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PHYTOCHEMICAL CONSTITUENTS AND BIOLOGICAL PROPERTIES OF EXTRACTS FROM *ACONITUM* SP. - A SHORT REVIEW

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Abstract
Used for hundreds of years in traditional medicine and ethnomedicine, the species of the genus Aconitum are the subject of many contemporary studies that focus on the biological and pharmacological functions of the active principles isolated (and purified) from extracts obtained from plants roots and/ or aerial parts. Well known for its strong neurotoxicity, aconitine and some other diterpenoid alkaloids extracted from Aconitum species or their derivatives have shown significant anticancer and apoptotic, analgesic, antimicrobial, antifungal, antidiarrheal and antioxidant potentials, as well as a high effectiveness in treating rheumatic fever, joint pains and some endocrine conditions.
Strating from the toxic potential of these plants, phytochemical, pharmacological and toxicological studies are highly needed for improving their quality and safe usage.

Keywords: Aconitum, extracts, alkaloids, bioactivity, pharmacological properties.

1. INTRODUCTION

The genus *Aconitum* (*Ranunculaceae*) comprises about 400 species, including some ornamental and medicinal plants, widely spread on the territories of Eurasia and North America and less prevalent in the tropical and arctic regions (Hess et. al., 1977, cited by Utelli et al., 2000); out of these, 76 species from China and the neighbouring countries in the Far East and Asia are used for different therapeutical purposes (Nyirimigabo et al., 2014).

The extremely toxic effect of the extracts or decoctions obtained from the different species of the genus *Aconitum* has been acknowledged since ancient times. It has been attributed to a certain fast-acting toxic compound. Thus, some species, such as *A. charmichaelii* Debx, *A. nagarum* Stapf., *A. ouvrardianum* Hand.-Mazz., *A. stylosum* Stapf. and *A. episcopale* H.Lév. were used by hunters to poison their arrow tips (Bisset, 1981; Manandhar, 2002). Furthermore, species like *A. kusnezoffii* Reichb., *A. brachypodum* Diels, *A. pendulum* Busch, *A. nagarum* Stapf., and *A. coreanum* H. Lév. have been used in traditional medicine and in some religious practices after detoxification/ purification (Bisset, 1981; Maurya et al., 2015).

The biological and pharmacological activies of each compound correspond both to their adverse reaction and to their beneficial action on life. The roots of *Aconitum* sp. have been used on a large scale as a source of poison even since ancient times, but afterwards the medical aspect has been explored to determine their therapeutical dosage. Correct processing (Park et al., 1990) and multi-herb formulations (Wang et al., 2009) may reduce their toxicity levels. Over time the active components of the *Aconitum* species have been reported to possess significant pharmacological and

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biological characteristics: diaphoretic, diuretic, antidiabetic (Research, I.C.o.M. Medicinal Plants of India, 1976, cited by Nyirimigabo), lipolytic (Buehrer et al., 2012), muscle relaxant (Dzhakhangirov and Bessenova, 2002), and antidepressive (Nesterova et al., 2011). It also acts as a bitter tonic for treating abdominal pain, fever and cough (Kletter et al., 2011).

2. OBTAINING EXTRACTS FROM *ACONITUM* SP.

In order to obtain *Aconitum* extracts, different authors have applied and used different parts of the plants.

Srivastava et al. (2011) obtained extracts of *A. heterophyllum* Wall. ex Royle using different solvents, such as petroleum ether, chloroform, ethyl acetate, methanol and water; the extraction temperature was adjusted based on the boiling point of the solvent. Solvents of descending polarity were used for the extraction of active principles from the rhizomes of *A. kashmiricum* Stapf ex Coventry by Pala and Mir (2014).

Different methods were used to obtain the extracts of the species *A. heterophyllum* Wall. ex Royle due to its special biological properties. For example, Munir et al. (2014) obtained ethanol and methanol extracts using the microwave-assisted extraction method from the dried and ground roots of *A. heterophyllum* Wall. ex Royle, Rajakrishnan et al. (2016) extracted the coarse powder from rhizomes using hydroalcoholic solution (ethanol/water 1:1), and Mathew (2017) first extracted the coarse rhizome powder using petroleum ether and then extracted the skimmed material using chloroform.

The extraction of active principles from different *Aconitum* species was carried out either using the aerial parts of the plants of *A. heterophyllum* Wall. ex Royle (Srivastava et al., 2011) or *A. toxicum* (Sutan et al., 2018), the entire plant, as in the case of *A. tanguticum* (Li et al., 2014), or the roots, previously dried and ground as fine or coarse powder. The active principles of the fine powder obtained from the roots of *A. chasmanthum* Stapf. ex Holmes were extracted with methanol (Dar et al., 2015), while the active compounds from roots of *A. flavum* Hand.-Mazz. dried in a vacuum oven after being soaked in water for 6 hours were extracted using 70% ethanol (Zhang et al., 2016) or 95% ethanol (Wang et al., 2016).

Etahnol and methanol are the most frequently used solvents for the extraction of the active principles from *Aconitum* roots. For example, the dried roots of *A. napellus* Linn. were used by Karuna et al. (2018) to obtain extracts through the technique of maceration in absolute ethanol at a temperature of 55°C, for 4 days; the subterranean parts of the species *A. szechenyianum* Gay (Wang et al., 2016) and the roots of *A. soongaricum* Stapf. (Buehrer et al., 2012) were macerated with 80% ethanol; the roots of *A. richardsonianum* var. *pseudosessiliflorum* (Lauener) W. T. Wang were subjected to extraction with 90% ethanol (He et al., 2011), and the powdered roots of *A. laciniatum* (Brühl) Stapf were subjected to extraction with methanol (Wangchuk et al., 2015). Other alcoholic extracts were also obtained from the species *A. taipeicum* Hand.-Mazz. (Yue et al., 2010), *A. brachypodum* Diels (Wang et al., 2014) and *A. vilmoriniani* Radix. (Guo et al., 2015). Sutan et al. (2018) obtained alcoholic extracts of *A. toxicum* Rchb. from plants kept in the freezer until the preparation of extracts. The solvents used for extraction were 96º ethanol and 96º methanol, and the maceration was performed at room temperature for 48 hours. The extracts obtained after filtration were used for the phytosynthesis of Ag and Au nanoparticles. Comparing the extraction efficiency of ethanol with that of the ethyl ether after alkalinization, Bao et al. (2011) concluded that ethanol is more efficient in the extraction of diterpenoid alkaloids, namely aconitine, mesaconitine and hypaconitine.

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The decoction obtained from lateral roots of *A. carmichaelii* Debx (Luo et al., 2016; Guo et al., 2018) or the use of chloroform as an extraction solvent for the active principles from roots of *A. laeve* Royle (Kumar et al., 2018) were more rarely reported. In order to obtain extracts of *A. heterophyllum* Wall. ex Royle and *A. chasmanthum* Stapf ex Holmes, Jabeen et al. (2011) used dried plant material in an oven at temperatures below 45 °C. The dried and ground samples were then subjected to extraction through sonication using a solution of HCl 0.05M and the aqueous extract was treated with ethyl acetate to remove non-alkaloid components.
The plants of *A. barbatum* var. *puberulum* Ledeb dried in the air and ground were percolated with 90% methanol at room temperature. After the evaporation of methanol under low pressure, the aqueous extract was obtained using ethyl acetate (Sun et al., 2009).

3. PHYTOCHEMICAL CONSTITUENTS OF EXTRACTS FROM *ACONITUM* SP.

In 2006 there were 54 *Aconitum* species investigated for the study of their chemical composition according to Rana (2006) and according to Xiao et al. (2006), a number of 421 de diterpenoid alkaloids were isolated from 84 species. The species of the genus *Aconitum* are rich sources of diterpenoid alkaloids and other classes of alkaloids, flavonoids, proteins, free fatty acids, steroids/triterpenes, saponins, carbohydrates, glycosides, cardiac glycosides gums and mucilages (Rahman, 1993, Pala and Mir, 2014).
Alkaloids are natural chemical compounds that contain nitrogenous bases. They are produced by a large series of organisms, ranging from bacteria to animals. These chemical compounds can be purified from crude extracts and used as narcotic or analgesic drugs. In addition to these therapeutic effects, alkaloids show a high degree of toxicity for animal organisms (Beyer et al., 2009; Lu et al., 2010; Tan et al., 2013). The first symptoms of poisoning caused by an *Aconitum* plant are quickly installed and include paraesthesia of the face and extremities, followed by chills, sweats, dryness of the mouth, cough, hypotension and arrhythmia. Later on, as well as in cases of severe intoxication, other symptoms occur, such as violent vomiting, strong colics and diarrhoea, disturbance of the heart's rhythm and paralysis of skeletal muscles, followed by death caused by ventricular arrhythmia and cardiovascular collapse (Lin et al., 2004; Shyaula, 2011).
According to Jaiswal et al. (2013), the methods used in Chinese traditional medicine or in Ayurveda allow for the effective detoxification of the *Aconitum* roots through the conversion of diester diterpenoid alkaloids to monoester diterpenoid alkaloids. By heating, aconitine is easily converted into compounds of lower toxicity, such as benzoylaconine, aconine or piraconine (Mizugaki et al., 1998; Wada et al., 2005) through deacetylation, debenzoylation or when hydrolized by intestinal hydrolase. Other studies have shown that the toxicity of aconitine is reduced or eliminated by encapsulation into nanoparticles of autoassembled proteins and their delivery in a microemulsion-type system (Ke et al., 2015; Zhang et al., 2015).
The most important alkaloid contained by the species of the genus *Aconitum* is aconitine. Aconitine was purified using the HPLC technique from methanol extracts of *A. napellus* L. (Ahmed, 2015), methanol and ethanol extracts of *A. toxicum* Reichenb. (Sutan et al., 2018) or from extracts of *A. carmichaeli* Debx, *A. pendulum* Bush, *A. hemsleyamun* Pritz and *A. transseltum* Diels (Wang et al., 2006). Tarbe et al. (2017) evaluated the effectiveness of the reverse-phase flash chromatography, reverse-phase semi-preparative HPLC, centrifugal partition chromatography (CPC) and recrystallization techniques for obtaining a higher than 96% degree of purity of aconitine extracted from *A. karacolicum* Rapcs.
Isolation of the active components from the extracts of medicinal plants is the initial and essential stage in biological and pharmaceutical studies. Many other alkaloids were identified in the extracts

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of *A. anthora* L., *A. moldavicum* L. (Borcsa, 2013; Borcsa et al., 2014), *A. chasmanthum* Stapf. ex Holmes (Dar et al., 2015), *A. carmiechaeli* Debx. (Xu et al., 2003), *A. coreanum* (Levl.) Rapaics. **(**Bessonova et al., 1990; Bessonova et al., 1991; Yusupova et al., 1991), *A. duclouxii* Levl. (Wang et al., 2015), *A. flavum Hand-Mazz* and *A. pendulum Busch* (Tang et al., 1984, Wang et al., 2011), *A. heterophyllum* Wall (Dar et al., 2001; Zhaobong et al., 2005; Ahmad et al., 2009; Nisar et al., 2009), *A. jaulense* (Shim and collab., 2003, cited by Srivastava et al., 2010), *A. karacolicum* Rapcs. (Chodoeva et al., 2005; Tarbe et al., 2017), *A. kusnezoffii* Reichb. (Xu et al., 2011; Liu et al., 2014), *A. laciniatum* (Brühl) Stapf (Wangchuk et al., 2015), *A. leucostomum* Worosch. (Amatjan et al., 2017), *A. spicatum* Stapf. (Gao et al., 2006), *A. variegatum* L. (Diaz et al., 2005), *A. taronense Fletcher et Lauener* (Yin et al., 2018), and *A. yesoense* Nakai (Takayama et al., 1982). A comprehensive synthesis of the diterpenoid alkaloids found in different *Aconitum* species in China is presented by Wang and Chen (2010).

The alkaloid content may vary dependant on the conditions in the environment where the *Aconitum* plants grow. The conditions often incriminated for these discrepancies include the temperature, light, stage of the vegetative cycle, composition of the *in vivo* or *in vitro* culture medium, altitude, photoperiod, etc (Srivastava et al., 2010).

Jiang et al. (2005) recorded a lower level of alkaloid content in the processed roots of *A. carmicaheli* Debeaux, compared with those that were unprocessed. The variations were attributed to the processing methods and to their places of origin.

Even though specialist literature abounds in scientific studies on the chemical constituents of *Aconitum* sp., there are few data regarding the specific characterization and standardization of these constituents.

The interest for the genus *Aconitum* is justified both by the diterpenoid alkaloids used in eastern medicine (Bisset, 1981) and by the flavonoids studied in the last years as chemotaxonomical markers (Lim et al., 1999). Flavonoids, included in the class of phenolic compounds with a low molecular weight, are largely distributed in the plant kingdom. These constituents are responsible for the colour of the flowers and the protection against ultraviolet radiations. They are also strong collectors of reactive oxygen species which prevent lipid peroxidation (Treutter, 2005). More flavonoids were identified in the butanolic fraction of methanol extracts obtained from aerial parts of *A. chiisanense* Nakai Jeong et al. (1997) and *Aconitum jaluense* for. *album* (Whang et al., 1994). Fico et al. (2001) identified 3 new flavonoids in extracts obtained from the flowers of *A. napellus* subsp. *neomontanum*. Mariani et al. (2008) determined the flavonoid content of the methanol extract from aerial parts of *A. anthora* L. by applying thin layer chromatography and magnetic resonance spectroscopy.

Besides alkaloids and flavonoids, other chemical components considered to have a beneficial effect on human health were also reported to be present in the *Aconitum* species. For example, free fatty acids were identified by Yue et al. (2010) in the species *A. taipeicum* Hand.-Mazz; of these acids, the linoleic acid was predominant. A polysaccharide soluble in water and called FPS-1 was isolated from the root of the species *A. carmichaeli* Debx. Tested for its pharmacological activities, FPS-1 demonstrated strong stimulatory effects on the proliferation of murine lymphocytes and on the production of antibodies both *in vitro* and *in vivo* (Zhao et al., 2006).

4. PHARMACOLOGICAL AND BIOLOGICAL ACTIVITIES OF EXTRACTS FROM *ACONITUM* SP.

In addition to the old eastern medical practices in which the roots of some *Aconitum* species are indispensable for the rehabilitation of the metabolism, for the treatment of paralysis and atony,

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being used as an analgesic, antipyretic and antirheumatic drug (Hikino et al., 1980; Shyaula, 2011, Jaiswal et al., 2013), today aconitine is well known for its hypotensive and bradycardic actions (Chan, 2009), for its effect on the central nervous system (Peng et al., 2009) and its lethal toxicity (Bock and Norris, 2016). Isolated aconitine, along with a series of alcoholic extracts from different *Aconitum* species displayed significant anticancer (Solyanik et al., 2004; Du et al., 2013; Huang et al., 2013) and apoptotic (Gao et al., 2017) potentials. Other studies demonstrated that the alcoholic and aqueous extracts of *A. flavum* and *A. pseudo-laeve* var. *Erectum* induced a decrease in blood glucose levels (Kim et al., 2013; Zhang et al., 2016), or appreciated that they are effective anti-aging agents (Kim et al., 2013). Recent studies revealed the antimicrobial and/or antioxidant activity of the root extracts of *A. kashmiricum, A. napellus subsp. tauricum, A. napellus subsp. neomontanum, A. paniculatum*, and *A. vulparia* (Braca et al., 2003; Pala and Mir, 2014).

Although it is considered one of the most toxic species of the genus *Aconitum*, *A. ferox* Wall. ex Ser. is used as an analgesic, especially for treating joint pains. Moreover, this species also has antiinflammatory properties due to its alkaloid content (Uprety et al., 2010). Hikino et al. (1980) reported that the aconitines from the methanol extracts of *A. carmichaelii* Debx. inhibited the increase in vascular permeability induced by acetic acid and the carrageenin-induced edema of the hind paw in mice, and in 2018 Guo et al. confirmed the analgesic effect of some diterpenoid alkaloids isolated from aqueous extracts of *A. carmichaelii* Debx.

Both leaves and roots of *A. kusnezoffii* Rchb. have been used on a large scale in Chinese traditional medicine, especially as an analgesic and cardiotonic (Yu and Jia, 2000). Their therapeutical effects have been attributed to diterpenoid alkaloids and polysaccharides isolated from the roots of this species (Zinurova et al., 2001). The antirheumatic effect on human fibroblast-like synoviocyte rheumatoid arthritis, possibly as a result of the inhibition of cell proliferation and intensification of cell apoptosis was observed by Yang et al. (2017) for the crude drug, processed products and monomer components obtained from *A. leucostomum* Worosch.

The bitter decoction of *A. naviculare* (Brühl) Stapf. is used to treat jaundice or fever (Bhattarai et al., 2006). Swatinine and a benzene derivative together with 4 known alkaloids, namely delphatine, lappaconitine, puberanine and N-acetylsepaconitine isolated from the overground parts of the species *A. leave* Royle (Shaheen et al., 2005), and a derivative of quercetin isolated from *A. anthora* L. (Mariani and collab., 2008) presented an antioxidant activity that recommends them for antioxidant complexes. The antioxidant activity was also attributed to the flavonoids identified in different *Aconitum* species (Mariani et al., 2008; Yadav and Verma, 2010).

The antiinflammatory activity of lappaconitine and puberanine isolated from *A. leave* Royle was reported by Shaheen et al. (2005) and fractions from the ethanol extracts of *A. flavum* (Zhang et al., 2015) had antiinflammatory and antinociceptive effects at high dosages. Using the technique of granulomatous lesions, Verma et al. (2010) underlined the antiimflammatory activity of the extracts of *A. heterophyllum*. The methanol fraction of *A. heterophyllum* Wall.ex Royle had a hypolipidemic effect (Subash and Augustine, 2012).

Among the alkaloids isolated from the species of the genus *Aconitum*, diester aconitine is also the strongest neurotoxin and a very effective analgesic, acting by persistent activation of the Na^+ channels in the heart, skeletal muscles and central nervous system (Ameri and Simmet, 1999; Wang and Wang, 2003; Bao et al., 2011; Ye et al., 2011; Wang et al., 2012). After performing their classification into three groups (very toxic, less toxic and low toxicity alkaloids) based on their structure, Ameri (1998) tested the effect of different alkaloids on the central nervous system. Ameri and Simmet (1999) also demonstrated that the anti-epileptiform effect of ajacine and lappaconitine is mediated by this interaction with the sodium channels, which reduces excitability. Songorine, a

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diterpenoid alkaloid found in the species of the genus *Aconitum* was proved to enhance the excitatory synaptic transmission in the hippocampus of rats (Zhao et al., 2003). Eleven alkaloids isolated from *A. coreanum* revealed a miorelaxant activity, with isoatisine and coryphine being the most active (Dzhakhangirov and Bessonova, 2002).

Significant antitumour properties against the tumour cells HL-60, A-549, SMCC-7721, MCF-7 and SW480 were reported for sinchiangensine A, a diterpenoid alkaloid isolated from the root of *A. sinchiangense* W. T. Wang (Liang et al., 2017). 8-O-azeloyl-14-benzoylaconine revealed antiproliferative properties against 3 human tumour cell lines in an *in vitro* culture (Chodoeva et al., 2005).

Lycaconitine, obtained from a few species of the genus *Aconitum* proved to be efficient in multidrug-resistant cancer chemotherapy (Kim et al., 1998). The diterpenoid alkaloids kobusine, pseudokobusine and 15-veratroylpseudokobusine, isolated from the roots of *A. yesoense* var. *macroyesoense* and purified, but especially acylated alkaloid derivatives inhibit cell growth by blocking the A549 human lung carcinoma cells in the G1 stage of the cell cycle (Wada et al., 2011). The derivatives of the alkaloids isolated from root extracts of *A. yezoense* var. *macroyezoense* and purified, but not the natural alkaloids, clearly presented an antiproliferative activity against the human tumour cell lines A172, A549, HeLa and Raji, respectively (Hazawa et al., 2009). Aconitine regulated the level of the PCNA (proliferating cell nuclear antigen) protein and of the signaling molecules for apoptosis induction and inhibited the *in vivo* tumour growth of the B16 cell melanoma (Du et al., 2013).

Furthermore, Wu et al. (2016) assumed that aconitine could lower the toxicity produced by chemotherapeutical agents against cells due to its induction of P-glycoprotein, which plays a crucial role in protecting the human body by pumping the external chemical substances outside the cells. The authors also identified possible drug-drug interactions when the alkaloids, especially aconitine are administered at the same time with other substrates of P-glycoprotein. In opposition to these results, Zhu et al. (2013) reported that the activity of the cytochrome P450 (CYP)3A (which metabolizes aconitine) was not influenced by the oral administration of aconitine in rats, indicating that aconitine does not cause CYP3A-related drug-drug interaction in the liver.

The antidiarrheal activity as well as the astringent and tonic properties were reported for the extracts of *A. heterophyllum* by Singh and Chaturvedi (1982). According to Prasad et al. (2014) the antidiarrheal activity of the roots of *A. heterophyllum* may be attributed to an antisecretory and anti-enteropooling type effect, as a result of the reactivation of Na^+ and K^+ ATPase mediated by nitric oxide. At the same time, the antidiarrheal activity was well supported by an antibacterial activity. The antimicrobial activity of the extracts of *A. heterophyllum* was later confirmed by Ahmad et al. (2009) and Srivastava et al. (2011). The active compounds from the extracts of *A. heterophyllum* are presently used as a key ingredient in the preparation of the drug called Diarex Vet (Mitra et al., 2001).

The evaluation of the antimicrobial potential of the raw methanol extracts of *A. chasmanthum* against gram-negative and gram-positive bacteria indicated an irrelevant activity compared with the standards. All the fractions tested presented a strong antifungal activity against *Trichophyton mentagrophyte* (Anwar et al., 2003).

In the studies by Pala and Mir (2014), the antibacterial and antifungal activities of the extracts of *A. kashmirikum* obtained with different solvents were determined through the diffusion method. The extracts of petroleum ether indicated the most effective antibacterial activity against the species *Serratia marcescens*, while the methanol extract showed the most effective antifungal activity against *Candida albicans* and *Trichophyton rubrum*.

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The studies conducted so far have revealed that the roots of *Aconitum* sp. have a considerable enzyme inhibitory potential. Shaheen and collab. (2005) showed that lappaconitine and puberanine induced a slight inhibition of tyrosinase. Nisar et al. (2009) reported that heterophyllinine-A and heterophyllinine-B isolated from extracts of *A. heterophyllum* Wall. inhibited the enzymes that control muscle contraction, namely acetylcholinesterase and butyrylcholinesterase, responsible for the Alzheimer disease. The anticholinesterase potential was also observed by Ahmad et al. (2017) for the diterpenoid alkaloids isolated from an alkaline fraction of *A. heterophyllum* Wall., and by Ahmad et al. (2018) as well, in the case of aconorine and lappaconitine extracted from roots of *A. leave*. Faleoconitine and pseudaconitine isolated from roots of *A. falconeri* showed a moderate inhibitory activity against acetylcholinesterase (Rahman et al., 2000).

4. CONCLUSIONS

The therapeutic potential of the active principles isolated from *Aconitum* species and then purified must be further explored with a view to standardize their use in modern medicine as a treatment for different medical conditions. Further studies on the chemical composition of the subterranean and aerial parts of the species in the genus *Aconitum*, as well as on their biological and pharmacological properties may show better means of using these very important species for therapeutical purposes in wiser and more efficient ways.

5. ACKNOWLEDGEMENTS

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