

Abhava pratinidhi dravya: A comparative phytochemistry of Ativisha, Musta and related species

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ABSTRACT

Authentic *Ativisha* (*Aconitum heterophyllum*) is a rare, endangered Himalayan species. Ayurveda classical texts of c. 15th–16th century, introduced “*abhava-pratinidhi dravya*” concept, wherein *Ativisha* was categorized as an *abhava dravya* (unavailable drug) and *Musta* (*Cyperus rotundus*) was suggested as a *pratinidhi dravya* (substitute) for it. *C. rotundus* is a weed, abundantly available pan-India. *Cryptocoryne spiralis* (*Naattu Athividayam*) and *Cyperus scariosus* (*Nagarmotha*) are also traded as *Ativisha* and *Musta*, respectively. Yet, there are no scientific studies to validate the use of substitutes. *A. heterophyllum* bears no similarity in terms of botanical classification with the other candidates. This article reviews published literature with an emphasis to look for similar phytochemicals or groups of phytochemicals in the species that could contribute to similar pharmacological activities, thereby supporting the drug substitution from a bio-medical perspective. Alkaloids like atisine were found to be the main focus of studies on *A. heterophyllum*, whereas for the *Cyperus* spp., it was terpenoids like cyperene. Although alkaloids and terpenoids were reported from both species, alkaloids in *C. rotundus* and terpenoids in *A. heterophyllum* were minor constituents. Reports on phytochemicals on *Cryptocoryne spiralis* and *C. scariosus* were very limited. Despite no significant similarities in chemical profiles reported, the *dravyaguna* (Ayurvedic drug classification) of *Ativisha* and *Musta* was quite similar warranting further exploration into the bio-functional aspects of the drug materials.

Key words: *Aconitum*, *Ativisha*, Ayurveda, *Cryptocoryne*, *Cyperus*, *Musta*, phytochemistry

INTRODUCTION

The concept of drug substitution is well-known in allopathy and resorted to when the patient develops resistance to a particular drug or suffers from undesirable side effects from

its use. In Ayurveda, single, pure compounds are seldom used, and the bulk of its medicines are derived from plants. Instances of drug resistance and side effects are rare or may be not recorded in Ayurveda. However, the concept of drug substitution has been in vogue in Ayurveda and documented in texts dating to 15th and 16th centuries. Such a concept is called as “*abhava-pratinidhi dravya*”, wherein an “*abhava dravya*” (unavailable drug) is replaced by a “*pratinidhi dravya*” (substitute drug).^[1-3] Neither the process of substitute identification nor reasons for using substitutes are available in the classical Ayurvedic texts. Hence, for scientists in contemporary times the substitution seems nonscientific and inappropriate, raising questions about the validity of their use in treatment. It is possible that unavailability of the original drug due to geographical and/or seasonal variations led to its substitution. Loss of biodiversity and habitat due to over-exploitation and expanding human population may also have pushed several species to near extinction.

A careful examination of Ayurvedic texts in the context of *abhava-pratinidhi dravya* enables us to understand the progression in the systematization of Ayurvedic knowledge.

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The *brhatrayis* (three classical texts of Ayurveda: Charaka and Sushruta samhitas and Ashtanga Sangraha) do not use the *abhava-pratinidhi dravya* nomenclature. This usage occurs for the first time in Bhavaprakasha (c. 16th century AD) and has been repeated in subsequent Ayurvedic literature.

Ayurvedic medicines are characterized based upon the principles of *dravyaguna vijnana*. In essence, each drug is identified/characterized using its *rasapanchaka* attributes of *rasa* (taste), *guna* (properties), *veerya* (potency), *vipaka* (taste after digestion) and *prabhava* (unique action) and *karma* (pharmacological action).^[1] Using this concept, it may be possible to explain the logic underlying the choice of *abhava-pratinidhi dravya* drug pairs.

More than 150 “*abhava-pratinidhi dravya*” pairs are mentioned in the Ayurvedic texts. Reasons for some of the substitutes suggested are simple: E.g. *Kusta* (*Saussurea lappa* C.B. Clark) as a substitute for *Pushkaramula* (*Inula racemosa* Hook.f.),^[2] where the species are morphologically similar (both belong to the Asteraceae family) and have chemical resemblances as well (both have constituents containing the biologically significant α -methylene γ -lactone functionality).^[4] However, there are also instances where the substitutes show no similarities either in morphology or chemical constituents with the original drug. E.g., substitution of the wood of *Rakthabandana* (*Pterocarpus santalinus* L.) with the root of *Ushira* (*Vetiveria zizanioides* L.) for use in *Pitta* dominated diseases.^[2] *P. santalinus* is rich in phenolics and flavonoids,^[5] whereas terpenoids are the major constituents present in *V. zizanioides*.^[6] In these examples, comparing the *dravyaguna vijnana* may prove to be useful.

Musta (*pratinidhi dravya*) is mentioned in Ayurveda as a substitute for *Ativisha* (*abhava dravya*) and they are strikingly different botanical entities.^[2,3] The Ayurvedic Pharmacopoeia of India (API) identifies *Ativisha* as *Aconitum heterophyllum* Wall. ex Royle (Ranunculaceae) and *Musta* as *Cyperus rotundus* L. (Cyperaceae). *A. heterophyllum* is a perennial herb found in the Himalayas at high altitudes from 3000 m,^[4] is classified as an endangered species^[7] and is in the negative list of exports of the Ministry of Environment and Forests, Government of India.^[8] *C. rotundus*, on the other hand, is a common weed widely distributed throughout India.^[7,9]

The main use of both *Ativisha* and *Musta* is in the treatment of diarrheal disorders as powders of dried tubers or dried rhizomes, respectively.^[9,10] According to the API, the suggested dose in powder form is 0.6–2.0 g for *Ativisha* and 3–6 g for *Musta*.^[11,12] This indicates that *Ativisha* possibly is more potent than *Musta*.

Although the API has identified *Ativisha* and *Musta* unequivocally as *A. heterophyllum* and *C. rotundus* respectively, *Cryptocoryne spiralis* (Retz.) Fisch ex Wydler is very often sold in the markets as *Naattu Athividayam* (Malayalam/Tamil: Local *Ativisha*).^[9] The original *Ativisha* is called *Athividayam* in Malayalam, Tamil and Telugu.^[13] While *Cryptocoryne spiralis* is inexpensive, freely available and has some properties similar to *Ativisha*, some Ayurvedic scholars do not accept it as *Ativisha*.^[9] In the case of *Musta* too some confusion exists. The Ayurvedic texts mention two types of *Musta*, namely “*Nagara Musta*” and “*Bhadra Musta*”. The former has been identified as *Cyperus scariosus* R. Br., and the latter, *C. rotundus*. However, both species of the Cyperaceae family are traded under the name *Musta*.^[9]

All the four species, namely *A. heterophyllum*, *C. rotundus*, *C. scariosus* and *Cryptocoryne spiralis* have been studied both phytochemically and pharmacologically. Most studies, however, are based on individual plants and are not on a comparative basis. Recent reviews on *A. heterophyllum* and *C. rotundus* cover most of the work done on these two species.^[14-16]

This article looks at the concept of *abhava-pratinidhi dravya*, with a focus on phytochemical similarities/differences between a selected pair, that is, *Ativisha* and *Musta*. To make use of this unique concept, a thorough understanding of the Ayurvedic logic behind substitution as well as phytochemical and pharmacological evidence is essential. This is an attempt to put together the vast information available on the chemistry of the four species in order to unearth any possible similarities in their chemical constituents. Similar review on the pharmacology aspect of the same species has also been put together for publication elsewhere by the authors. A complete picture thus obtained could help in understanding the basis for the substitution of *Ativisha* by *Musta*. It may also throw some light on the basis of Ayurvedic ways of drug identification.

TRADE AND DISTRIBUTION

It has been estimated by Ved and Goraya that the annual consumption of *Ativisha* in India is around 200–500 tonnes with price varying from Rs. 2000 to 4000/kg. The same authors have given a consumption figure of 2000–5000 tonnes for *Musta* and a cost range of Rs. 15–30/kg.^[7] No such data is available for *C. scariosus* and *Cryptocoryne spiralis*. The consumption data for *Ativisha* is disproportionately high when compared with the likely availability of *A. heterophyllum*, suggesting that what is traded as *Ativisha* is not exclusively *A. heterophyllum*. Substitution and adulteration appear to be rampant.

BOTANICAL DESCRIPTION

Aconitum heterophyllum Wall. ex Royle (Ranunculaceae – Dicotyledonae)

More than 300 species are known in the *Aconitum* family.^[17] In China alone, there are more than 200 *Aconitum* species, although only *Aconitum kusnezoffii* Reichb., and *Aconitum carmichaeli* Debx. are recorded in the Chinese Pharmacopoeia 2005 edition.^[18] In India, there are around 24 species, of which the major ones found in the Indian markets are *A. napellus* Linn., *A. chasmanthum* Stapf. ex Holmes, *A. ferox* Wall. ex Ser., *A. palmatum* D.Don and *A. heterophyllum* Wall.ex Royle.^[19]

Aconitum heterophyllum is a perennial herb found in the alpine and sub-alpine regions above 3000 m.^[13,20] It flowers in the second year. The flowers are helmet-shaped, bright blue or greenish blue in color and have a purple vein. For medicinal use, the roots from plants that are 2 years old and bearing fully developed tubers are collected. The tubers sometimes occur as a pair of mother and daughter tubers [Figure 1]. In India, the plant is most commonly found in Jammu and Kashmir, Himachal Pradesh and in Uttarakhand. As it is an endangered species, the Director General of Foreign Trade prohibits the export of *Aconitum* species of plants, plant portions and their derivatives and extracts obtained from the wild.^[8] Cultivation has been undertaken in Uttarakhand as a resource augmentation effort.^[20]

Cyperus rotundus L. (Cyperaceae - Monocotyledonae)

Cyperus rotundus, also known as purple nutsedge or nutgrass, is a common weed found all over India in fields, agricultural land, and moist waste land.^[13] It is a tufted, grass-like perennial plant, whose stem is three angled at the top with brown spikelets. Inflorescences are small, consisting of tiny flowers with a red-brown husk. Tubers are 3–20 mm in diameter, rust-colored turning black with a characteristic odor [Figure 2]. The rhizomes from 2-year-old plants are used for medicinal purposes.



Figure 1: *Aconitum heterophyllum* Wall. ex Royle: Habit and tubers

Cyperus scariosus R.Br. (Cyperaceae - Monocotyledonae)

Cyperus scariosus is a perennial herb with a creeping rhizome up to 5 cm long. Stems are slender and rounded, but 3-angular in the upper part [Figure 3]. There are utmost 3 short leaves. It is a coastal species found in swampy, brackish localities.^[21]

Cryptocoryne spiralis (Retz.) Fisch.ex Wydler (Araceae - Monocotyledonae)

Cryptocoryne spiralis, also known as *Naattu Athividayam*, is a perennial herb found in seasonally inundated places along rivers, roadside ditches and wet sandy places along the coast.^[21-23] Corms are up to 1 cm thick and up to 30 cm long. Leaves are erect or spreading with green petioles and elongate-elliptical to linear leaf blades [Figure 4]. It is a plant popularly used in aquariums.

PHYTOCHEMISTRY

In this section, the published literature on *A. heterophyllum* and *C. rotundus*, the substitute as per Ayurveda and their market substitutes (*viz.* *C. rotundus*, *Cryptocoryne spiralis* and *C. scariosus*) have been reviewed. This is with the aim of looking for similarities between them in terms of phytoconstituents and groups of phytochemicals.

Aconitum heterophyllum

Phytoconstituents of *Aconitum* species

The main alkaloid reported in *Aconitum* is aconitine that is highly toxic. In mice, the oral LD₅₀ is < 2 mg/kg.^[24] However, unlike the other *Aconitum* species which have aconitine as the major alkaloid, atisine is the main alkaloid in *A. heterophyllum*.^[25] It is comparatively nontoxic in nature, making *A. heterophyllum* a safer herb to use when compared with other *Aconitum* species such as *A. ferox*.^[9] In Ayurvedic practice, the tuber of *A. ferox* (*Vatsanabhi*) undergoes a thorough process of purification (*shodhana*) before being used as a drug,^[26] whereas no such process is mandatory for *A. heterophyllum*.



Figure 2: *Cyperus rotundus* L.: Habit and rhizomes



Figure 3: *Cyperus scariosus* R. Br.: Habit and tubers

Alkaloids of *Aconitum heterophyllum*

Jowett has documented the early investigations on the tubers of *A. heterophyllum*, beginning with Broughton (1873), Wasowicz (1879) and Wright (1879).^[27] Broughton was first to isolate atisine. Different salts (sulphate, hydrochloride and platinichloride) were prepared from the alkaloid, and the molecular formula was deduced. Wasowicz showed that the aconitic acid is also present along with atisine. He suggested slight modifications in the molecular formula of atisine. Wright proposed a new formula for atisine based on analysis of its aurichloride salt [Figure 5]. Subsequently, Jowett investigated the properties and composition of atisine and its salts in great detail. They did not find any alkaloid other than atisine.^[27] Jacob and Craig in 1942–1943 confirmed the structure of atisine and also isolated three other alkaloids hetisine, heteratisine and benzoylheteratisine.^[28,29]

Detailed studies by Pelletier on hetisine^[30] atisine and heteratisine^[31-33] in the years 1962–1964 helped in their structure elucidation. Further investigations on *A. heterophyllum* in 1967–1968 by Pelletier *et al.* led to the isolation and structure elucidation of additional new diterpene alkaloids: Atidine, F-dihydroatisine, hetidine and hetisone as well as lactone alkaloids heterophyllisine, heterophylline and heterophyllidine.^[34,35] In 1982, a new entatisene diterpenoid lactone, atisenol, was isolated from the tuber.^[36] Dvornik and Edwards in 1963 established the structure and more importantly, the stereochemistry of atisine and related alkaloids.^[37]

Work on *Aconitum* alkaloids by Ahmad *et al.* in 2008 led to the isolation of two new aconitine-type norditerpenoid alkaloids 6-dehydroacetylsepaconitine and 13-hydroxylappaconitine along with known norditerpenoid alkaloids lycocotinine, delphatine and lappaconitine.^[38]

Although aconitine, which is the major alkaloid of the other *Aconitum* species, is not a major constituent of *A. heterophyllum*, high performance liquid chromatography (HPLC) studies carried out on the tubers from Kumaon and Garhwal regions of the Himalayas showed that it is present in different populations and varies from 0.13% to 0.75% (dry weight basis).^[39,40] Bahuguna



Figure 4: *Cryptocoryne spiralis* (Retz.) Fisch ex Wydler: Rhizomes

and others reported higher content of atisine (0.35%) and aconitine (0.27%) in green house grown *A. heterophyllum* when compared with the naturally grown plants (0.19% and 0.16%, respectively).^[41] Similar HPLC studies on the quantification of aconitine from tubers of *A. heterophyllum* from the Kashmir valley have reported 0.0014–0.0018% aconitine.^[42] From the reported literature, it is evident that, alkaloids were the main focus of study in *A. heterophyllum*. Several pharmacological actions of *Ativisha* have been attributed to their alkaloids.^[24]

Cyperus rotundus

Terpenes

At least two exhaustive review articles listing out the different constituents and the pharmacological activities have been published on this species.^[15,16] Most of the studies on the rhizomes of *C. rotundus* are on essential oils.

In 1964, while studying the composition of the essential oils, Trivedi *et al.* isolated a new sesquiterpene, cyperene, which is a tricyclic hydrocarbon. Earlier work by them had also confirmed the presence of β -selinene.^[43] Around the same time, Kapadia *et al.* isolated a new ketone, which was named mustakone, after a local name for *C. rotundus*, *Mustaka*. They also achieved a direct conversion of copaene to mustakone, further confirming the structures for both.^[44] Additional studies by the group in 1967 described in detail the structures of copadiene (a conjugated diene), epoxyguaiene (an epoxide), rotundone and cyperolone (a hydroxy ketone) - all found in *C. rotundus*.^[45]

Paknikar *et al.* in 1977 reported the isolation and structure elucidation of the sesquiterpenoids rotundene and rotundenol.^[46]

Singh and Singh in 1980 isolated from the benzene extract of *C. rotundus* the triterpenoid acid oleanolic acid and its glycoside. The glycoside, on acid hydrolysis, produced glucose and rhamnose. This glycoside, oleanolic acid-3-*O*-neohesperidoside, had not been isolated previously from any plant source.^[47]

Dhillon *et al.* in 1993 were the first to report the presence of caryophyllene in *C. rotundus*.^[48]

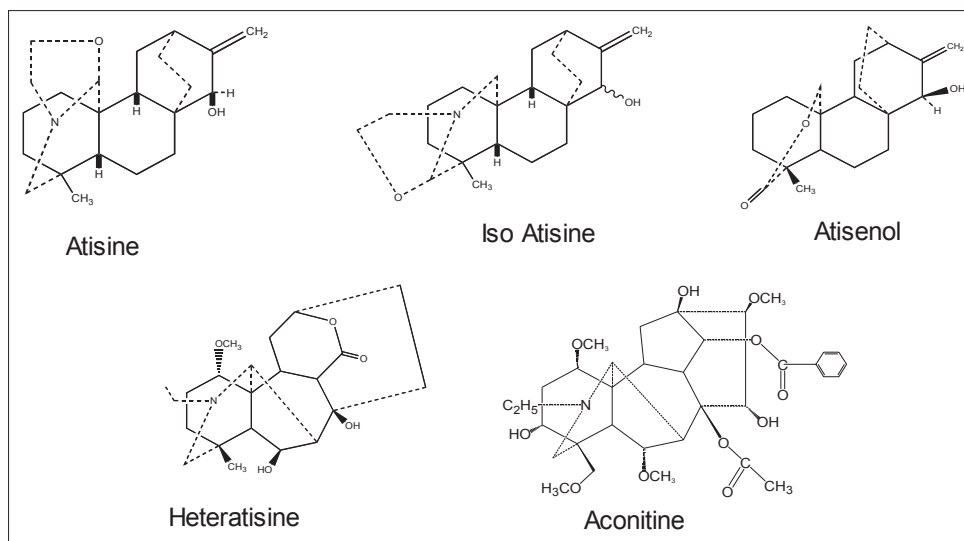


Figure 5: Important chemical constituents of *Aconitum heterophyllum*

The rhizomes of *C. rotundus* have been used in Thailand as an antimalarial. Thebtaranonth *et al.* in 1995 isolated the constituents responsible for its antimalarial activity: Patchoulone, caryophyllene alpha-oxide, 4, 7-dimethyl-1-tetralone and a novel sesquiterpene endoperoxide 10, 12-peroxyalamenene of which the endoperoxide (containing peroxide oxygen atoms) showed the strongest antimalarial effect with an EC_{50} of 2.33×10^{-6} M.^[49] The peroxide linkage is a known antimalarial pharmacophore.^[50]

Ohira *et al.* characterized three new sesquiterpenoids from *C. rotundus*. Two of the newly isolated oils had 4, 5-secoeudesmane skeletons and were identified as 2 α -(5-oxopentyl)-2 β -methyl-5 β -isopropenyl cyclohexanone and 2 β -(5-oxopentyl)-2 β -methyl-5 β -isopropenyl cyclohexanone. The third oil isolated had a cyperolone carbon skeleton and was characterized as a tetracyclic acetal.^[51]

Analysis of the essential oil of *C. rotundus* by GC and GC-MS in 2001 by Sonwa and König enabled positive identification of a number of constituents.^[52]

Work was done on optimization of the method of extraction of essential oils from the tubers of *C. rotundus* by CU Tam *et al.* in 2006. It was observed that the three methods investigated-hydro distillation, pressurized liquid extraction and supercritical fluid extraction-showed differences in the contents of the main volatile components studied.^[53] In a recent development, Korean scientists isolated two new patchoulane type sesquiterpenes and three known patchoulane and two eudesmane types from the rhizomes of *C. rotundus*.^[54] The rhizomes also afforded on extraction two new sesquiterpenoids with rearranged

secoeudesmane and germacrane skeletons, a new 9, 10-seco-cycloartane triterpenoid as well known compounds comprising a monoterpene, five sesquiterpenoids and a nortriterpenoid.^[55]

Phenolics and flavonoids

Nagulendran *et al.* in 2007 estimated the total phenolic content in the ethanol extract of dried rhizome to be 73.27 ± 4.26 g/100 g extract in terms of catechin equivalents.^[56]

Many phenolics and flavonoids have been isolated from *C. rotundus*. Samariya and Sarin obtained four known flavonoids, quercetin, kaempferol, catechin and myricetin from the leaves and roots of the plant.^[57] A new flavanone, 7, 8-dihydroxy - 5,6 - methylenedioxyflavone as well as five known compounds, namely quercetin, kaempferol, luteolin, ginkgetin and isoginkgetin were isolated from the rhizomes.^[58] The rhizomes are also the source of two new phenolics, 1 α -methoxy -3 β - hydroxy-4 α (3',4'-dihydroxyphenyl)-1,2,3,4-tetrahydronaphthalene and its demethylated parent.^[59]

Ito *et al.* isolated several stilbene oligomers from *C. rotundus*. They are (+) and (-)-E- cyperusphenol A, E-mesocyperusphenol A, cyperusphenol B as well as the known cyperusphenols C and D, scirpusins A and B, piccid and luteolin.^[60]

Glycosides

The rhizomes of *C. rotundus* were shown to contain two new iridoid glycosides, rotundusides A and B.^[61,62] Methanolic extract of the rhizomes of *C. rotundus* gave a keto-alcohol characterized as 21-oxo-n-tricontanol and two new triterpenoid glycosides, 18-epi- α -amyrin

glucuronoside and oleanolic acid arabinoside besides the known compounds alpha and beta amyryn glucopyranosides.^[63]

Analysis of different extracts (aqueous, total oligomers flavanoids, essential oil, ethyl acetate and methanol) of the tubers was carried out by Kilani *et al.* in 2007. Tannins, flavanoids and coumarins were found to be present in all the extracts. Composition of the essential oil was investigated by GC and GC-MS and around 70 sesquiterpene hydrocarbons were identified along with oxygenated sesquiterpenes and a few monoterpene hydrocarbons.^[64]

Study of the rhizomes of *C. rotundus* in 2008 led to the isolation and structure elucidation of a novel norsesquiterpene norcyperone.^[65] Xu *et al.* in 2009 isolated 2 new compounds-epiguaidiol A and sugebiol-along with four known sesquiterpenes guaidiol, sugetriol triacetate, cyperenoic acid and cyperotundone.^[66] Klahn *et al.* reported in 2012, the total synthesis of cyperolone, a sesquiterpenoid found in *C. rotundus*, starting from carvone.^[67]

Interest in the discovery of new secondary metabolites in traditional Chinese Medicines led to the work by Yang and Shi in 2012 on the rhizomes of *C. rotundus*. They investigated the ethanolic extract of the dried and powdered rhizomes of *C. rotundus* that were further partitioned with petroleum ether. They succeeded in isolating two new sesquiterpenoids – rotundusolide A and B having secoeudesmane sesquiterpenoids skeleton as well as a new triterpenoid rotundusolide C.^[55]

Alkaloids of *Cyperus rotundus*

In 2000, Jeong *et al.*, in their search for alkaloids from medicinal plants, isolated 3 sesquiterpene alkaloids from the rhizomes of *C. rotundus*. Rotundines A-C. This was the first report on the presence of alkaloids in this plant. This was also the first time that such sesquiterpene alkaloids with a cyclopenta pyridine structure were isolated from natural sources. These alkaloids were colorless oils and gave a positive reaction to Dragendorff's reagent. However, the quantities obtained were very small (in the range of 0.7–1.1 ppm).^[68] Adams *et al.* reported a complex mixture of terpenoids and alkaloids as well as condensed tannins in the rhizomes of *C. rotundus*, using histochemical studies.^[23]

Studies on chemotypes of *Cyperus rotundus*

It is not surprising that such a widely distributed species like *C. rotundus* has four major chemotypes. These have been classified as H, K, M and O, based upon the composition of the essential oils. H, M and O chemotypes are found in Asia, with O being the most widely distributed. K is reported to be the dominant type in the Hawaiian islands.^[69]

Studies carried out on the composition of essential oils of *C. rotundus* from two regions in South Africa support the conclusions of the above data and show that there is a compositional difference between *C. rotundus* found in South Africa and the rest of the world.^[70] Similarly, Ghannadi *et al.* in 2012 carried out the phytochemical screening and essential oil analysis of *C. rotundus* from Iran. The phytochemical screening revealed the presence of flavanoids, tannins, alkaloids and essential oils. The essential oil analysis was carried out by GC-MS. The major constituents were cyperene, caryophyllene and α -longipinane. These results also showed differences from the analysis done by earlier investigators from other parts of the world.^[71]

Within India, the composition of the essential oil of *C. rotundus* shows a geographical variation. Jirovetz *et al.* showed in 2004 that the composition of the essential oils of *C. rotundus* from South India is dominated by the presence of α -copaene (11.4%), valerenal (9.8%), caryophyllene oxide (9.7%), cyperene (8.4%), nootkatone (6.7%), and trans-pinocarveol (5.2%). GC-FID and GC-MS analysis were carried out to identify the constituents and olfactive evaluations were also done to correlate the aroma attributes with the compounds responsible for the aroma.^[72] A similar GC-MS study on the essential oils of *C. rotundus* from Dehradun showed that the major components were 5-oxo-isolongifolene (16.27%), α -gurjunene (10.22%), valeranyl acetate 8.88% α -salinene (4.48%), valerenic acid (3.67%) and γ -cadinene (3.4%).^[73]

From the above, it is clear that, terpenoids are the major phytoconstituents in *C. rotundus*. Phenolics and flavonoids are also present and there is only one report on the occurrence of alkaloids in this species.

Cyperus scariosus

When compared to *C. rotundus*, little information is available on the chemical constituents of *C. scariosus*. The essential oil was shown to contain mainly bicyclic and tricyclic sesquiterpenes.^[74] In 1957 Dhingra and Dhingra established that the essential oil of *C. scariosus* contains a bicyclic ketone, a tricyclic tertiary alcohol and a tricyclic sesquiterpene hydrocarbon.^[75] Nerali *et al.* in 1965 reported the isolation of a new sesquiterpene ketone from *C. scariosus*, which they called isopatchoulone, due to its structural similarity to patchoulone.^[76] In the same year, Nigam isolated a sesquiterpene ketone, which he called cyperenone, from the same species.^[77] Similarly, Hikino *et al.*, in 1967, also isolated a sesquiterpene ketone from the three species of the *Cyperus* genus (*C. rotundus*, *C. scariosus* and *C. articulatus*) which they named cyperotundone.^[78] Neville *et al.* in 1968 also isolated a ketone and established by spectral data that the ketones isolated by the earlier investigators

were one and the same and proposed a new name, isopatchoul-4 (5)-en-3-one.^[79] Nerali *et al.* in 1967 isolated two sesquiterpene alcohols from the alcoholic fractions of the essential oils of the tubers. These were named cyperenol and patchoulenol.^[80] Other sesquiterpenes isolated from *C. scariosus* include rotundene and rotundenol,^[46,81] the known hydrocarbon (-)-beta-selinene and the new compound isopatchoula-3,5-diene.^[82] Uppal, along with Chhabra *et al.*, while studying the species for plant growth regulators, isolated a new hydrocarbon, isopatchoul-3-ene. This compound was subjected to spectral characterization and found to be a tricyclic compound with an isopatchoulane type carbon skeleton.^[83]

The essential oil derived from rhizomes of *C. scariosus* grown in Bangladesh was analysed by GC-MS and as many as 31 compounds were identified.^[84] A similar analysis of the essential oil from fresh tubers of *C. scariosus* collected in central india showed the presence of 30 compounds.^[85]

Bhatt *et al.* in 1981 studied the phytoconstituents of the leaves of *C. scariosus* and isolated a phenolic glycoside, which on acidic hydrolysis gave an aglycone along with glucose and rhamnose. The aglycone was identified as leptosidin and the structure of the new glycoside was assigned as leptosidin 6-O-β-D-glucopyranosyl-O-α-L-rhamnopyranoside.^[86] The leaves were also the source of two more glycosides, leptosidin-6-O-[β-D-xylopyranosyl (14)-β-D-arabinoside^[87] and stigmasta-5, 24 (28)-diene-3 β-O-α-L-rhamnopyranosyl-O-β-D-aabinopyranoside.^[88]

Sahu *et al.* in 2010 isolated from the tubers of *C. scariosus* a new compound, namely 2, 3-diacetoxy-19-hydroxy-urs-12-ene-24-O-β-D-xylopyranoside.^[89] The presence of alkaloid-terpenoid complex in the rhizomes of *C. scariosus* by histochemical studies was reported by Adams *et al.* in 2013. However, the occurrence of this complex is not as extensive when compared to *C. rotundus*.^[23]

Cryptocoryne spiralis

As mentioned earlier, *Cryptocoryne spiralis* is known in Tamil Nadu as “*naattu adhividayam*” and sold in the markets in the place of *A. heterophyllum*. It is also known as “Indian Ipecacuanha.”^[90] While the actual Ipecacuanha root (*Radix ipecacuanha*) found mainly in Brazil, contains the alkaloids emetine and cepheline, these are absent in the Indian variety.^[91]

Gupta *et al.* in 1983 isolated 4 compounds, including 2 new oxo fatty acid esters, ethyl 14-oxotetracosanoate and 15-oxoeicosanyl 14-oxoheptadecanoate from the hexane extract of the corms.^[92] Further studies in 1984 led to the isolation of two new fatty acids, 22-oxononacosanoic acid and 26-oxohentriacontanoic acid.^[93] Two steryl esters from

the same plant, 5α-stigmast-11-en-3 β-yl palmitate and 24-ethyl-5α-cholesta-8 (14), 25-dien-3 β-yl stearate were also isolated.^[94]

DISCUSSION AND CONCLUSION

Aconitum heterophyllum is an endangered species available only at high altitudes; while *C. rotundus*, *C. scariosus* and *Cryptocoryne spiralis* are widely available. Although in all four species, the tuber/rhizomes are used, the similarity ends there. While *C. rotundus* and *C. scariosus* belong to the Cyperaceae family, *Cryptocoryne spiralis* belongs to the Araceae family and *A. heterophyllum* belongs to Ranunculaceae family. The former three are monocots while *A. heterophyllum* is a dicot. The four species also differ in their habitat.^[23]

The phytochemistry of *A. heterophyllum*, *C. rotundus*, *C. scariosus* and *Cryptocoryne spiralis* is summarized in Tables 1 and 2. As per published reports, no significant similarity in chemical composition was apparent between *A. heterophyllum* and *C. rotundus*. However, alkaloids and terpenoids were common classes of compounds reported as being present in both species, nevertheless only as minor constituents in *C. rotundus* and *A. heterophyllum* respectively. Alkaloids of *A. heterophyllum* and essential oils of *C. rotundus* have been studied extensively. Except for the lone report by Jeong *et al.* on the presence of alkaloids (Rotundines A-C)^[68] [Figure 6], no other alkaloids have been reported as detected in *C. rotundus*. Furthermore, the extensive worldwide studies on essential oils of *C. rotundus* have shown that there is a lot of chemical diversity within the species. A recent review of the phytochemistry and pharmacology of *C. rotundus* by Sivapalan stresses on the

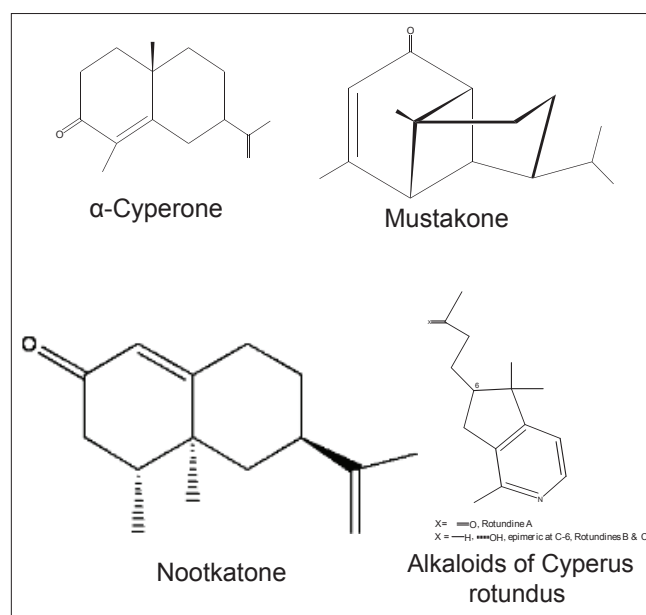


Figure 6: Important chemical constituents of *Cyperus rotundus*

Table 1: Ativisha and Musta species with reported phytoconstituents

Ayurvedic candidate	Species	Chemical group/class	Chemical constituent (with reference)	
Ativisha	<i>A. heterophyllum</i>	Alkaloids	Aconitine, ^[24] atisine, ^[25,36] hetisine, heteratisine, benzoylheteratisine, ^[29] atidine, F-dihydroatisine, hetidine, hetisone, heterophyllisine, heterophylline, heterophyllidine, ^[35] 6-dehydroacetylsepaconitine, 13-hydroxylappaconitine, lycotonine, delphatine and lappaconitine ^[38]	
		Terpenoid	Atisenol ^[56]	
	<i>Cryptocoryne spiralis</i>	Fatty acids and esters	Ethyl 14-oxotetracosanoate, 15-oxoeicosanyl 14-oxoheptadecanoate, ^[92] 22-oxonacosanoic acid, 26-oxohentriacontanoic acid, ^[93] 5 α -stigmast-11-en-3 β -yl palmitate, 24-ethyl-5 α -cholesta-8 (14) and 25-dien-3 β -yl stearate ^[94]	
Musta	<i>C. rotundus</i>	Hydrocarbon	Hentriacontane ^[93]	
		Terpenoids	Cyperene, β -selinene, ^[42] copaene, mustakone, ^[44] copadiene, epoxyguaiene, cyperolone, ^[45] rotundone, ^[45,46] rotundenol, ^[46] oleanolic acid-3-O-neohesperidoside, ^[47] caryophyllene, ^[48] patchoulone, caryophyllene alpha-oxide, 4, 7-dimethyl-1-tetralone, ^[49] 2 α -(5-oxopentyl)-2 β -methyl-5 β -isopropenyl cyclohexanone, 2 β -(5-oxopentyl)-2 β -methyl-5 β -isopropenyl cyclohexanone, tetracyclic acetal, endoperoxide 10, 12-peroxycalamenene, ^[51] cyprotene, cypera-2,4-diene, α -copaene, α -selinene, rotundene, valencene, ylanga-2,4-diene, γ -gurjenene, trans-calamenene, δ -cadinene, γ -calacorene, epi- α -selinene, α -muurolene, γ -muurolene, cadalene, nootkatone, cyperol, isocyperol, α -cyperone, isorotundene, cypera-2, 4-diene, norrotundene, cyperadione, ^[52] clovane-2,9-diol, rosenonolactone, ^[65] epiguidiol A, sugebiol, guaidiol, sugetriol triacetate, cyperenoic acid, cyperotundone, ^[66] rotundusolide A, B and C, 3, 4-O-isopropylideneshikimic acid, sesquiterpenoids with rearranged secoeudesmane and germacrane skeletons, dehydrocostuslactone, (+)-alismsoxide, sugetriol triacetate, 2 β -hydroxy- α -cyperone, eudesma-4 (14), 11 (13)-diene-7 α , 8 α , 12-triol and 3, 4-seco-mansumbinoic acid, ^[55] α -longipinane, ^[73] nootkatone, valeranal, trans-pinocarveol, ^[72] 5-oxo-isolongifolene, α -gurjunene, valeranyl acetate α -salinene, valerenic acid, γ -cadinene, ^[73]	
		Glycosides	Oleanolic acid-3-O-neohesperidoside, ^[47] 6''-O-p-coumaroylgenipin gentiobioside, isoaragoside, chinoside ahelioside C, 10-O-p-hydroxybenzoyltheviridoside, 10-O-vanniloyltheviridoside, 6''-o_ (trans-p-coumaroyl)-procumbide, loganic acid, rotundusides A and B, ^[61,62] 18-epi-alpha-amyrin glucuronoside, oleanolic acid arabinoside, alpha and beta amyryn glucopyranosides ^[63]	
		Phenolics and flavonoids	9,10-seco-cycloartane triterpenoid, known compounds with monoterpene, five sesquiterpenoids and a norriterpenoid, ^[55] quercetin, kaempferol, catechin, myrcetin, ^[57] 7,8-dihydroxy-5,6-methylenedioxyflavone, luteolin, ginkgetin, isoginkgetin, ^[58] 1alpha-methoxy-3beta-hydroxy-4alpha (3',4'-dihydroxyphenyl)-1,2,3,4-tetrahydronaphthalene and its demethylated parent, ^[59] (+) and (-)-E-cyperusphenol A, E-mesocyperusphenol A, cyperusphenol B, cyperusphenols C and D, scirpusins A and B, piceid, luteolin ^[60]	
		Keto-alcohol	21-oxo-n-tricontanol ^[63]	
		Tannins and coumarins ^[64]	No individual compound is identified	
		Steroids	5 α ,8 α -epidoxy-(20S, 22E, 24R)-ergosta-6,22-dien-3 β -ol ^[65]	
		Alkaloids ^[23]	rotundines A-C ^[68]	
		<i>C. scariosus</i>	Terpenoids	Bicyclic and tricyclic sesquiterpenes, ^[74] isopatchoulone, ^[76] cyperenone, ^[77] cyperotundone, ^[78] isopatchoul-4 (5)-en-3-one, ^[79] cyperenol, patchoulenol, ^[80] rotundene, rotundenol, ^[46,81] isopatchoula-3,5-diene, ^[82] isopatchoul-3-ene, ^[83] α -pinene, β -pinene, caryophyllene oxide, copaene, longiverbenone, nyrtenal, spathulenol and trans-pinocarveol, ^[84] cyperone caryophyllene oxide, eudesma-4 (14)-11-diene, rotundone, gurjunene and guaiazulene ^[85]
			Hydrocarbon	(-)-beta-selinene ^[82]
Glycoside	Leptosidin 6-O- β -D-glucopyranosyl-O- α -L-rhamnopyranoside, ^[86] leptosidin-6-O-[β -D-xylopyranosyl (1 4)- β -D-arabinoside, ^[87] stigmasta-5, 24 (28)-diene-3 β -O- α -L-rhamnopyranosyl-O- β -D-aabinopyranoside, ^[88] 2, 3-diacetoxy-19-hydroxy-urs-12-ene-24-O- β -D-xylopyranoside ^[89]			

A. heterophyllum: *Aconitum heterophyllum*, *C. rotundus*: *Cyperus rotundus*, *C. scariosus*: *Cyperus scariosus*

need for further exploration of various pharmacological uses of this herb because of this chemical diversity.^[95] Studies carried out on *C. scariosus* and *Cryptocoryne spiralis* are few and far between and do not mention the presence of alkaloids.

As per Ayurveda, *dravyas* (materials) are characterized based upon *dravyaguna vijñana*, where elements of *rasapanchaka* (taste, properties, potency, postdigestive effect and action) are considered. *Dravyaguna* way of characterization of plants is different from modern botanical or chemo-taxonomical ways of characterizing

herbal drugs. E.g., Charaka samhita describes *Panchashat Mahakashaya* (fifty therapeutic groups of medicinal herbs) classifying herbal drugs according to their pharmacological actions.^[10] It is interesting to note that despite lack of apparent similarities in botanical aspects as well as chemical composition, the *rasapanchakas* of *Ativisha* and *Musta* were similar [Table 3]. Both of them have bitter and pungent taste, cause dryness in the body, are easily digestible, retain pungency even after digestion and pacify *kapha* and *pitta doshas*. They are prescribed to increase digestive fire, to prevent fluid loss from the body and to control pyrexia and diarrhea. However, their *viryas* (potency) are different.

Table 2: Comparison of Ativisha-Musta species based on reported phytoconstituent classes

Phytoconstituents	<i>A. heterophyllum</i>	<i>Cryptocoryne spiralis</i>	<i>C. rotundus</i>	<i>C. scariosus</i>
Alkaloids	+	-	+	-
Terpenoids	+	-	+	+
Fatty acids and esters	-	+	-	-
Hydrocarbons	-	+	-	+
Glycosides	-	-	+	+
Phenolics and flavonoids	-	-	+	-
Keto-alcohol	-	-	+	-
Tannins and coumarins	-	-	+	-
Steroids	-	-	+	-

+: Presence. -: Absence/no reports available, *A. heterophyllum*: *Aconitum heterophyllum*, *C. rotundus*: *Cyperus rotundus*, *C. scariosus*: *Cyperus scariosus*

Table 3: Rasapanchaka of Ativisha and Musta

Rasapanchakas	Ativisha	Musta
Rasa (taste)	Tikta (bitter) and katu (pungent)	Tikta (bitter), katu (pungent) and kashaya (astringent)
Guna (-properties)	Laghu (-easily digestible) and ruksha (causes dryness)	Laghu (-easily digestible) and ruksha (causes dryness)
Vipaka (-state after digestion)	Katu (pungent)	Katu (pungent)
Dosha karma (action on doshas)	Kapha-pittahara (pacifies kapha and pitta doshas)	Kapha-pittahara (pacifies kapha and pitta doshas)
Karma (pharmacological actions)	Dipana (-increases digestive fire), pachana (-digestive), grahi (-absorbing extra-cellular fluids), jwarahara (antipyretic), atisaraghna (antidiarrheal), shotahara (anti-inflammatory), vishaghna (antidote), krimihara (-anthelmintic), arshoghna (anti hemorrhoid), jwarahara (anti pyretic) and kasahara (anti tussive)	Dipana (-increases digestive fire), pachana (-digestive), grahi (-absorbing extra-cellular fluids), jwarahara (antipyretic), atisaraghna (antidiarrheal), trishnahara (reduces morbid thirst) and kandughna (cure itching)

A. heterophyllum: *Aconitum heterophyllum*, *C. rotundus*: *Cyperus rotundus*

Ativisha has a hot potency (*usna*), while Musta is cold (*shita*). These facts enable us to conclude that the substitution of *Musta* (*pratinidhi dravya*) for *Ativisha* (*abhava dravya*) is most likely based on *dravyaguna*. Probably Ayurvedic seers looked at the similarities at *rasapanchaka* and *karma* levels of *abhava-pratinidhi dravyas*, rather than their morphological similarity.

It has to be borne in mind that the phytochemical studies published in the literature have not been done with a purpose of comparing the species. Dedicated scientific studies of *Ativisha* and *Musta* as well as other *abhava-pratinidhi* drug pairs are warranted to understand this concept better. In conclusion, understanding the concept of *dravyaguna vijnana* is essential to understand the logic behind selection of substitutes mentioned in Ayurveda. This in turn will be useful in identifying new substitutes, especially for drugs that are unavailable for use since they are endangered, seasonal, regional or expensive.

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