibiting Wnt-5a mediated JNK and NF-*κ*B signaling pathways [96] and also inhibited ConA- and LPS-induced splenocyte proliferation [97]. Benzoylaconitine suppressed IL-1*β*-induced expression of IL-6 and IL-8 *via* inhibiting the activation of the MAPK (ERK, JNK, and p38), Akt, and NF-*κ*B pathways in SW982 cells [98]. In type II collagen-induced arthritis (CIA) mice, higenamine reduced the elevation of clinical arthritis scores and inhibited inflammatory reactions, oxidation damage and caspase-3/9 activation, which was possibly related to the heme oxygenase (HO)1 and PI3K/Akt/Nrf2 signaling pathways [99]. In addition, higenamine also increased myelin sparring and enhanced spinal cord repair process *via* promoting M2 activation macrophage, and reduced Hmgb1 expression dependent on HO-1 induction in

Table 3 Effects of *Aconitum* alkaloids on the immune system

Component/Dose/Duration	Cell type/Animal model	Effects	Mechanisms	Ref.
Nagarine A 72.63 ± 0.39 μmol·L^{-1} for 24 h; nagarine B 52.98 ± 0.50 μmol·L^{-1} for 24 h	LPS-induced RAW264.7 cells	Anti-inflammation	Inhibit the production of IL-6	[88]
Bulleyanine A 10, 20 and 40 μmol·L^{-1} for 24 h	LPS-induced RAW264.7 cells	Anti-inflammation	Inhibit the production of NO	[89]
Mesaconitine, hypaconitine, napelline, songorine and 12-epinapelline *N*-oxide, 0.025 mg·kg^{-1} for 5 d	Carrageenan-induced acute inflammation in mice, histamine-induced inflammation in mice, and acetic acid-induced peritonitis in mice	Anti-inflammation	Inhibit inflammation at various stage and show highly anti-exudative activity	[90]
Szechenyianine B, szechenyianine C, *N*-deethyl-3-acetylaconitine, and *N*-deethyldeoxyaconitine 0.05, 0.1, 0.5, 1, 5 and 10 μmol·L^{-1} for 18 h	LPS-induced RAW264.7 cells	Anti-inflammation	Inhibit the production of NO	[91]
Lappaconitine and puberanine, 100 μg·mL^{-1} for 30 min	Zymosan activated serum-induced neutrophils	Anti-inflammation	Inhibit the production of superoxide	[92]
Aconitine 0.125 and 0.25 mmol·L^{-1} for 1, 2, 8, 24 h, 4 d or 7 d	RANKL-induced RAW264.7 cells	Inhibit RANKL-induced osteoclast differentiation	Inhibit the RANKL-induced activation of NF-κB and NFATc1 and suppress the expression of osteoclast specific genes and DC-STAMP	[93]
Total alkaloids of *Aconitum tanguticum* 30 and 60 mg·kg^{-1} for 6, 12 and 24 h	LPS-induced acute lung injury in rats	Exhibit potent protective effects on LPS-induced acute lung injury in rats through anti-inflammation	Increase the value of PaO_2 or PaO_2/FiO_2, decrease myeloperoxidase activity and TNF-α, IL-6 and IL-1β leveles in BALF and inhibit NF-κB activation in lung tissue	[94]
14-*O*-acetylneoline 10, 20 and 50 μg for 3 d	TNBS-induced colitis in mice	Mitigate inflammation against ulcerative colitis	Significantly lower the clinical score, macroscopic pathology and grades of histological inflammation and reduce colonic IFN-γ mRNA level	[95]
Alkaloids extract removed lappaconitine from *Aconiti Sinomontani* Radix (MQB) 1, 10 and 20 μg·mL^{-1} for 12, 24 and 36 h	SW982 cells	Inhibit the proliferation and migration of human synovial fibroblast cells	Inhibit the mRNA expression of Wnt5a, Runx2, Bmp2 and MMP3 and inhibit the phosphorylation of JNK and NF-κB p65 and the expression of MMP3	[96]
Szechenyianine E, 8-*O*-methyl-14-benzoylaconine,and spicatine A 0.16, 0.8, 4, 20 and 100 μmol·L^{-1} for 48 h	ConA-induced or LPS-induced splenocytes	Suppress immune for the treatment of autoimmune diseases	Inhibit splenocyte proliferation	[97]
Benzoylaconitine 5 and 10 μmol·L^{-1} for 1, 6, 12 and 48 h	IL-1β-stimulated SW982 cells	A potential therapeutic agent for rheumatoid arthritis treatment	Inhibit the expression of IL-6 and IL-8 gene and protein, decrease the activation of MAPK and the phosphorylation of Akt and inhibit the degradation of IκB-α and the phosphorylation and nuclear transposition of p65 protein	[98]
Higenamine 10 mg·kg^{-1} for 14 d	Type II collagen induced arthritis mice	Ameliorate collagen-induced arthritis	Resuppress inflammatory reactions, oxidation damage and caspase-3/9 activation, increase HO-1 protein expression and upregulate of the PI3K/Akt/Nrf-2 signaling pathway	[99]

Continued

Component/Dose/Duration	Cell type/Animal model	Effects	Mechanisms	Ref.
Higenamine 5, 10 and 15 mg·kg^{-1} for 1, 3, 7, 14, 28 and 42 d	A murine model of spinal cord injury	Promote locomotor function after spinal cord injury	Increase the expression of IL-4 and IL-10, promote M2 macrophage activation and reduce Hmgb1 expression dependent on HO-1 induction	[100]
Aconitine 25 and 75 μg·kg^{-1} for 9 weeks	Pristine-induced systemic lupus erythematosus in mice	Improve the pathological damage of systemic lupus erythematosus	Decrease the blood leukocyte counts and the level of anti-dsDNA antibody in serum, ameliorate renal histopathologic damage, reduce IgG deposit in the glomerular and decrease the levels of PGE2, IL-17a and IL-6	[101]

spinal cord injury mice [100]. Aconitine ameliorated the renal pathology through inhibiting pro-inflammatory cytokines and inflammation in the kidneys, and decreasing blood leucocyte counts and the level of anti-dsDNA antibody in serum in a pristane-induced murine model, which indicated that aconitine is a potential compound for the treatment of systemic lupus erythematosus [101].

Anti-cancer effects

Diterpenoid alkaloids isolated from *Aconitum* plants have great potential to treat cancer in many *in vitro* experiments (Table 4). Accumulating studies showed that *Aconitum* diterpenoid alkaloids were effective against proliferation in human cancer cell lines [102-108], which might be caused by activation of p38 MAPK-, death receptor-, mitochondrial-, caspase-meditated apoptosis [109]. C_{19} Diterpenoid alkaloids significantly inhibited the growth of HepG2 cells possibly through blocking the cell cycle at the G_1/S phase, up-regulating the expression of B-cell lymphoma 2 (Bcl-2)-associated X (Bax) and caspase-3 protein and down-regulating the expression of Bcl-2 and CCND1 [108, 110]. Furthermore, aconitine inhibited the proliferation of hepatocellular carcinoma cells in the context of ROS-induced mitochondrial-dependent apoptosis [111]. Meanwhile, aconitine also up-regulated the expression of cleaved-caspase-3, cleaved-caspase-9, and cleaved poly (ADP-ribose) polymerase 1 (PARP1), which induced the apoptosis in Miapaca-2 and Panc-1 cells, producing anti-human pancreatic cancer activity [112]. Hpyaconitine inhibited transforming growth factor-β1 (TGF-β1)-induced epithelia-mesenchymal transition, and adhesion, migration and invasion of lung cancer cells by inhibiting the NF-κB signaling pathway [113]. Moreover, alkaloids from *Aconitum taipeicum* showed anti-leukemia activity [114, 115]. Therefore, *Aconitum* alkaloids played potential inhibitory effects on many types of cancer.

Other pharmacological effects

Aconitum alkaloids also showed antimicrobial, antivirus, antiplasmodial, antioxidant and reparative activities. The new C_{19}-diterpene alkaloids extracted from *Aconitum duclouxii* such as ducloudines C, D, E and F exhibited good biological activities against pathogenic fungi and pathogenic bacteria [116, 117]. Norditerpenoid alkaloids from the roots of *Aconitum heterophyllum* Wall were proved to have antibacterial activity [118]. Carmichaedine, a new C_{20}-diterpenoid alkaloid from the lateral roots of *Aconitum carmichaeli*, exhibited potent antibacterial activity against *Bacillus subtilis* [119]. Meanwhile, demethylenedelcorine and 18-*O*-methylgigactonine isolated from *Aconitum sinomontanum* Nakai were proved with pesticidal activities against *Mythimna separata* [120]. Other studies concluded that *Aconitum* alkaloids showed little inhibitory effect on *Escherichia coli* and *Helicobacter pylori*, but exerted potential inhibitory effects on the growth of *Staphylococcus aureus* [121, 122].

Moreover, tanguticulines A and E extracted from *Aconitum tanguticum* inhibited H1N1-induced cytopathic changes, exhibiting obvious antivirus activities *in vitro* [123]. The major alkaloid from *Aconitum orochryseum*, atisinium chloride, proved moderate antiplasmodial activity against the TM4 strain and the K1 strain of *Plasmodium falciparum* [124]. The mixture of diterpene alkaloids of *Aconitum baicalense* showed significant regenerative hemostimulating effects on a model of cytostatic myelosuppression, which were achieved by activating hematopoietic progenitor cells [125]. Besides, songorine stimulated the mitotic activity and differentiation of mesenchymal progenitor cells through activating the JAK/STAT signaling pathway [126]. Aconite alkaloids directly stimulated the growth of fibroblasts, which might contribute to reparative regeneration of the plane dorsal skin [127]. *Aconitum* alkaloids also showed strong binding capacity to metal ions and used as effective antioxidants [128, 129].

Toxicology of *Aconitum* Alkaloids

In addition to therapeutic activities, *Aconitum* alkaloids have subsantial cardiotoxicity, neurotoxicity and liver toxicity at high doses or for long-term use. A large number of studies indicated that *Aconitum* diterpenoid alkaloids possibly caused disordered ion channels and DNA damage, resulting in mitochondrial-induced cardiomyocyte apoptosis [130-132]. Aconitine, one of the most bioactive component of *Aconitum* alkaloids, remarkably aggravated Ca^{2+} overload to induce arrhythmia and trigger apoptosis *via* the p38 MAPK signaling pathway in rat ventricular myocytes [133], and induced cardiotoxicity in zebrafish embryos [134]. Aconitine also

Table 4 Anti-cancer effects of *Aconitum* alkaloids

Component/Dose/Duration	Cell type/Animal model	Effects	Mechanisms	Ref.
14-Benzoylaconine-8-palmitate IC_{50} 11.9, 27.6,and 31.8 μmol·L^{-1} for 72 h	MCF-7, HepG2 and H460 cell lines	Anti-tumor	Inhibit the proliferation of cancer cells	[102]
Sinchiangensine A, lipodeoxyaconitine	HL-60. A-549, SMCC-7721, MCF-7 and SW480 cell lines	Anti-tumor	Inhibit the proliferation of cancer cells	[103]
Aconitum alkaloids	CT26. SW480, HeLa, SkMel25 and SkMel28 cell lines	Anti-tumor	Inhibit the proliferation of cancer cells	[104]
Navicularine B IC_{50} 13.50, 18.52, 17.22, 11.18 and16.36 μmol·L^{-1}, respectively	HL-60, SMMC-7721, A-549, MCF-7 and SW480 cell lines	Anti-tumor	Inhibit the proliferation of cancer cells	[105]
Lipojesaconitine IC_{50} 6 to 7.3 μmol·L^{-1} for 72 h	A549, MDA-MB-231, MCF-7, KB and KB-VIN cell lines	Anti-tumor activities except a multidirectional-resistant subline	Inhibit the proliferation of cancer cells through possibly being exported by P-glycoprotein	[106]
Delelatine IC_{50} 4.36 μmol·L^{-1} for 72 h	P388 cell line	Anti-tumor	Inhibit the proliferation of cancer cells	[107]
Taipeinine A 7.5, 15 and 30 μmol·L^{-1} for 24, 48 and 72 h	HepG2 cell line	Anti-tumor *via* apoptosis	Inhibit proliferation and invasiveness, block the cell cycle at the G_1/S phase and up-regulate the expression of Bax and caspase-3 protein anddown-regulate the expression of Bcl-2 and CCND1 protein	[108]
Aconitum szechenyianum Gay alkaloids 100, 200, 400, and 800 μg·mL^{-1} for 24 h	HepG2, HeLa and A549 cell lines	Anti-tumor through the p38-MAPK, death receptor-, mitochondria- and caspase-dependent adoptive pathways	Upregulate TNF-R1 and DR5 through activation of p38 MAPK, upregulate p53, and phosphorylate p53 and Bax, Down-regulate Bcl-2 and activate caspase 3/8/9	[109]
Aconitine, hypaconitine, mesaconitne andoxonitinefor 72 h	HepG2 cell line	Anti-tumor	Inhibit the proliferation of cancer cells	[110]
Aconitine 25 and 50 μg·mL^{-1} for 72 h	HepG2, Huh7 and L02 cell lines	Inhibit the proliferation of hepatocellular carcinoma	Release of cytochrome c from the mitochondria, activate apoptosis, increase the cleavage of caspases 3/7 and Bax protein level and decrease Bcl-2 level	[111]
Aconitine 15, 30, and 60 μmol·L^{-1} for 48 h (cell); and 50, and 100 mg·kg^{-1} for 28 d (mice)	Miapaca-2, PANC-1 cells, Miapaca-2 cells and, a xenograft mouse model	Induce apoptosis in human pancreatic cancer	Up-regulate the expression of pro-apoptotic factors Bax, cl-caspase-3, cl-caspase-9, and cleaved PARP1 and decrease anti-apoptotic protein Bcl-2 and NF-κB expression	[112]
Hypaconitine 2, 4 and 8 μmol·L^{-1} for 48 h	TGF-β1-induced A549 cells	Inhibit the adhesion, migration and invasion abilities of lung cancer	Inhibit TGF-β1-induced u-pregulation of *N*-cadherin, NF-κB and inhibit TGF-β1-induced adhesion, migration and invasion abilities	[113]
Amide alkaloids from *Aconitum taipeicum*; andditerpenoid alkaloids from *Aconitum taipeicum*	HL60 and K562 cell lines	Anti-leukaemia	Inhibit the proliferation of cancer cells	[114-115]

up-regulated a series of pro-apoptotic proteins including P53, BAX, and caspase-3 but down-regulated anti-apoptotic proteins Bcl-2 and TnT, which induced cardiotoxicity in rat myocardial cells [133, 134]. Aconitine induced cardiomyocyte damage *via* the mitochondria-mediated apoptosis pathway [135] and mitigated BNIP3-dependent mitophagy [136]. Moreover, aconitine blocked HERG and Kvl.5 potassium channels to induce arrhythmias [137]. Aconitine and mesaconitine induced cardiotoxicity and apoptosis, and influenced the expression of cardiovascular relative genes including Tbx5, Gata4, and Nkx2.5 in embryonic zebrafish [138]. As another toxicalkaloid,hypaconitineinducedcardiotoxicitythroughinhibiting the KCNH2 (hERG) potassium channels in conscious dogs [139].

Notably, clinical reports also confirmed that improper intake of aconite alkaloids might cause severe cardiotoxicity. *Aconitum* herbs with poor quality such as incompletely processing, poor quality of prescription such as overdose, inadequate boiling or dispensary errors [140, 141] and 'hidden' aconite poisoning which refers to the toxicity caused by the contaminants in other dispensed herbs are the main reasons for aconite poisoning [142]. Patients with aconite poisoning often showed cardiotoxicity such as bidirectional ventricular tachycardia [143] and ventricular dysrhythmias [144], as well as prolonged hypotension and sinus bradycardia [145]. Acute aconite poisoning also induced myocardial infarction with elevated cardiac enzymes and chest tightness [146], and even caused death [147].

In addtion to cardiotoxicity, *Aconitum* alkaloids also caused hepatoxicity and neurotoxicity, and aconitine promoted liver autophagy via the PI3K/Akt/mTOR signaling pathway in mice [148]. Aconitine, mesaconitine and hypaconitine possibly penetrated the blood-brain barrier (BBB) *via* a proton-coupled organic cation antiporter and stimulated dynorphin A expression to cause anti-hypersensitivity [13], which partly revealed the underlying mechanism of their severe neurotoxicity [149].

Pharmacokinetic Studies of *Aconitum* Alkaloids

Currently, the pharmacokinetic characteristics of *Aconitum* alkaloids are extensively investigated from the perspective of absorption, distribution and metabolism.

Absorption

Efflux transporters, such as P-glycoprotein (P-gp), multidrug resistance-associated protein 2 (MRP2), and breast cancer resistance protein (BCRP), play a major role in regulating the absorption of *Aconitum* alkaloids in the intestine [150]. Aconitine was rapidly eliminated with a short half-life (i.v., 80.98 ± 6.40 min), and its total oral bioavailability was only 8.23% ± 2.5% in rat plasma [151]. Further studies confirmed that P-gp was involved in poor intestinal absorption of aconitine, resulting in reduced toxicity [30,152-154]. In a pharmacokinetics study using urine and fecal samples of SD rats, 87.71% of mesaconine was excreted without changes after oral administration. The oral bioavailability of mesaconine was only 14.9%, which may be related to its low intestinal permeability due to lack of lipophilicity or the inhibitory effect of P-gp [154, 155]. Moreover, the bioavailability of hypaconitine was also extremely low due to inhibition of P-gp [154]. After oral administration, benzoylmesaconine, benzoylaconine and benzoylhyaconine achieved the maximal plasma concentrations at 0.222, 0.306, and 0.222 h, respectively and their bioavailability was also very low due to the inhibitory effect of P-gp [30,156]. In addition, the pharmacokinetics studies of urine and plasma samples from healthy subjects showed that 94% of higenamine was excreted from the body after administration within 30 min (approximately four half-lives) [157]. However, compared with aconitine and benzoylaconine, aconine did not significantly increase the expression of P-gp in LS174T and caco-2 cells [158], and its transport was not significantly differet in the presence of P-gp inhibitor, implying that aconine might be absorbed through passive diffusion [30]. Additionally, *Aconitum* alkaloids significantly increased the protein and mRNA levels of MRP2 and BCRP, which contributed to the safe application of *Aconitum* alkaloids [12, 150, 159].

Distribution

Aconitum alkaloids were widely distributed in the body after oral administration. The amounts of toxic alkaloids were significantly higher in the liver and kidneys, and relatively lower in the heart and blood, with only trace amounts in the brain due to the action of the blood-brain barrier [160-162]. The distribution data are useful to elucidate the pharmacokinetics process of *Aconitum* alkaloids in the body.

Metabolism

CYPs are abundant in the liver, kidneys, lungs and gastrointestinal tract, which are responsible for metabolizing exogenous and endogenous compounds through hydroxylation or oxidation [163]. As expected, CYPs are of great significance to the metabolism of *Aconitum* alkaloids, which can transform toxic compounds into more soluble derivatives, suitable for excretion from the body, thereby greatly reducing toxicity [164, 165]. *Aconitum* alkaloids are mainly metabolized by CYP 3A4/5, and slightly metabolized by CYP 2C8, 2C9, and 2D6 [166-168]. Further research found that the main metabolic pathways of DDAs in the body were demethylation-dehydrogenation and hydroxylation, which were more likely to occur in human liver microsome (HLM) and intestine microsome (HIM) incubations, while MDAs were mainly metabolized by demethylation-dehydrogenation in HIM incubation [164, 165]. Aconitine was transformed into at least 6 metabolites through *O*-demethylation and *N*-demethylation in rat liver microsomal incubations [31]. These results may contribute to the research of *Aconitum* alkaloid poisoning and metabolic detoxification.

Conclusions and Future Perspectives

Aconitum alkaloids have been widely used as heart medicine or analgesic agents for the treatment of coronary heart disease, chronic heart failure, rheumatoid arthritis and neuro-

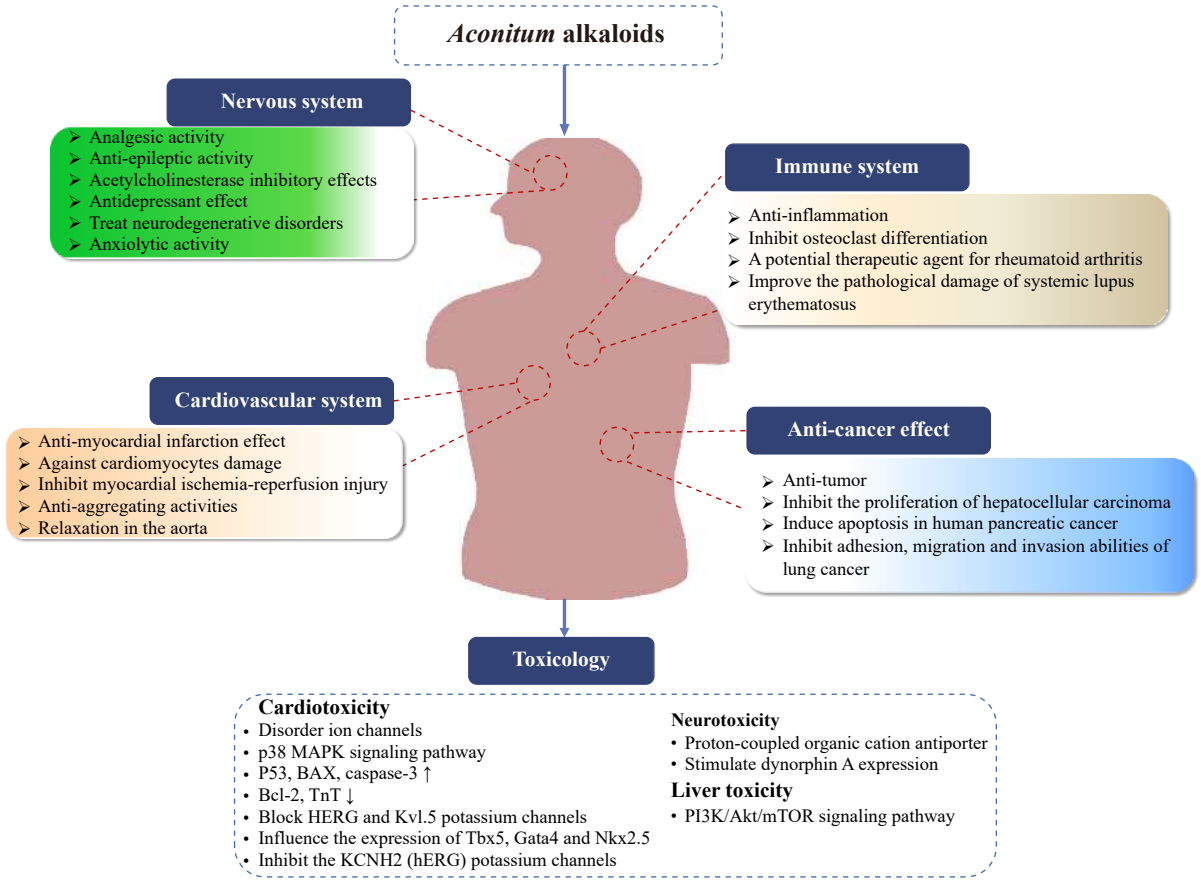

Fig. 2 Schematic representation of the pharmacological and toxicological effects and related molecular mechanisms of *Aconitum* alkaloids

pathic pain [98, 169-171]. This review summarizes the pharmacological and toxicological effects and related molecular mechanisms of *Aconitum* alkaloids in the past twenty years, with the schema presented in Fig. 2. *Aconitum* alkaloids exert significant protective effects on the cardiovascular system, nervous system, and immune system as well as anti-cancer activity. However, due to a narrow therapeutic window, *Aconitum* alkaloids are easily to trigger strong cardiotoxicity, neurotoxicity and liver toxicity, which restrict its practical use. Therefore, the processing methods of *Aconitum* such as decoction are commonly used to reduce toxicity, which is also used in combination with dried ginger, licorice and ginseng to form traditional Chinese medicine compound prescriptions, such as Sini decoction and Shenfu decoction to achieve decreasing toxic and synergic effects [29, 172]. However, there are still some cases concerning poisoning in clinical practice. Therefore, it is of great significance to standardize *Aconitum* alkaloids in medicinal materials. Although *Aconitum* alkaloids are characterized by poor absorption, rapid excretion and low bioavailability *in vivo*, they can still show significant pharmacological activity. Therefore, further exploration of the molecular mechanism of action and toxicological mechanism of *Aconitum* alkaloids *in vivo* will be helpful to ensure their safety application, which may become a research hotspot for *Aconitum* plants.

Abbreviations

ACh: Acetylcholine; AV-shunt: arterio-venous shunt; Bax: B-cell lymphoma 2-associated X; BBB: blood-brain barrier; Bcl-2: B-cell lymphoma 2; BCRP: breast cancer resistance protein; CIA: collagen-induced arthritis; CPAR: conditioned passive avoidance response; CYPs: cytochrome P450 proteins; DDAs: diester-diterpenoid alkaloids; DIC: disseminated intravascular coagulation; ETs: efflux transporters; FDP: fibrinogen/fibrin degradation product; FTA: fuzi total alkaloid; HDAs: hydramine diterpenoid alkaloids; HIM: human intestine microsomes; HLM: human liver microsomes; HO: heme oxygenase; MDAs: monoester-diterpenoid alkaloids; MRP2: multidrug resistance-associated protein; ox-LDL: oxidized low-density lipoprotein; PA: processed aconite root; PARP1: poly ADP-ribose polymerase 1; P-gp: P-glycoprotein; PT: prothrombin time; RAE: Radix Aconiti Lateralis Preparata extract; TGF-β1: transforming growth factor-β1; VMH: ventromedial hypothalamic.

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