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Review Article

A Comprehensive Review on *Aconitum ferox* Wall and Its Pharmacological Perspectives

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ABSTRACT

Aconitum ferox Wall, Ranunculaceae, has played a pivotal role in the history of mankind since ancient days. It is recognized colloquially as Monk's hood in English, while described as "Vatsanabha" in Ayurvedic texts. It is covered in E1 Schedule of Drug and Cosmetic Act, 1945 under poisonous plants and is used as herbal remedy after detoxification process as mentioned in Ayurvedic literature under "Sodhana". The plant is used in targeting different ailments such as pain, fever, rheumatism in Western, Chinese and Indian traditional medicine. Several scientific experiments are done to validate its safety and efficacy for the usage of this plant in herbal formulations. Excessive commercialization of *Aconitum ferox* roots has pushed the plant to the endangered category as mentioned in Appendix II, Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). The information was collected through internet and by accessing different search engines like Wiley, CNKI, PubMed, Baidu Scholar, ACS, Scifinder, ScienceDirect, Web of Science, Google Scholar and libraries from the year 1958 to 2026. Some classical texts of Ayurveda were used for the traditional use of *Aconitum ferox* in Ayurvedic and folk medicines. This review provides a summarized view on the ethnopharmacology, therapeutic uses, pharmacokinetics, pharmacodynamics, drug characterisation, mode of administration of the drug, safety and toxicity, efficacy, contra-indication and interactions about the plant. This will further help to understand the plethora of its medicinal properties and thereby urging the researchers for its judicious use and give a thought on its conservation strategies.

Keywords: *Aconitum ferox*, Efficacy, Medicinal property, Pharmacodynamics, Pharmacokinetic.

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INTRODUCTION

In the advancing world of technology and development in synthetic drugs, the researchers around the world are shifting to herbal treatments for different diseases to avoid life risking side effects of the synthetic drugs. Herbal formulations are used to cure ailments and being practiced since ancient ages but has been suppressed due to lack of passing on the legacy of traditional knowledge from one generation to another.

Aconitum ferox Wall is one such species which is endemic to the Himalayan range and distributed throughout the western and eastern Himalayas. It belongs to the family Ranunculaceae and has 27 species and 5 subspecies inhabited in the Indian Himalayas (Agnihotri *et al.*, 2015). It is popularly known as "Vatsanabha" in Ayurveda and has been proved to have promising biological effects like analgesic, anti-rheumatic, antifungal, antihelmintic, antiviral and anti-diarrheal properties. It is used in irregular menstruation, edema, asthma, gastroenteritis, neurological disorders, paralysis, leprosy and as a carminative astringent, appetizer and also against some tumors (Jabeen *et al.*, 2013; Jaiswal *et al.*, 2013; Shyaula, 2011). The plant is recognised with characteristics like "Balya" (tonic), "Kaṇṭharukhara" (reliever of throat pain), "Rasāyana" (rejuvenation), "Vyavāyī" (stimulation of Central Nervous System followed by depression), etc. As a solitary drug, this is used in about twenty-seven clinical conditions like "Madāvaha" (alcoholism), "Kāsa" (cough), "Agnimāndhya" (impairment of digestion), "Gulma" (lump in abdomen), etc. This drug is also used for "krāmaṇa" (base metals transformation into gold), "Śodhana" (procedure of purification), and "Vedhana" (alchemy) (Buha *et al.*, 2020) and also used in homeopathy to cure fever, stress and anxiety (Gaur and Sharma, 2019). Classical texts of Ayurveda details 1378 formulations, having this drug as an ingredient and recommends its use to combat in almost 79 varied diseases, where maximum are indicated for the supervision of "Jvara" (fever), trailed by "Vātavyādhi" (neuro-muscular

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anomalies) and "Kuṣṭha" (skin disease) etc. (Buha *et al.*, 2020). The roots of the plant attributes to its medicinal property due to the presence of aconitine alkaloid (Sharma *et al.*, 2009).

In the language of Ayurveda, it is mentioned that even a poison can act as a medicine when administered in correct dose and vice versa (Uniyal *et al.*, 2007). *Aconitum ferox* is one such poisonous plant which when administered properly can work wonders on different ailments especially on rheumatoid arthritis. 'Akonitos' is the native word to '*Aconitum*' which means 'struggle free' which is predicted to be related to the effortless death caused by its consumption. The etymology reveals 'ak' means pointed or sharp and 'konos' means cone which probably refers to its pointed leaves. Many believe that the plant has been named from Acona, a city in Greece where it was pioneered (Acharya, 2001). The Latin word '*ferox*' means fierce and strong which actually means the intensity of its toxicity being identified as the most poisonous plant in the living world (Kakkar *et al.*, 2023). This has been called as 'wolf's bane' or 'arrow poison' and was wolf killing weapon (El-Shazly *et al.*, 2016; Regmi *et al.*, 2020).

Rheumatoid arthritis and other inflammations are globally common in about 1% of the adult population especially in women above the age 55 years. There are adverse side effects and high cost of the Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) hence are getting replaced by the medicines of natural origin especially from plants. The purified roots (through Ayurvedic "Sodhana" process) of *Aconitum ferox* are used to treat rheumatoid arthritis which is considered as one of the chronic diseases globally (Vogel, 2018).

The present review article deals with summarizing the traditional and modern therapeutic potential of *A. ferox* which will help the readers to get holistic information regarding such an important medicinal plant in spite being toxic. It will also open the conscience among the researchers about its medicinal values and will instigate an urge among the young researchers for its conservation. Presently, further work on this plant is being done by the authors and hence a review is made by the collected data.

METHODOLOGY

This particular review aimed to assimilate all the traditional and scientific facts which exists on *Aconitum ferox* in relation to ethnopharmacology, experimental pharmacology (*in vitro* and *in vivo*), clinical pharmacology, drug characterization, pharmacokinetics, pharmacodynamics, mode of administration and posology, safety and toxicity which includes acute toxicity, repeated dose toxicity, overdose toxicity, mutagenicity, carcinogenicity, teratogenicity and reproductive toxicity. This review also highlights the effect of *Aconitum ferox* during pregnancy and lactation, its influence on driving and use of machines, efficacies, contra-indications, interactions, special warning and precautions for use and undesirable effects / adverse reactions. The information were collected by using the keywords like *Aconitum ferox*, toxicity, ethnobotany + *Aconitum ferox*, dose of administration + *Aconitum ferox*, characterization of drugs, *Aconitum ferox* + pharmacokinetics, *Aconitum ferox* + pharmacodynamics, *Aconitum ferox* + efficacies, *Aconitum ferox* + contra-indications, drug interaction + *Aconitum ferox, Aconitum ferox* + warning during usage, through internet and by accessing different search engines like Wiley, CNKI, PubMed, Baidu Scholar, ACS, Scifinder, ScienceDirect, Web of Science, Google Scholar and libraries from the year 1958 to 2026. Recent articles were selected and were chronologically mentioned in the manuscript mentioning different prospects. Some classical books like Charaka Samhita (Acharya, 2001), Sushruta Samhita (Srikantha Murthy, 2010), Dhanvantari Nighantu (Singh, 2008), Sodhala Nighantu (Sodhala, 2019), Kaiyadev Nighantu (Sharma and Sharma, 2013), Bhava Prakasa Nighantu (Chunekar, 2015), Ayurvedic Pharmacopoeia of India (Pharmacopoeia Commission for Indian Medicine and Homoeopathy, 2005), Flora of Sikkim (Gogoi *et al.*, 2021), Flora of Eastern Himalayas (Hara, 1996) were also explored for the traditional use of *Aconitum ferox* in Ayurvedic and folk medicines along with its geographical location and morphological description.

RESULTS AND DISCUSSION

Taxonomic Classification

Kingdom: Plantae; Phylum: Magnoliophyta; Class: Magnoliopsida; Subclass: Magnoliidae; Order: Ranunculales; Family: Ranunculaceae; Genus: *Aconitum*; Species: *ferox*.

Distribution

In India it is found in Uttarakhand, Sikkim, Lohit district and Tawang district of Arunachal Pradesh, East Himalaya, Nepal (Vogel, 2018). Worldwide it is distributed in Japan, East Asia, central Europe and both Eastern and north-western America, Bhutan, China, Pakistan, Myanmar, Afghanistan and Turkestan (Agnihotri *et al.*, 2015).

Variability

There are a total 32 species of *Aconitum* genus out of which 27 are species and 5 are varieties In India. Among the 32 species, 16 are restricted to the Eastern Himalayas, 12 are endemic to the Western Himalayas and 4 are common to both the regions (Agnihotri *et al.*, 2015).

Macroscopic and Microscopic description

Macroscopically, the stems are woody, 3 to 6 feet tall, pubescent. Leaves are 3 to 6 with lobes, cuneate-ovate and incised. Inflorescence raceme, erect, 6 to 12 inches, simple sometimes branched below, tomentose, Flowers pedicillate, 1 to 2 inches, bracteate, bracteolate, bracts pinnatified, bracteolate linear, large in size, pale dusty blue, with helmet shaped corolla, helmet twice

high than other corolla, follicles 5, erect, densely villous, seeds in pods (Chandewar and Harode, 2022; Sharma and Kulshreshtha, 2024). Roots are paired, with tapering end, wrinkled, rough, dark brown, very hard, inside the cambium white (Pharmacopoeia Commission for Indian Medicine and Homoeopathy, 2001).

Microscopically, *Aconitum ferox* roots possess several characteristic pharmacognostical features which make it easier for its identification such as vessels, aseptate fibres, presence of various shaped sclerieds (stone cells), simple and compound starch grains measuring 6-18 μm in diameter. Some anatomical features are two to three layers of epidermis, primary and secondary cortex prominently divided by endodermis, bundles compact, xylem exarch, several starch grains filled cortical, phloem and xylem parenchyma (Pharmacopoeia Commission for Indian Medicine and Homoeopathy 2001).

Ethnopharmacology

Aconitum ferox belongs to the family Ranunculaceae which is an erect herb of 1m tall and with blue flowers (Chandewar and Harode, 2022). The tuberous roots of *Aconitum ferox* are traditionally being used in the cure of arthritis pain and also in fever, hypertension and sciatica (Ffrench, 1958; Makino *et al.*, 2009; Rastogi, 2011). The root powder is used in treating joint pain, pyrexia and as antimicrobial agents (Kakkar *et al.*, 2023).

In Ayurveda, eleven diverse species of *Aconitum* is being employed for their curable efficacies in inflammation, emetic, rheumatism and diarrhoea (Sarkar *et al.*, 2012; Sharadini and Urmila, 2000). These species are treated in diseases which are closely connected to body elements like space and air, which is called "Vata" and also in digestive and nervous syndromes in combination with different herbs. Some of these species of *Aconitum* mentioned in traditional knowledge are *Aconitum chasmanthum, A. atrox, A. deinorrhizum, A. ferox, A. falconeri, A. laciniatum, A. heterophyllum, A. palmatum, A. luridum, A. violaceum* and *A. spicatum* (Rahman *et al.*, 2000). *Aconitum ferox* has a plethora of efficacies which includes anti-inflammatory, anti-pyretic, analgesic, astringent and antispasmodic activities (Sharadini and Urmila, 2000; Wali *et al.*, 2022). This plant is highly toxic (Shyaula, 2011) but was first used as medicine by Baron Storck, native of Vienna, which was published in 1762 (Henriette's Herbal Homepage, 2024). In Ayurveda, to overcome the toxicity of this plant several methods of "Sodhana" have been subjected to the raw root materials of the plant which minimises the concentration its toxic substances. In comparative accounts on "Sodhana", processes by Ayurvedic methods and detoxification through modern methods have proved that Ayurvedic "Sodhana" process for detoxification showed less toxicity in advanced phytochemical analysis (Purohit, 2013). The toxicity of this plant can also be reduced when used in combination with other herbs which enhances their efficacies, such as, when *Aconitum* sp. is used with *Zingiber officinale* (ginger) and *Glycyrrhiza glabra* (licorice) for treating respiratory diseases (Sharadini and Urmila, 2000). *Aconitum ferox* is used in cure of ailments due to the presence of alkaloids in its extract which is responsible for its magical efficacies (Uprety *et al.*, 2010). The tubers are also used in tonsilitis, gastritis, sore throat and debility (Shyaula, 2011). In Mustang, the paste formed out of the roots are used in boils, allergies, cuts, wounds and edema in combination with different herbs (Bhattarai *et al.*, 2010). In Humla and Helambu, several ethnomedicinal uses of *Aconitum* are mentioned (Bhattarai, 1989; Rokaya *et al.*, 2010); the root extract is used as anti-pyretic after "Sodhana" (Mahajani *et al.*, 1990).

There are several herbal formulations of this plant in Ayurveda like "Rasnairandadi Kvatha Churna", "Mahavisagarbha taila", "Sudarsan Churna", "Lakasminarayana rasa", "Rodhrasava Siva Guika", "Panchatikta guggulu ghrita", "Bala chaurbhadrika churna" which are therapeutically used for "Krmiroga" (intestinal worms), "Jvara" (fever), "Chardi" (emesis), "Amatisara" (diarrhoea) and "Kasa (cough)" (Sharma, 1993; Lochan, 2006).

In vitro Studies

The treatment of H9c2 cell line (derived from embryonic rat heart tissue) with alkaloidal fractions of "Mahamrutyunjaya rasa" formulations containing *Aconitum ferox* showed decrease in cell viability and affected its normal cardiac cellular architecture even at lower concentration. The dose dependant cell viability decreased from 85.55% to 34.71%, 94.98% to 7.68% and 96.15% to 7.23% after 12hr, 24 hr and 48 hr of treatment respectively, indicating its toxic nature (Rai and Rajput, 2011). *Aconitum* sp. metabolites were studied on different cell lines viz. non-small cell lung cancer, human adenocarcinoma A549 cells, rat H9c2 cardiomyocytes and have been proved to have cytotoxic properties (Hao *et al.*, 2017). Aconitine, hypaconitine, mesaconitine, and oxonitine have been proved to have growth inhibition activity on HepG2 cells (human liver cancer cell line) due to the occurrence of ester group in their diterpene alkaloids (Gao *et al.*, 2012). Atisine- type alkaloids present in *Aconitum* roots inhibits cell proliferation on A549 human lung adenocarcinoma cell line (Xu *et al.*, 2010). *Aconitum* alkaloids those who are having acyl groups at C-11 and C-15 arrest the G1 phase and are more effective than hydroxyl groups at those positions which restricts the proliferation in the cell lines (Wada *et al.*, 2011). The amide group alkaloids of *Aconitum* sp. inhibit the activity on HL-60 leukemia cells and show cytotoxic actions on K562 myelogenous leukemia cell line (Xu *et al.*, 2010). Taipeinine A, is C19 diterpenoid alkaloids which arrests a cell in a cell cycle at G1/S phase and has proved to have antiproliferative activity against HepG2 human liver cancer cell lines (Zhang *et al.*, 2014). 8-O Methylcolumbianine, neoline, lycoctonine, delphatine, browniine, deacetylajadine, etc. are non-diterpenoid alkaloids from *Aconitum* which possess toxicity against carcinogenic cells by inhibiting the production of ATP (De Inés *et al.*, 2006). The proliferation of A172 glioblastoma cell line was also inhibited by

Aconitum alkaloids showing its antiproliferative activity (Wada *et al.*, 2007).

In vivo Studies

In a study on mice with Ehrlich's carcinoma, the aconitine comprising agent, BC1 repressed the development by 77.3% (Garmanchouk *et al.*, 2005). A study conducted on cardiovascular system of frogs showed that *Aconitum ferox* aqueous extract significantly increased the contraction of cardiac muscles at lower dose (2 mg/mL) and complete cardiac arrest was noticed at higher dose (256 mg/mL) (Sahoo *et al.*, 2013).

In another study, the dose of 10 mg/kg ethanolic extract of *Aconitum ferox* showed reduction in the rat paw edema model besides normalizing the haemoglobin, locomotion and biochemical disturbances in Complete Freund's Adjuvant (CFA) -induced arthritis model in rats. The reduction in volume of the paw (58.32%), weight of the body, ESR (8.1-7.5 mm/hr), and Lipid Peroxidation (LPO) level (37.5 nmol/g) was noticed. The locomotors activity, haemoglobin and Superoxide Dismutase (SOD) level increased to 92.95%, 13.42 g/dL and 201 U/mg, respectively (Singhai *et al.*, 2022).

Pharmacology

The plant has been used in an herbal formulation called "Mahamrytunjaya rasa" along with other three herbs which shows cardioprotective activity in scientific experiments where patients suffered from cardiac damage (Lochan, 2006). A case study has been reported about an overdosing of herbal formulation called "Mahashankha Vati" which was proved to cause bradycardia and hypertension with symptoms like numbness, nausea, severe headache and vertigo (Panda and Debnath, 2010).

Twelve more successive cases of aconitine intake have been reported to show cardiac arrhythmias, mainly ventricular tachycardia, ventricular ectopics and various gradations of Arterio-Ventricular (AV) blocks (Dwivedi *et al.*, 2011), which are discussed here.

Cardiac effects

The diterpene alkaloids control the action of voltage-gated Na^+ channels and they affect the cardiac and the central nervous system (Dzhakhangirov *et al.*, 1997). On the basis of the activity of *Aconitum* alkaloids, they can be classified into arrhythmogenic and anti-arrhythmic alkaloids. Arrhythmogenic alkaloids: During the resting potential of a cardiac cell, the action potential of the neighbouring cells is triggered followed by opening of voltage-gated sodium channels which allows the entry of sodium ions into the cell maintaining the chemical gradient thereby causing repolarization. These voltage-gate sodium channels get inactivated after rapid depolarization in normal cells. These arrhythmogenic alkaloids inhibit this inactivation when interacted with the voltage-gated Na^+ channels. The depolarization of cell gets sustained hence delaying the final repolarization of the heart cells. Due to this premature and activated excitation, the cell's in-excitability may lead to cardiac arrest (Ameri, 1997a). Aconitine is considered as a highly toxic and fatal arrhythmogenic alkaloid which has tremendous affinity to open the Na^+ channel at neurotoxin binding site 2. Its cardiotoxicity is attributed to namely β-OH on C-13, α-aroyl on C-14, β-acetate on C-8, and a positively charged nitrogen atom. In order to minimise their toxicity, these substituents should be dismantled which reverses the aconitine skeleton alkaloids (Acharya, 2001).

Anti-arrhythmogenic alkaloids: Anti-arrhythmic alkaloids are made up of diterpene skeletons. They act opposite to arrhythmogenic alkaloids as they inhibit the opening of voltage-gated sodium channel thereby blocking the potassium ion channel which generally makes the cell membrane potential more negative due to leakage of potassium ions. Both these types of alkaloids are antagonist to sodium channels. C-18 diterpene alkaloids are more active due to the methoxy groups on C-1, C-14, and C-16; acetylanthranilic or anthranilic acid on C-4; and an OH on C-8 (Heubachl and Schüle, 1998). A study on Guinea pig heart revealed that the beating frequency of heart gradually decreased (Mazur *et al.*, 1986). 14-benzoyltalatisamine has the potential to block the potassium channel act as a vital anti-arrhythmic agent as it regulates the heart rate by influencing the potassium channel. 6-Benzoylheteratisine is another potent anti-arrhythmic alkaloid. Napelline, songorine, and their 1-benzoyl derivatives are very active and influence the sodium channel. LD_{50}/ED_{50} ratio has also been studied in *Aconitum* sp. and compared with other anti-arrhythmic drugs (Heubachl and Schüle, 1998) and showed that some alkaloids such as N-deacetyllappaconitine, lappaconitine and 6-benzoylheteratisine exhibited better results. Drug allapinin (lappaconitine hydrobromide) showed effective result as anti-arrhythmic drug in the clinical trials (Sokolov and Dzhakhangirov, 2002) and paroxysmal atrial fibrillations is also prevented (Wong *et al.*, 1997).

Other effects on cardiac health

Higenamine is another alkaloid of *Aconitum* that helps in relaxation of aorta which was revealed when studies were done on isolated rat atria. In plasma where there are more platelets, this alkaloid inhibits the aggregation of collagen-induced platelets, and epinephrine which lowers blood pressure in rats, and the rate of recovery increases in acute thrombosis model (Wang *et al.*, 2009). Both *Aconitum* root extracts (before and after "Sodhana") improved the contractile force in toad's heart (Jian *et al.*, 2012). Mesaconitine improved the inotropic effect and diastolic function of the left ventricle when tested on isolated perfused bullfrog hearts (Kiss *et al.*, 2013). Aconitine, a diterpenoid alkaloid from *Aconitum ferox*, was found to block GIRK channel but did not affect the hERG channel (Lin *et al.*, 2007). When activation of G-protein couple receptor occurs, GIRK channel hyperpolarizes the neurons thereby controlling their excitability through slow

synaptic potentials and self-inhibition which are again mediated by GIRK channels. The aconitine activity hence indicates its nature of inducing cardiotoxicity (Acharya, 2001). Radix *Aconiti lateralis* shows hypotensive activity on portal vein ligation in rats (Yamada *et al*., 2005). The aconite roots elevate the nitrite and nitrate levels in plasma, which increase the NO levels and affect the functioning of peripheral vascular system (Friese *et al*., 1997).

Effect on nervous system

The *Aconitum* alkaloids also affect the nervous system by activation of sodium channels. They have antinociceptive properties which indicate their eligibility to activate the voltage-gated Na^+ channel, permanent depolarization of neurons which will block the conduction in the nerves (Polyakov *et al*., 2005; Murayama *et al*., 1984). These alkaloids also exhibit analgesic effect which showed reduction in opioid μ-receptor knockout mice (Seitz and Ameri, 1998). Similar to this mechanism of analgesic activity, some of these alkaloids also inhibit the uptake of noradrenaline (Ameri *et al*., 1996). In spite of established analgesic activity, these *Aconitum* drugs are prone to severe risk due to their toxicity. The processed root tubers of *Aconitum*, exhibit less analgesic activity than the raw material but still not considered as entirely safe (Acharya, 2001).

Anti-epileptiform effect

The alkaloids of *Aconitum* also exhibit anti-epileptiform activity which inhibits the sodium channel by involving in pathophysiological attributes of epilepsy, where there is disturbed nerve activity which causes seizures. Lappaconitine is a sodium channel blocker that inhibits the epileptiform activity (Ameri *et al*., 1996). Some aromatic substituent containing *Aconitum* alkaloid such as 1-benzoylnapelline, 6-benzoylheteratisine, 14-benzoyltalatisamine and lappaconitine show anti-epileptic activity and inhibit rat hippocampal excitability (Ameri, 1997b; Ameri, 1997c; Ameri and Simmet, 1999; Ameri, 1998; Heubachl and Schüle, 1998). Aconitine and 3-acetylaconitine supresses the epileptiform activity of neuron and inhibit its regular activity (Chatuphale, 2018; Heubachl and Schüle, 1998).

Drug Characterisation

The phytoconstituents of *Aconitum* species were traditionally used as arrow and spear toxins for hunting due to their highly poisonous nature. Earlier, this plant was known for its toxicity rather than its medicinal values but later on with development of technology and scientific advancement, its medicinal properties were discovered which revealed that after undergoing certain Ayurvedic detoxification process, the toxicity of the plant could be reduced and further used in the formulation of herbal medicines (Srivastava *et al*., 2010). Several diterpene alkaloids like aconitine, hypaconitine and mesaconitine are present in the root tubers which get converted to less toxic compounds like aconine, benzoylaconine and pyroaconine when undergone through alkaline treatment, heating or oxidation and deacetylation reactions (Srivastava *et al*., 2010). *Aconitum ferox* contain diterpene alkaloids (0.4%-0.8%) and its percentage ranges from 0.3%-2.0% in tubers and 0.2%-1.2% in leaf. The vital alkaloids present in the plants are aconitine, pseudaconitine, bikhaconitine, di-Ac-Y-aconitine, picro-aconine, diacetyl pseudaconitine, veratryl gama aconine, veratry pseudaconitine, aconine and chamaconitine (Jyothi, 2016), neopelline, nepalline, neoline, trace of spartein, traces of ephedrine, aconitic acid, succinic acid and starch (Kokate, 2010). Four other lipoalkaloids have also been isolated from the root tubers namely linoleoyl, C-8 stearoyl, and palmitoyl esters of norditerpenoid alkaloids which were revealed through spectral analysis (Hanuman and Katz, 1994). A nor-dipertene alkaloid namely 8-O-methylhypaconine was reported from *Aconitum* tuber cultivated in Korea. The structural establishment was done on the basis of spectroscopy and chemical analysis (Jose *et al*., 2020; Lee, 2007). Some chemical compounds found in *Aconitum ferox* along with their pharmacological aspects have been listed in Table 1.

Pharmacokinetics

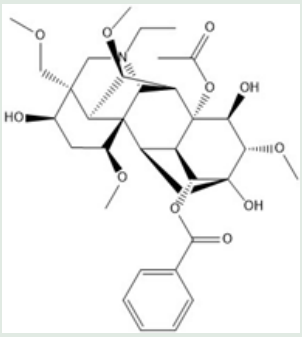
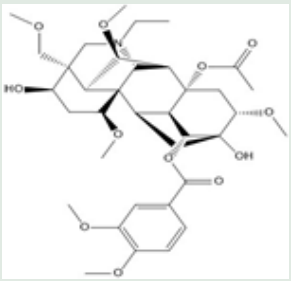
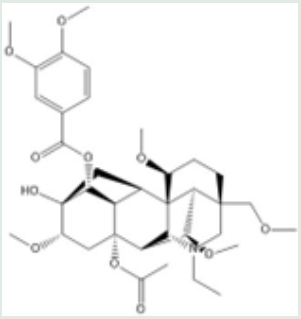
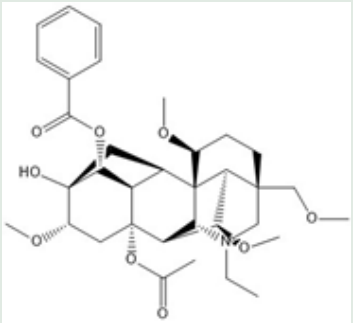
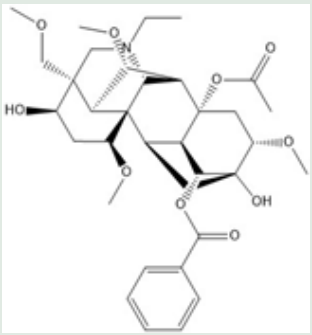
The pharmacokinetics of *Aconitum* sp. has not been easy to study and several attempts have been made earlier due to low absolute bioavailability of aconitine. Low aconitine plasma level (C_{max} = 5.83 ± 0.97 ng/mL) after administration of aconitine orally (0.2 mg/kg) in rats with short t_{max} (0.70 ± 0.18 hr) and 22.80% absolute bioavailability was reported by several researchers (Tang *et al*., 2012). The compounds like aconine and aconitine are excreted out through urine, whereas, benzylaconine is excreted through the faeces (Zhang *et al*., 2016). The metabolism of both benzylaconine and aconine were more difficult than aconitine. An experiment on tissue distribution revealed that *Aconitum* alkaloids circulated throughout the organs, but the rate of distribution of aconitine was slower than aconine and benzylaconine (Wong *et al*., 1997). When pure aconitine and processed (detoxified) roots of *Aconitum* were administered intravenously (0.04 mg/kg) and orally (0.5 mg/kg) in single and multiple doses (7 days, once daily) in rats, the aconitine bioavailability remained truncated which absolutely made no difference in their pharmacokinetics in both the doses. Besides, the processed (detoxified) roots of *Aconitum* in multiple doses (7 days, once daily, 4.5 g/kg of crude methanol "Fuzi" extract where 0.118 mg/kg aconitine is present) showed increase in the aconitine bioavailability which triggers the chances of toxicity. Moreover, aconitine has found to get excreted rapidly thereby signifying its lower ability to bind with plasma proteins (Tang *et al*., 2012).

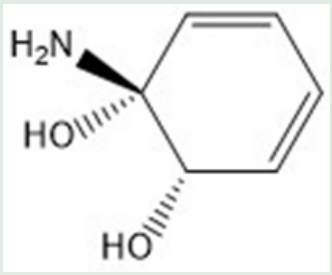
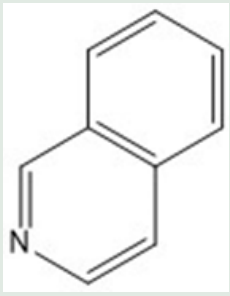
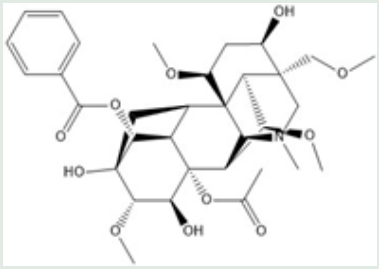
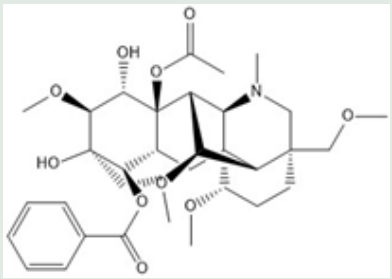
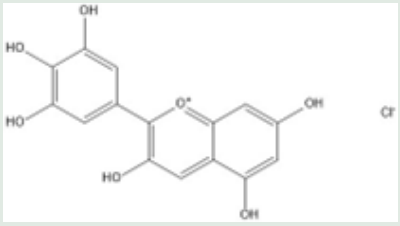
Pharmacodynamics

Aconitum ferox has been a prominent medicinal plant which has been used in traditional Chinese medicine system for years.

It's been documented in the Chinese material Shennong Bencao Jing two thousand years ago (Yin *et al*., 2019). It has been used in

Table 1: Chemical composition of *Aconitum ferox* along with its chemical structure and pharmacological aspects.

Sl. No.	Compounds	Structure	Pharmacological effects	References
1.	Aconitine		Inhibits the production of prostaglandins; inhibits nociceptive activity of the spinal cord inhibitor of the enzyme acetylcholinesterase.	(Chan 2009; Xie *et al.*, 2021)
2.	Pseudoaconitine		Inhibitor of the enzyme acetylcholinesterase.	(Rahman *et al.*, 2000)
3.	Bikhaconitine		Active dyspnea, irregularity of heart, vagus stimulation.	(Cash and Dunstan,1905)
4.	Chasmaconitine		Inhibits or kills the growth of Leishmania parasites.	(Shyaula *et al.*, 2016)
5.	Indaconitine		Arythmia, failure of effective respiratory movement.	(Cash and Dunstan,1905)

Sl. No.	Compounds	Structure	Pharmacological effects	References
6.	Catecholamine		Neurotransmitter and maintenance of homeostasis through the autonomic nervous system; vasopressor agents to treat acute hypotensive states and commonly used in psychiatric treatment.	(Khalil, *et al.*, 2025)
7.	Isoquinoline		Used in dyes, fungicides, insecticides and paint manufacturing; in liquid-liquid extraction of resins and terpenes; used as a solvent and as an inhibitor of corrosion.	(McNaught *et al.*, 1998)
8.	Mesaconitine		Used as local sedative, reducespain ofrheumatoid arthritis and also decreases high body temperature during fever.	(Gowtham *et al.*, 2021)
9.	Hypaconitine		Reduces arthritis pain, reduces high body temperature, and is used as a local anesthetic agent.	(Gowthaman *et al.*, 2021)
10.	Delphinine		Reduces pain related to rheumatoid arthritis	(Singhai *et al.*, 2022)

activating blood, removing stasis, dissipating cold, severe injuries, arthritis, stroke, pain related to neuropathy, paralysis, stomach pain, gastroenteritis, menstrual problems and ulcer related issues (Hao *et al.*, 2015). This plant is immensely used in different herbal formulations such as "Fuzi", also known as *Aconiti Lateralis Radix Praeparata*, is a traditional Chinese medicine formulation which is prepared from the lateral roots of *Aconitum* sp. (Liu *et al.*, 2020), and is used to cure rheumatic arthritis (Köberl *et al.*, 2013). It is used for 7 days, once daily, 4.5g/kg of crude methanol "Fuzi" extract where 0.118 mg/kg aconitine is present (Tang *et al.*, 2012). Their processed (detoxified) roots constitute heishunpian, yanfuzi, and baifupian, which differ in processing and influence the lower toxicity and more clinical safety in the formulation (Sun *et al.*, 2012). "Shen-Fu" is another herbal formulation which treats cerebral infarction and failure of heart (Zhang *et al.*, 2013). The usage of *Rhizoma zingiberis* (ginger roots) in "Shen-Fu"

enhances its efficacy to cure failure of heart (Peng *et al.*, 2013). A combination of "Fuzi" and herba ephedrae showed analgesic effects when it was administered in rats; its clearance rate was high from the body as compared to methylephedrine and was excreted through urine and faeces respectively (Song *et al.*, 2015). "Chuan Wu" is another herbal formulation constituting radix aconite and radix *Paeoniae alba*. It is highly toxic due to presence of radix aconite which inhibits cytochromes. Radix *Paeoniae alba* (*Paeonia lactiflora* roots) elevates the efficacy by increasing the presence of monoester-diterpene alkaloids where mainly the voltage-gated Na^+ channels are affected. The cardiac and the nerve tissue membranes get excited which causes extended depolarization and delayed repolarization leading to palpitations, arrhythmia, paralysis and numbness in the upper and lower body limbs. Mesaconine isolated from the tubers of this plant is known to ameliorate the diastolic function of the left ventricle which brings inotropic effect in the heart. The main focus of scientific research on diterpene alkaloids of *Aconitum* has been mostly done to comprehend the effectiveness on the cardiac and central nervous system (Nyirimigabo *et al.*, 2015).

MODE OF ADMINISTRATION AND POSOLOGY

Therapeutic dose

By considering all other factors "Vatsanabha" should be administered in a dose of 1/16 to 1/8 ratti (traditional Indian unit of measurement for mass and weight) (7 to 15 mg) (Chatuphale, 2018). The human dose is 15-30 mg (Sodhala, 2019). The purified root of "Vatsanabha" (*A. ferox* Wall.) has 15 mg of the recommended dose (Panda and Debnath, 2010).

Safety and toxicity

As aconitine, mesaconitine and hypaconitine are present in *Aconitum* sp. it has cardiotoxic and neurotxic effects but is still used in some parts of the world. Even at very low quantity, intake of aconitine or the raw plant leads to toxicities. This occurs due to wrong identification of the plant, over consumption or inappropriate processing of raw material before intake. About 5000 cases have been reported for *Aconitum* poisoning in China since 2013, where the fatality rate is about 2.4%. Some reported case studies are as follows: In the year 2009, a woman was reported to be killed due to the consumption of *Aconitum ferox*. The presence of highly toxic pseudaconitine was responsible for the death (BBC News, 2010).

In China, an old man (54 years) was reported to have hypotension, lower consciousness followed by heart attack with pulseless ventricular tachycardia due to the accidental ingestion of homemade infusion of *A. ferox* used as topical painkiller (Bonanno *et al.*, 2020).

Another case was reported in Toronto where a customer got sick after consuming a dish at the restaurant which was later discovered that an accidental poisoning of food occurred due to contamination of spice product with aconites (BBC News, 2022).

The diagnosis of *Aconitum* poisoning is very crucial as it does not have any established antidote and is dependent to supportive care for treatment where activated charcoal being one. Hemodialysis or extracorporeal filtration does not provide effective treatment against cardiotoxic poisoning of the plant (Jha and Padmaprakash, 2018; Magnani and Woolf, 2017). Nausea and vomiting is treated by antiemetic drugs. In a case study, aconite poisoning was treated with amiodarone which normalized the sinus rhythm and treated arrhythmias (Jesrani *et al.*, 2022). Recently, a 23-base pair genus-specific nucleotide sequence was identified to detect the traces of *Aconitum* in adulterated food samples (Wang *et al.*, 2022).

Some experimentally established toxicity studies are described below

Acute toxicity

In an acute toxicity study, no mortality was observed at the dose of 50 mg/kg and above (Singhai *et al.*, 2022). The lethal dose of aconitine in Acute Oral Toxicity study in mice was found to be 1.8 mg/kg (Kakkar *et al.*, 2023). The lethal dose for acute oral toxicity was 35 mg/kg in rats and LD_{50} was found to be 22.5 mg/kg in a study done on Wistar albino rats (Sarkar *et al.*, 2017). Aconitine was administered in Four-week-old Kunming mice (20 g) in high (0.56 μmol/L), mid (0.28 μmol/L) and low doses (0.14 μmol/L). There was significant difference in the weight when compared between control and high dose group. Other organs such as heart, liver, lungs, spleen, cerebrum, cerebellum and kidney showed significant changes in their weight and histopathology; the blood vessels of the brain showed dilation, and filled with red blood cells. The Purkinjee cells were found to be swollen degenerated and necrotized (Lu *et al.*, 2022).

Sub-acute toxicity

In a study on sub-acute toxicity with LD_{50} 29.57 mg/kg body weight of dried crude powder on Wistar albino rats for 28 days showed no significant changes in the blood parameters. The platelet counts increased and the haemoglobin and RBC decreased non-significantly. The total bilirubin decreased whereas blood sugar was increased in all the study groups. Shrunken, basophilic vacuolated degenerated neuron was noted in the brain cells. Mild inflammation with congestion degenerated vacuolated muscle fibres with lack of cross striations were seen in heart tissues. Single cell necrosis was noted in hepatocytes of liver. Degenerated tubules are noticed in the cortico-medullary area of kidney (Regmi *et al.*, 2021).

Overdose toxicity

The fatal dose of *Aconitum ferox* is 2 g of the root powder, 25 drops of the tincture, 250 mg of the extract or 2-6 mg of the

alkaloids and average fatal period is 6 hr (Regmi *et al.*, 2021). A 100% mortality was seen with crude aconitine at 2.6 mg/kg in mouse (Panda and Debnath, 2010). At 2 mg, aconitine causes death and *Aconitum* plant is fatal when consumed 1 g of crude drug (Lin *et al.*, 2004).

Mutagenicity

No mutagenicity potential was seen in *Aconitum* sp. in toxicological studies done on "Balacaturbhadrika churna", which is a popular formulation used in pediatric practice in Ayurveda, especially in the treatment of vomiting, diarrhea, fever and respiratory disorders (Nariya *et al.*, 2011).

Carcinogenicity

No carcinogenicity is reported so far.

Teratogenicity

A study showed that a capsule which contains *Aconitum ferox* as one of the ingredients showed no teratogenicity as reported in the study (Panigrahi, 2017). A study on chloroform root extract of the *Aconitum* sp. showed no teratogenicity (Mathew, 2017).

Reproductive Toxicity

It is reported that *Aconitum ferox* should be strictly avoided in pregnant woman (Buha *et al.*, 2020).

Pregnancy and lactation

It is contraindicated in pregnancy and lactation and should be avoided (Malviya and Choudhuri, 2018). It is recommended that to be strictly avoided during pregnancy (Buha *et al.*, 2020).

Other Bioactivities

The plant is really potent and has several medicinal properties. It's been documented in ancient literature and several experimental studies have also been done to scientifically validate the traditional claims.

Anti-feedant activity

The crude aqueous extract of *Aconitum ferox* showed toxicity towards red pumpkin beetle, mustard fly, wheat aphid, kharif grass-hopper, mustard aphid and radish aphid (Jacobson 1975; Tripathi, 1998). The aqueous extract of this plant is reported to show anti-feedant activity towards *Siphocornye indobrassicae* and *Aphis maidis* (aphids) (Prakash *et al.*, 2008).

Anti-inflammatory activity

The ethanol extract of *A. ferox* showed anti-inflammatory activity in rats when treated in carrageenan induced paw edema model. The group treated with 500 mg/kg and 250 mg/kg of the plant extract showed 77.85% and 65.31% inhibition, respectively (Chouhan and Kushwah, 2023). The plant is reported to have anti-inflammatory efficacy in the traditional use (Aslam and Ahmad, 2016).

Anti-rheumatic activity

In a study, the ethanol extract of *A. ferox* showed potent anti-rheumatoid activity in Lewis rats when induced with Complete Freund's Adjuvant (CFA). The plant extract was used at 10 mg/kg, where paw volume reduction was noticed (58.32%), body weight was reduced, the ESR and Lipid Peroxidase (LPO) decreased in blood serum, the haemoglobin counts increased, and fewer abnormalities were noticed in treated groups when compared to arthritis induced groups in histological studies (Singhai *et al.*, 2022).

Cytotoxic activity

The *Aconitum* alkaloids showed growth-inhibitory activities on human breast cancer cell line (MCF-7), Human Colon carcinoma cells (HCT-116) and human hepatic carcinoma cell line (HepG-2). Hypaconitine inhibited the NF-κB signaling pathway by inactivating it which proves its cytotoxicity. Aconite alkaloids showed autophagy through activation of p53, signalling cascade of ERK1/2and p38 MAPK which provides protection. The combination present in the herbal formulation has synergistic nature which increases the potency of the drug, minimises its toxicity and helps in optimization on cancer (Kakkar *et al.*, 2023).

Antimicrobial activity

In a study, the antimicrobial efficacies were analysed for ethanol extract of *A. ferox* against three Gram-positive, three Gram-negative bacteria and one pathogenic fungus. It prevented the growth of *Staphylococcus aureus, Escherichia coli, Vibrio* sp. and *Salmonella* sp. with 20 mm, 19 mm, 18 mm and 17 mm zone of inhibition respectively which proved that it has bioactive constituents which showed efficacy against drug resistant microbes present in the hospital area and hence can be further utilized for its broad-spectrum activities (Thakre *et al.*, 2021).

The *Aconitum ferox* root extracts in different solvents like ethanol, ethyl acetate, methyl acetate, acetone, chloroform and aqueous showed no zone of inhibition against *Aspergillus niger* (Thakre *et al.*, 2021).

Anti-diabetic activity

The root extract of *A. ferox* showed anti-diabetic activity in Wistar rats at 10 and 20 mg/kg when induced with alloxan, and a significant reduction in blood parameters like blood glucose, lipid profile and improvement in body weight was noticed (Srivastava *et al.*, 2023). Traditionally, it is used as an anti-diabetic in Sikkim and Darjeeling Himalayas where 10-15 mL of decoction of the root is consumed along with a cup of milk once in a day for consecutive 7 to 10 days (Chhetri *et al.*, 2005).

Anti-pyretic activity

In a study on rabbits and rats, the hexane and chloroform extract of *Aconitum* plant showed antipyretic efficacies at 150 mg/kg orally in induced pyrexia model by yeast injection (Ikram *et al.*, 1987). In Nepal the root tubers of *Aconitum* sp. are used as antipyretic drug (Shyaula, 2011). "Anandabhairava Rasa" is an herbal formulation where one of the ingredients is *A. ferox*, and is documented to have antipyretic activity when administered (11.25 mg/kg body weight) on brewer's yeast induced pyrexia model in albino rats (Varsha and Jeevesh, 2018).

Antioxidant activity

In a study done on micropropagated plants of *A. ferox*, it was concluded that the plant extract showed antioxidant activity by both DPPH and ABTS assay method where BHT was used as the standard. The methanol extract of wild plant showed IC_{50} of 579 µg/mL and 481 µg/mL in DPPH and ABTS assay, respectively, whereas, the root methanol extract showed IC_{50} values of 833 µg/mL and 587 µg/mL in DPPH and ABTS assays, respectively, revealing their mild radical scavenging property (Singh *et al.*, 2020).

Contra-Indications

The consumption of *A. ferox* is restricted to people of young age, old age, suffering from diseases, pregnant ladies and patients with tuberculosis and heart problems. It should be used in shorter time period due to its toxicity and in minute quantity (Chatuphale, 2018). Salty, sour, hot foods should be avoided during the usage of this plant. Persons suffering from brain related disease, kidney and liver problems should avoid the medication where this plant is used as it increases "Pitta" (bile). It gets absorbed dermally and hence should be used by necessary protection. Consumption of milk, sugar products, rice, ghee and honey should be avoided during administration of *A. ferox* (Malviya and Choudhuri, 2018).

Interaction

Now-a-days the use of traditional medicine has hyped immensely due to less side effects and traditional usage history, and hence has been integrated into Western medicine (Izzo, 2012). Consumers might not consult doctors or professionals before consuming the herbal drugs and generally self-administer the plants. It is very difficult to unfold the interactions of herbal products due to lack of understanding of their pharmacokinetics and heterogeneity of their composition and the uncertainty of the constituents (Brantley *et al.*, 2014).

The drugs in combination with the herbs might cause antagonistic effects when inhibiting the transporter of the enzyme function that is metabolized by the drug. There are several limitations likely, less importance given to dose effect, regimen and mode of medications, requirement of information and investigation on drug transporters and lack of information regarding the drug interactions (Wang *et al.*, 2012).

The pharmacokinetics and pharmacodynamics can be altered by using herbal products which can also have undesirable effects with prescribed drugs. Hence, the traditional system of medicine always prefers to use a concoction made of single herb and not any combination with drugs (Wang *et al.*, 2012).

The main objective behind using combination in herbal formulation is to regulate other targets, thereby, minimising the harmful effects of the herbs and enhancing the pharmacological efficacies of the agents. "Fuzi" is an herbal formulation made up of *Aconitum* sp. and used in rheumatoid arthritis and pain (Sun *et al.*, 2012). "Sodhana" (detoxification) is done before the use of *Aconitum* in the herbal formulation which contains "Hei-Shun-Pian" (processed *Aconitum carmichaeli* Debeaux lateral roots with peel). The other herb used along with "Fuzi" is *Rhizoma zingiberis* (ginger) which enhances its efficacy by reducing its toxicity. Another mixture of "Fuzi" and *Panax ginseng*, called *Shen-fu* is used in treating cardiac failure and cerebral infarctions. The ephedra and *Aconitum* alkaloids are discharged through urine and faeces respectively. A mixture of *Radix Aconite* (RA) and *Radix Paeoniae Alba* (RPA), RA inhibits cytochromes (Bi *et al.*, 2014). The presence of RPA nullifies the toxicity of RA, which elevated the overall potency of the formulation. In comparison to single herb drug, the combination of herbs increases the residence time and elimination of *Aconitum* alkaloids thereby decreasing the accumulation of drug which has adverse effects on the system (Hao *et al.*, 2015).

Special Warnings and Precautions for Use

Aconitum ferox when inhaled can cause adverse effects. The plant should undergo the process of "Sodhana" (purification) and "Marana" (death) in an open area to avoid being inhaled and necessary precautionary measures should be followed like use of face mask, protection of eyes, hair cap and gloves. When inhaled accidentally, the patient should be treated with *Sudarshana churna* (Ayurvedic herbal formulation), *Sitopaladi Churna* (Ayurvedic herbal formulation), *Snehapana* (oleation) with *Goghrita* (cow ghee) and *Nasya* (administration of drugs by the route of nasal cavity, a Panchakarma treatment for body cleansing used in Ayurvedic medicine) with *Goghrita Manda* (supernatant liquid part of cow "ghee") which are found to be effective Ayurvedic treatments for aconite poisoning by inhalation. Exposure should be strictly avoided for pregnant woman (Buha *et al.*, 2020). The plant is very toxic in nature and is recommended to take precautionary measure during handling. Overdose of this plant is fatal and causes poisoning due to presence of cardio and neurotoxins. It should be used only in proper prescribed doses by medical practitioners.

Undesirable effects / adverse reactions

There are several cases of aconite poisoning and adverse effect when consumed with products which increases "Pitta" (bile), hence should be avoided.

Trade and Conservation

The trading of *A. ferox* in the Indian market is sold under the name of "Vatsanabha" which is found to be highly adulterated by other species of *Aconitum*. *Aconitum spicatum* Stapf., *A. falconeri* Stapf., *A. chasmanthum* Stapf. ex Holmes, *A. laciniatum* Stapf., *A. balfourii* Holmes ex Stapf. and *A. deinorrhizum* Holmes ex Stapf. were found to be sold under the name of "Vatsanabha" in the market (Sarkar *et al*., 2012). Alheroo, a Persian physician described the toxicity of the plant and named in "Bish" in the tenth century, while, in nineteenth century the Europeans were the first to be aware of this plant during their expedition to Nepal. At that time innumerable trading was done in the root tubers of this toxic plant which pushed it to the edge of its present endangered status (Sheokand *et al*., 2012).

Considering the endangered status and highly potent medicinal value, *Aconitum ferox* needs conservation. There are several experimental studies done on *in vitro* micropropagation of the plant for its conservation and cultivation in large scale production which can open new avenues for its sustainable utilization along with conservation of biodiversity (Sheokand *et al*., 2012).

Research Gaps

Aconitum ferox being extensively used in Ayurvedic formulations due to its immense medicinal property, its being overexploited and pushed among the endangered category. Researchers need to be aware about this fact and find an alternative herb substitution for usage in herbal formulation. *In vitro* micropropagation through tissue culture techniques should also be encouraged among conservationist. The present review is an effort to exhibit a holistic use of this medicinal plant and create awareness among the young researchers to find ans establish a substitute herb based on the Ayurvedic concept of "*Abhava Pratinidhi Dravya*".

CONCLUSION

In spite of being a highly toxic plant, *Aconitum ferox* is found to be very potent medicinal plant. It has several biological efficacies which are traditionally documented in different literatures and have also been proved scientifically. The commercial scale utilization of this plant has pushed it to the stage of vulnerability and hence it is endangered in nature now. Besides, utilizing the medicinal value of this potent plant one should also show concern about its conservation status. An alternative substitute of this plant with almost equal potency should be given a thought which will be further standardized and validated scientifically for conserving *Aconitum ferox* without depriving mankind from its medicinal values.

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ABBREVIATIONS

ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); **CNS:** Central Nervous System; **DMARDs:** Disease-Modifying Antirheumatic Drugs; **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs; **CFA:** Complete Freund's Adjuvant; **DPPH:** 2,2-Diphenyl-1-Picrylhydrazyl; **HCT-116:** Human Colon Carcinoma Cells; **HepG-2:** Human Hepatic Carcinoma Cell Line; **IC_{50}:** Half-Maximal Inhibitory Concentration; **LPO:** Lipid Peroxidation; **AV:** Atrioventricular; **GIRK:** G Protein-Coupled Inwardly Rectifying Potassium; **hERG:** Human Ether-À-Go-Go-Related Gene; **NO:** Nitric Oxide; **MCF-7:** Human Breast Cancer Cell Line; **RA:** Radix Aconiti; **RPA:** Radix *Paeoniae alba*; **SOD:** Superoxide Dismutase; **CITES:** Convention on International Trade in Endangered Species of Wild Fauna and Flora; **NF-κB:** Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells; **ERK1/2:** Extracellular Signal-Regulated Kinases 1 and 2; **MAPK:** Mitogen-Activated Protein Kinase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTION

Sharmistha Ganguly: Review of literature, conceptualization, preparation of the manuscript and drafting of the manuscript; **Sharad D. Pawar:** Conceptualization, drafting, correction and expert suggestions in the manuscript; **Anupam K. Mangal:** Correction and expert suggestions in the manuscript; **Mradu Gupta:** Correction and expert suggestions in the manuscript; **Rabinarayan Acharya:** Correction and expert suggestions in the manuscript.

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