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Clinical and therapeutic potential of *Aconitum heterophyllum*

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ABSTRACT

Aconitum heterophyllum is a plant that has very important medicinal value. Lots of phytochemical constituents (metabolites) are extracted from this plant, especially diterpene alkaloids which are the main compounds having pharmacological activities such as analgesic and anti-inflammatory. Study of the structures of these compounds was done by the technique of nuclear magnetic resonance.

1. Introduction

Aconitum which is also acknowledged as aconite, is a genus consisted of 250 species of angiosperm plants. These perennial herbs occur in mountainous parts of the Northern Hemisphere according to Chisholm[1]. They grow in the moisture-retentive but well-drained soils of mountain meadows. Most species show poisonous nature and should be handled with care.

Amongst various species of genus *Aconitum*, *Aconitum heterophyllum* also known as "Atees", is widely distributed in the alpine and sub-alpine region of Himalayas, showing vital medicinal assets because they hold prime position.

2. Morphological characters

The species *A. heterophyllum* belongs to the genus *Aconitum* (kingdom: Plantae, phylum: Magnoliophyta, class: Magnoliopsida and family: Ranaunculaceae) (Figure 1).

Roots are biennial, paired and have tubers. They are whitish or grey in colour. Stems are known to be erect, simple and branched. They are 15–20 cm high, glabrous below and finely crispo-pubescent in the upper part. Leaves are known to be heteromorphous and glabrous possessing long petioles, and blades are orbicular-cordate or ovate-cordate in outline with a usually narrow sinus (1–1.5 cm deep). The leaves are usually 5-lobed.



A. heterophyllum.

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3. Inflorescence

3.1. Slender raceme, leafy panicle and crispo-pubescent

Sepals are bluish or violet (rarely whitish) and navicular, obliquely erect and shortly or obscurely beaked with 18–20 mm high and 8–9 mm wide. Carpels are five and elliptic-oblong.

Follicles are linear-oblong, straight and contagious. They are 16–18 mm long and black in colour. Seeds are 3–4 mm long and blackish brown in colour. They are pyramidal in appearance. The perennials are stemless development. *A. heterophyllum* prefers moist soil. Cultivation needs loamy, sandy-loamy, gritty-loamy, clay, sandy clay or loamy clay soil.

The research has documented that *A. heterophyllum* is becoming critically endangered wild medicinal herb of alpine Himalaya[2]. Owing to its big demand in the herbal market and to ensure the preservation of wild habitats, its cultivation is recommended. Observing floral biology, pollen germination, pollination, fruit and seed setting after suggesting different breeding systems were carried out for its successful domestication and improvement in agricultural practices. Studies have revealed that the plants growing in greenhouse conditions showed considerable variation in the production of flowers and seeds. *A. heterophyllum* in the second week of September to late October are peak flowering with 20 days. The pollen grains are estimated as 80000 pollen grains per flower. At anther dehiscence, nectar production starts and coincides with maximum stigmatic receptivity. Bees functioned as pollinators. Maximum pollen germination was in 5% sucrose. It is revealed that under controlled pollination, this species is self-incompatible, though few fruits developed from selfing. Such fruits were smaller than the fruits produced by open pollinated and hand-crossed flowers. Most are aborted early in development.

Gajalakshmi *et al.* notified that Chinese and Bhutanese used *Aconitum* plant as the chief component in their herbal medicines[3]. Many phytochemical compounds are present in these species showing various therapeutic activities. The main compounds present in *A. heterophyllum* are diterpene alkaloids which show pharmacological activities such as analgesic and anti-inflammatory. This alkaloid has certain toxic hydrolysed bases that could be detoxified by using modern technologies. *A. heterophyllum* also possesses several alkaloids, amides alkaloids, flavonoids, flavonol glycosides, diterpenoid and diterpenoid compounds showing therapeutic values. Isolation and characterization of these compounds was done by using chromatographic techniques. Spectroscopic studies especially nuclear magnetic resonance techniques interpreted their structures. These compounds were very important for the medicinal chemists as they owned medicinal as well toxic nature. Aconitine and atisine, the marker components, are isolated from *A. heterophyllum* and are employed commercially in number of preparations testified by Srivastava *et al.*[4].

Tuberous roots of *A. heterophyllum* are non-poisonous and are the main portions for medicinal uses. *Aconitum* has been verified as an essential constituent in the formulations of Chinese and Japanese traditional medicines which exhibit various pharmacological properties such as cardio-tonic effects, blood pressure, analgesic, anaesthetic and anti-inflammatory effects documented by Zhao *et al.*[5].

The plant tubers and roots are usually preferred in Chinese herbal medicines for curing collapse, fainting, rheumatic fever, aching joints, gastroenteritis, diarrhea, swellings, bronchial asthma, tumors and some endocrinal disorders like irregular menstruation but the cardio and neurotoxicity of the drug is still found to be potentially lethal and it is said that the improper use

of *Aconitum* in China, India, Japan and some other countries have stemmed severe risks as they cause severe intoxications. The State Food and Drug Administration of China has put up a regulation, which says that only the processed and detoxified tubers and roots of *Aconitum* are allowed to administer orally. They are used in clinical decoctions and considered as raw materials for pharmacological manufacturing as there were around 70 techniques which are useful for the processing of *Aconitum* roots for their medicinal use notified by Singhuber *et al.*[6]. *Aconitum* species are characterized chemically by means of the diterpene alkaloids which are highly toxic and are used as a complete source of arrow poison in China. Overdoses of the constituent can cause diseases such as irregular heartbeat, named as arrhythmias documented by Gajalakshmi *et al.*[3].

4. Medicinal uses

Plants are rich sources to search new active compounds that become a trial to modern pharmaceutical industry and many synthetic modern medicines are made from plant reported by Benamar *et al.*[7]. Plants have secondary metabolites that suppress the growth and development of adjacent biological systems named as allelochemicals[8]. Phenolic and flavanoid compounds are extracted from this plant which has antioxidant and antibacterial effects[9,10].

Sufficient knowledge about herbs is very important to know their uses and potential of drugs. Demands of the herbal drugs are increasing day by day but the supply is decreasing, so there is an crucial need to cultivate and conserve these valuable plant species for their maintainable utilization. Unscientific extraction of the medicinal plant from nature has pushed some species to extinct and some others are at an endangered stage. Considering the medicinal importance of the species and the lack of satisfactory cultivation practice, the study was carried out to get the maximum profit by improving the productivity of the species during the cultivation.

One of endangered specie (*A. heterophyllum* Wall) has been used for a long time to cure diarrhea, dysentery, cough, dyspepsia, chronic enteritis and as a febrifuge and bitter tonic in combating debility after malaria[11].

4.1. External uses

The crushed leaves of *Aconitum*, mixed with rock salt are applied focally. The seeds crumpled in honey are applied locally on throat and in tonsillitis. Inhalation of roots by nose is beneficial in headache, especially migraine.

4.2. International uses

A. heterophyllum affects some systems. For respiratory system, the juice of roots with milk is an expectorant and powder of root is given orally in cervical lymphadenitis. For digestive system, seeds and roots are used in ascites and seeds have laxative properties. For urinary system, seeds are used as diuretic and decoction of roots reduces burning of urinary tract and increases volume of urine. For reproductive system, roots are used in spermatorrhoea and the decoction of root is also used in burning of vagina. For circulatory system, juice of leaves along with juice of Zingier reduces perspiration. But overdosage (more than 5–6 g) causes symptoms like dryness of mouth and tremors *etc.*

A. heterophyllum is found as the main active ingredient of the herbal preparation Diarex-vet with other essential medicinal plants and has been efficiently used in the cases of indigestion, flatulence and diarrhoea of varying aetiologies like bacterial, fungal and protozoal[12].

5. Phytochemical constituents

A. heterophyllum possesses some phytochemical constituents which have medicinal values. The composites of *A. heterophyllum* such as alkaloids, amide alkaloids, flavonoids, flavonol glycosides, diterpenoid and norditerpenoid compounds were isolated and characterized with the help of chromatographic separation techniques and their structures were explained by the using nuclear magnetic resonance techniques. These compositions were the chief target of the medicinal chemists as they hold both medicinal and toxic nature.

A complete study of the basic components of the roots of *A. heterophyllum* has directed to the isolation of seven new diterpene alkaloids. The weak base fraction yielded heteratisine and three more alkaloids labelled as heterophyllisine, heterophylline and heterophyllidine. These compounds are lactone alkaloids which have structure relation to heteratisine. The strong base fraction produced two new alkaloids (atidine and F-dihydroatisine). The very strong base fraction yielded alkaloids designated as hetidine and hetisinone. The latter had been encountered earlier as a chemical transformation product of hetisine^[13].

6. Anti-inflammatory activity of *A. heterophyllum* on cotton pellet-induced granuloma in rats

Verma *et al.* demonstrated that the anti-inflammatory activity of ethanolic root extract of *A. heterophyllum* (225, 450 and 900 mg/kg *p.o.*) was calculated in cotton pellet-induced granuloma in rats^[12]. The extract has reduced inflammation as evidenced by reduced weight of cotton pellet in cotton pellet-induced granuloma in rats. The results revealed that the anti-inflammatory properties of extract and the effects were analogous to diclofenac sodium, a standard non-steroidal anti-inflammatory drug.

In recent years, there is growing awareness that apart from being safer, economical and simply available herbs, phytochemicals and herbal products can effect the course of inflammatory diseases and may provide an amalgamation of nutritional substances, which help in re-establishing and maintaining wear and tear of tissues. Therefore, it would be rational to logically evaluate the traditional medicines used for their potential use in inflammatory diseases. *A. heterophyllum* plant has been reported to hold antifungal cytotoxic, antiviral and immune-stimulant properties^[14-17]. Other compounds extracted from *A. heterophyllum* include flavonoids, tannins, saponins and sugars^[12].

Conflict of interest statement

We declare that we have no conflict of interest.

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