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Between Poison and Medicine: Historical Legacy, Molecular Toxicity, and the Pharmacological Paradox of Aconitum Diterpenoid Alkaloids

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Abstract: *Aconitum has long occupied a contested position between poison and medicine, yet the relationship between its historical uses, chemically defined constituents, and contemporary toxicological evidence remains difficult to interpret across species. This narrative review aimed to the historical legacy, botanical identity, phytochemical diversity, molecular pharmacology, and therapeutic evidence concerning Aconitum-derived diterpenoid alkaloids, with particular emphasis on Aconitum episcopale H.Lév. and Aconitum napellus L. Historical medicinal accounts are considered alongside modern taxonomic evidence to distinguish traditional botanical designations from currently accepted species. Investigations of A. episcopale have identified structurally characterized episcopines and episcopalines exhibiting preliminary antinociceptive activity, whereas evidence concerning A. napellus includes phytochemical characterization and documented severe human poisoning. Mechanistic investigations implicate disturbances in voltage-gated sodium-channel function, intracellular calcium homeostasis, and neuronal and cardiac cellular integrity, although the observed responses vary across experimental systems. Comparative research involving lappaconitine and bulleyaconitine A, including selected clinical investigations, showed compound- and formulation-dependent analgesic effects without establishing therapeutic safety for either species. Processing, structural modification, and metabolism can alter alkaloid activity and toxicity but do not guarantee a favorable therapeutic margin. In concusion, the available evidence accentuates the importance of species authentication, molecular identity, experimental context, and exposure-dependent toxicity when interpreting the medicinal potential of Aconitum. Whether reproducible antinociceptive effects can be achieved at exposures sufficiently separated from neurocardiac injury remains a central unresolved question.*

Introduction

Aconitum species have long been used as both medicines and poisons. Their diterpenoid alkaloids exhibit antinociceptive activity, but can also cause severe neurological and cardiac toxicity, making the separation of therapeutic effects from harmful responses a central challenge. For centuries, aconite occupied an uneasy position between poison and remedy. European and Chinese medical traditions recognised its potency long before individual alkaloids were characterised. Historical uses explain why these plants attracted medical interest; they do not establish modern efficacy or safety. The challenge is now experimental: can a pain-related response be demonstrated without concomitant injury?

Two Species, Two Stories

A. episcopale — native to southwestern China; a source of characterised episcopines and episcopalines with preliminary animal antinociceptive activity. *A. napellus* — native to western and central Europe; studied for organ-specific alkaloid profiles and implicated in severe human poisoning. Historical taxonomic names might be reconciled before results are attributed to either species. Diterpenoid alkaloids contain highly modified, nitrogen-bearing polycyclic frameworks. The conventional C18, C19, and C20 categories (Figure 1) describe the parent carbon skeleton, whereas C18 examples include lappaconitine; C19 compounds include aconitine and related molecules; C20 frameworks include atisine- and napelline-type structures.

Molecular Mechanisms of Neurological and Cardiac Toxicity

Aconitine disrupts voltage-gated sodium-channel function and intracellular calcium homeostasis, contributing to abnormal excitability and cellular injury. In cardiac toxicity disturbed ion currents and calcium handling promote conduction abnormalities, ventricular arrhythmias, and cardiomyocyte injury. In specific animal assays, episcopine A (ID_{50} 66.1 µmol/kg) and episcopaline B (ID_{50} 55.0 µmol/kg) showed antinociceptive responses. In neurological toxicity altered neurotransmission, mitochondrial dysfunction, oxidative stress, and calcium overload contribute to neuronal dysfunction and apoptosis. These effects depend on the alkaloid, exposure, and experimental model.

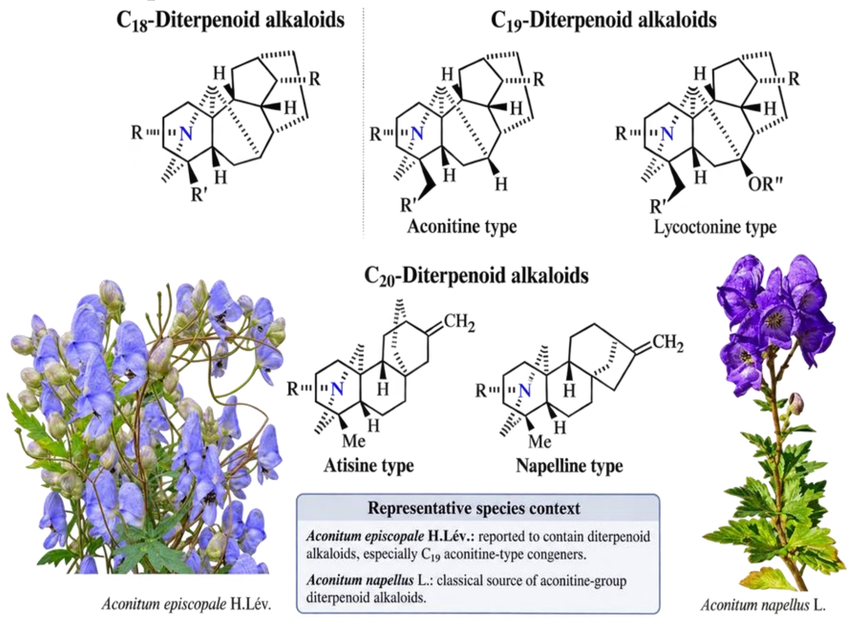


Figure 1. Structural diversity of C18, C19 and C20 diterpenoid alkaloids from *Aconitum*.

As illustrated in Figure 2, aconitine and related alkaloids can alter voltage-gated sodium-channel function and intracellular Na^+/Ca^{2+} homeostasis, triggering abnormal electrical signalling, conduction disturbances, and neuronal dysfunction. These molecular events may culminate in severe ventricular arrhythmias, myocardial injury, and neurotoxicity.

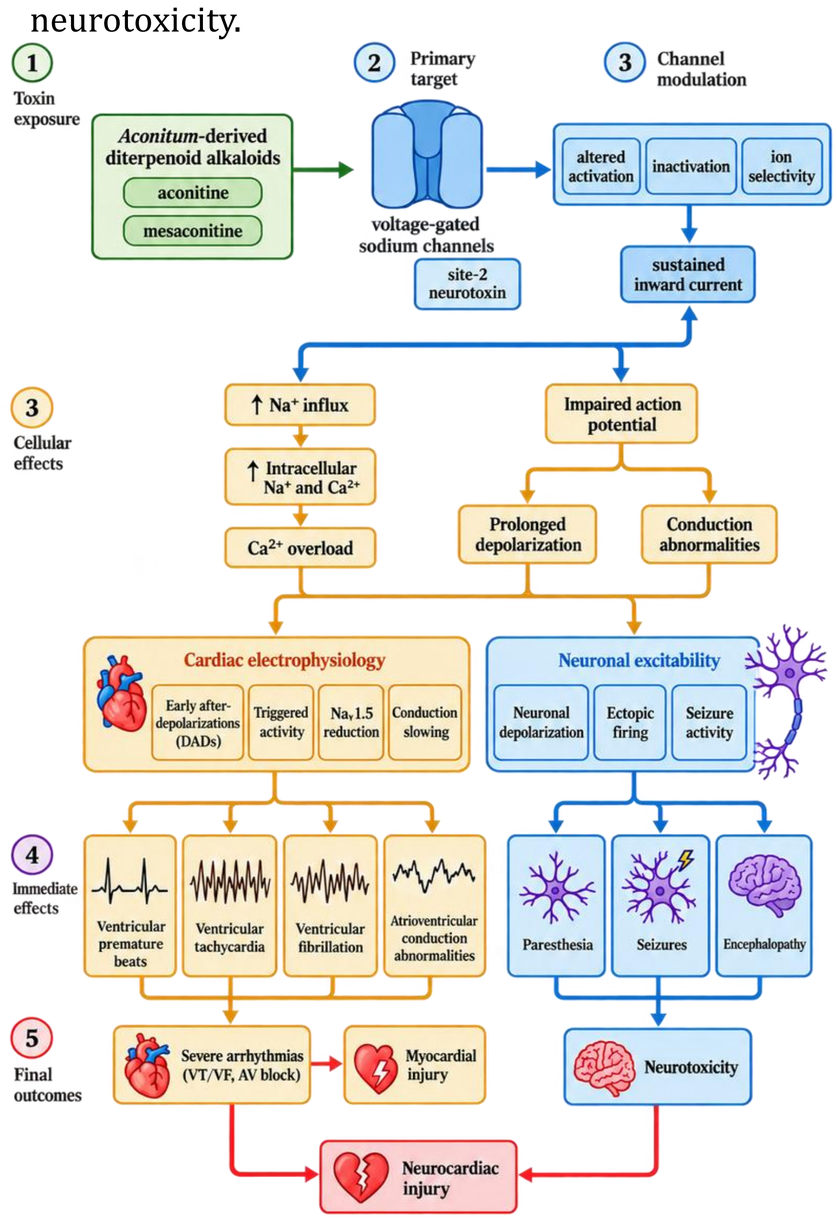


Figure 2. Molecular mechanisms of aconitine-induced cardiac and neurological toxicity.

Conclusions Aconitum-derived diterpenoid alkaloids offer promising pharmacological leads, but biological activity does not imply therapeutic safety. While *A. episcopale* has yielded compounds with preliminary antinociceptive effects, *A. napellus* has been associated with severe human poisoning. Their structural diversity and the complex mechanisms of neurocardiac toxicity emphasise the importance of compound identity, exposure, and species-specific evaluation. Future research must establish whether beneficial pharmacological effects can be achieved at exposures sufficiently aside from serious toxicity.