

# Pharmacology of *Ativisha*, *Musta* and their substitutes

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## ABSTRACT

The Ayurvedic literature during the medieval period suggests the use of *Musta* (*Cyperus rotundus*), a common weed, as a *pratidinhi dravya* (substitute) for *Ativisha* (*Aconitum heterophyllum*), an endangered species. Contemporary Ayurvedic practice also uses *Cryptocoryne spiralis*, (known as *Naattu Atividayam* in South India) and *Nagaramusta* (*Cyperus scariosus*) as substitutes for *Ativisha* and *Musta*, respectively. This article reviews published literature on the pharmacology of the above four species. Both *A. heterophyllum* and *C. rotundus* are reported to possess antiinflammatory, antipyretic, antibacterial and antidiarrhoeal properties, while antiinflammatory and antibacterial activities are attributed to *C. scariosus*. No reports exist on the bioactivity of *Cryptocoryne spiralis*. It is interesting to note that other than the *veerya* which is different, the biological properties of *Ativisha* and *Musta* are similar according to Ayurvedic classification of *dravyaguna*. This is also supported by modern pharmacological studies, which show that, both *A. heterophyllum* and *C. rotundus* have antidiarrheal, antipyretic, antiinflammatory, antihyperlipidemic and hypoglycemic activities. However, the similarities between the discussed species cannot be attributed to their phytochemical composition or taxonomical classification as these are quite distinct. The *dravyaguna* method of classifying materials, which we are calling as "pharmaco-taxonomy", offers a unique way of classifying those plant materials which lack similarity at the botanical or chemical level, but are similar at the level of biological functions.

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

## INTRODUCTION

As per the Ayurvedic concept of *abhava-pratinidhi dravya*, a rare or unavailable medicinal plant (*abhava dravya*) is substituted by a more readily available species (*pratidinhi dravya*). Although this concept dates back to Caraka,<sup>[1]</sup> it

was systematically codified by Bhavamishra.<sup>[2]</sup> Later works such as Bhaishajya Ratnavali<sup>[3]</sup> and Yogaratnakara<sup>[4]</sup> give an elaborate list of substitutes for unavailable drugs.

*Ativisha* (*Aconitum heterophyllum* Wall. ex Royle) is a commonly prescribed herb in Ayurveda for diarrhea, fever and inflammation. Having a natural habitat only in sub alpine Himalayas, *Ativisha* is an endangered species.<sup>[5]</sup> Trade in *Ativisha* far exceeds the natural availability of this plant, leading to rampant substitution/adulteration. The solution to this problem of nonavailability of *Ativisha* is suggested in Ayurvedic books like Bhavaprakasha<sup>[6]</sup> and Yogaratnakara,<sup>[4]</sup> where *Ativisha* (*abhava*) is substituted by *Musta* (*pratidinhi*). *Musta* (*Cyperus rotundus* L.) is a common weed, with a widespread distribution<sup>[7]</sup> *Naattu Athividayam* [*Cryptocoryne spiralis* (Retz.) Fisch ex Wydler] and *Nagara Musta* (*Cyperus scariosus* R. Br.) are other traded species as substitutes for *Ativisha* and *Musta*, respectively.<sup>[7]</sup>

This article reviews the published literature on the pharmacology of botanical entities used as *Ativisha* and *Musta* in order to compare the similarities and differences between the species. Though it would be ideal to present the phytochemical and pharmacological details of the

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species together in a single review article, the enormous information available on the phytochemistry of the species discussed, necessitated a separate presentation of the same.

The scope of this review covers the published literature on the pharmacology information on the selected species till November 2013 as available in the databases PubMed, SciFinder, and Agricola. Ayurveda details were obtained from classical Ayurveda texts of *Brhatrayi* and *Nighantus*.

## PHARMACOLOGY

### *Aconitum heterophyllum* Wall. ex Royle Use of *Aconitum heterophyllum* Wall. ex Royle (*Ativisha*) in Ayurveda and other traditional systems of medicine

*Aconitum* species are used in Ayurveda and Chinese systems of medicine. A brief review of the use of *A. heterophyllum* in Ayurveda has been published.<sup>[8]</sup> Aconitine, the most abundant alkaloid in most *Aconitum* species, is a known cardiotoxin.<sup>[9]</sup> Therefore, *Aconitum* species are used only after due process of detoxification.<sup>[10,11]</sup> *A. heterophyllum*, on the other hand, contains atisine as the principal alkaloid, and the species is considered to be nonpoisonous.<sup>[12]</sup> Ayurveda does not mandate and practice detoxification of *A. heterophyllum*.

As per Ayurvedic pharmacology, *Ativisha* (*A. heterophyllum*) has *tikta* (bitter) and *katu* (pungent) taste; *laghu* (light) and *ruksha* (dry) properties; *ushna veerya* (hot potency) and *katu vipaka* (attains pungency after digestion). In terms of actions, it is *kapha-pittahara* (reduces *kapha* and *pitta doshas*), *dipana* (increases digestive fire), *pachana* (digests undigested material), *grahi* (prevents water loss from the body), *shotahara* (antiinflammatory), *vishaghna* (antipoisonous), *krimihara* (anthelmintic), *arsbhogha* (antihemorrhoid), *jwarahara* (antipyretic), *kasahara* (antitussive) and *atisaraghna* (antidiarrhoeal). In the classical Ayurvedic text Caraka Samhita, *Ativisha* is listed in the following categories: *Tikta skandha* (bitter tasting drugs), *lekhaneeya* (has scraping action on tissues and *kapha*), *arsbhogha* (treating

hemorrhoids) *sirovirechana* (clearing morbid doshas from head and neck) [Table 1].<sup>[1,2,7]</sup>

The drug finds common use in the treatment of fevers, diarrhea, indigestion, inflammation, helminthiasis, hyperlipidemia and as an antiemetic in children.<sup>[13,14]</sup> *Sudarshana Churna*, *Balachaturbhadra Churna*, *Rasnerandadi Kwatha* and *Panchatiketa Guggulu Ghrta* are some of the popular multi-drug formulations in which *Ativisha* is one of the main ingredients.<sup>[13]</sup>

Similar uses for *A. heterophyllum* are also found in Unani and Siddha systems of medicines as well.<sup>[15,16]</sup>

Although anti-diarrheal activity is one of the major indications for which *A. heterophyllum* is used in traditional medicine, modern scientific studies are missing, except for one preliminary report. Venkatasubramanian *et al.* showed the anti-diarrheal activity of alcoholic extract of *A. heterophyllum* tubers in castor oil induced diarrhea and gastric transit time in mice. However, the active molecule responsible for this activity has not been reported.<sup>[17]</sup>

### Antiinflammatory and antipyretic activity

In order to assess the antiinflammatory activity of *A. heterophyllum*, Verma *et al.* employed the widely used cotton-pellet induced granuloma method. Their investigations showed that *A. heterophyllum* tuber (ethanolic extract) has significant antiinflammatory activity, thereby providing scientific evidence for a traditional medicinal claim as *shotha/shophahara karma* (antiinflammatory action).<sup>[18]</sup> The antipyretic effects of roots of *A. heterophyllum* in the form of aqueous, chloroform and hexane extracts were examined using the method of yeast induced pyrexia, with aspirin as a standard antipyretic agent for comparison. These studies, by Ikram, showed that the extracts were nontoxic (up to 1.6 g/kg) and had no significant antipyretic activity. However, in Ayurveda *A. heterophyllum* is administered as a powder (*churna*) and *kashaya* (decoction) for controlling fever.<sup>[19]</sup>

### Antibacterial activity

The new aconitine type nor-diterpenoid alkaloids 6-dehydroacetylsepaconitine and 13-hydroxylappaconitine, isolated from the tubers of *A. heterophyllum* along with the known alkaloids lycocotonine, delphatine and lappaconitine, were screened for antibacterial activity against different bacterial strains. They showed antibacterial activity against gram negative (diarrhea causing) bacteria *Escherichia coli*, *Shigella flexineri*, *Pseudomonas aeruginosa* and *Salmonella typhi*.<sup>[20]</sup> This reports strengthens the prescription of *Ativisha* as *Krimihara* (antimicrobial/anthelmintic). These tests were however not carried out using the plant extracts.

**Table 1: Summary of properties and actions (*rasapanchakas*) of *Ativisha-Musta***

Attributes	Common properties
Taste ( <i>rasa</i> )	Pungent ( <i>katu</i> ), bitter ( <i>tikta</i> )
Properties ( <i>guna</i> )	Light to digest ( <i>laghu</i> ), dry ( <i>ruksha</i> )
Taste after digestion ( <i>vipaka</i> )	Pungent ( <i>katu</i> )
Pharmacological action ( <i>karma</i> )	Reduces <i>kapha</i> and <i>pitta doshas</i> , increases digestive fire ( <i>dipana</i> ), absorbing extra-cellular fluids (~ <i>grahi</i> ), antipyretic ( <i>jwarahara</i> ), antidiarrheal ( <i>atisaraghna</i> )

### Immunomodulatory activity

The immunomodulatory activity of ethanolic extract of *A. heterophyllum* tubers along with other medicines of the Ayurveda and Unani systems of medicine were investigated on delayed type hypersensitivity (DTH), humoral responses to sheep red blood cells, skin allograft rejection and phagocytic activity of the reticuloendothelial system in mice. It was found that the extract appeared to enhance the phagocytic function and to inhibit the humoral component of the immune system. The results obtained from these preliminary studies show that, *A. heterophyllum* has immunomodulatory activity, which could possibly lead to new immunomodulating agents of herbal origin.<sup>[22]</sup>

### Action on the nervous system

Hamet showed that, *A. heterophyllum* has the ability to make the sympathetic nervous system more sensitive to physiological stimuli. He found that while atisine had a hypotensive effect at every tested dose, the plant extract as a whole showed hypertensive properties. Hypertension produced by high doses of aqueous extract was attributed to the excitement of the sympathetic nervous system.<sup>[22,23]</sup>

Two new diterpenoid alkaloids heterophyllinines A and B, isolated from the roots of *A. heterophyllum* were about 13 times more selective in inhibiting the enzyme butyrylcholinesterase than acetylcholinesterase. These enzymes are involved in the transmission of nerve impulses.<sup>[24]</sup>

### Anthelmintic activity

Aqueous and alcoholic extracts of tubers of *A. heterophyllum* gave encouraging results when evaluated against *Pheritema postuma* (earthworm), using piperazine citrate as standard. Time required for initial three paralytic attacks and death was used as parameters to evaluate the drug.<sup>[25]</sup> Though *Ativisha* is considered to have *kermihara* (anthelmintic) property as per Ayurveda, the results obtained here need to be compared with other standard Ayurvedic anthelmintic agents like *Vidanga* (*Emblia ribes*) to establish the utility of this drug in practice.

### Antihyperlipidemic activity

The methanolic extract of tubers of *A. heterophyllum* had a hypolipidemic effect on diet induced obese rats. It was observed that the pharmacological effect was due to two factors; (i) inhibition of Hydroxymethylglutarate-Coenzyme A reductase (HMGR) and (ii) activation of Lecithin-cholesterol acyltransferase. This resulted in lowering of total cholesterol, low-density lipoprotein cholesterol (LDL-c), triglycerides and apolipoprotein B in blood serum, decrease in intestinal fat absorption and increase of high-density lipoprotein cholesterol (HDL-c) and apolipoprotein A, supporting the classification of

*Ativisha* as a drug having “*lekaneeya*” (scraping) action with antihyperlipidemic properties.<sup>[26]</sup> It is worth mentioning here that, two common classes of compounds used in modern medicine to control hyperlipidemia are statins and fibrates. The former act on HMGR and the latter regulate HDL-LDL ratios. *A. heterophyllum* is active at both levels and hence could prove to be a valuable antihyperlipidemic agent.

### *Cyperus rotundus* L.

#### Use of *Cyperus rotundus* L. in Ayurveda and other traditional systems of medicine

*Musta* (*C. rotundus*) is widely used in Ayurveda. It has *katu* (pungent), *tikta* (bitter) and *kashaya* (astringent) taste; *laghu* (light) and *ruksba* (dry) properties; *sita* (cold) potency and *katu* (pungent) taste after digestion. It is *kapha-pittahara* (reduces *kapha* and *pitta dosha*), *dipana* (increases digestive fire), *pachana* (digests undigested material), *grahi* (water absorbing), *jvarahara* (antipyretic), *atisaraghna* (antidiarrhoeal) and *kanduhara* (antiitching).<sup>[1,2,7]</sup> The similarity of properties and activity between *Ativisha* and *Musta* as elucidated in Ayurveda is both unique and striking and forms the cornerstone of the concept of *abhava-pratinidhi dravya* in Ayurveda<sup>[3,4]</sup> [Table 1].

*Musta* is categorized as *lekhaneeya* (scraping action on body fat and *kapha*), *trishnanigravana* (alleviating morbid thirst), *kandughna* (reducing itch) and *stanyashodbhana* (clearing the problems of breast/breast milk).<sup>[1,7,13]</sup>

*Musta* is used extensively in the management of fevers, diarrhea, thirst, inflammation, tastelessness, helminthiasis, indigestion and obesity.<sup>[2,7,27,28]</sup> The commonly prescribed forms are powder, decoction and hot water infusion. It is also a component of formulations such as *Mustakadi Churna*, *Mustakarishhta*, *Mustakadikwatha*, *Ashokarishhta*, *Shadangananiya* and *Balachaturbhadra Churna*.<sup>[4,19]</sup>

Similar uses for *C. rotundus* are found in the Siddha system as well.<sup>[16]</sup> A review of the phyto-pharmacotherapeutics of *C. rotundus* has been published recently, detailing its uses in Ayurveda.<sup>[29]</sup>

*Cyperus rotundus* is also used extensively in traditional Chinese medicine. Its popularity in that system is evident from the over 500 patents issued in the past decade, governing its use in various formulations.

### Antidiarrhoeal activity

Daswani *et al.* examined the action of *C. rotundus* rhizome on adherence and enterotoxin production of 2 groups of enteropathogenic *E. coli*, and enterotoxigenic *E. coli* ETEC. The aqueous decoction did not affect the adherence; however, there was significant inhibition in labile toxin and stable toxin production. An important observation

was that there was an inverse correlation observed between stable toxin production and concentration of the decoction that is, maximum inhibition was seen at 1:1000 dilution.<sup>[30]</sup> Their results suggest that *C. rotundus* exhibits limited antibacterial/antiviral activity. *Musta's* antidiarrheal effect is probably due to the action on some feature of bacterial virulence such as colonization, production of cholera toxin or labile toxin rather than killing the bacteria.<sup>[31]</sup>

The antidiarrheal effect of the methanol extract of *C. rotundus* rhizome against castor oil induced diarrhea in mice was also established by Uddin. The methanol extract was found to significantly suppress the frequency of the diarrheal episodes as well as prolong the latent period for the onset of diarrhea when compared with standard drug loperamide. They, however, did not identify the active principles responsible for the activity.<sup>[32]</sup> The aqueous extracts also exhibited antidiarrheal activity in the same model.<sup>[17]</sup> *Musta* is a well-known *atisaraghna* (antidiarrheal) and *grahi* (absorbing/preventing water loss from the body) drug of Ayurveda. It is mentioned in *Nighantus* (lexicons) of Ayurveda that, it is increasing *agni* and thereby cure the problems of gastro intestinal tract.

#### Antiinflammatory activity

Biradar *et al.* studied the antiinflammatory, antiarthritic, analgesic and anticonvulsant (for treatment of epilepsy) effect of essential oils of *C. rotundus*. The antiinflammatory activity was determined using carrageenan-induced paw edema in Swiss albino rats. A dosage of 500 mg/kg was found to be comparable to the control (indomethacin 10 mg/kg). The aqueous, ethanol and ether extracts of *C. rotundus* showed good activity at 400 mg/kg with the ethanol extract exhibiting best inhibitory activity at 65.4%. These studies validate the use of *C. rotundus* as an antiinflammatory drug in traditional medicine.<sup>[33]</sup>

Tsoyi *et al.* have studied the role of heme oxygenase-1 (HO-1) in systemic inflammatory disorders such as sepsis. As part of their research to unearth potential HO-1 inducible agents from traditional medicinal herbs, they studied the extracts of *C. rotundus* rhizome, use of which is mentioned against inflammatory diseases. Their work on RAW264.7 cells led them to conclude that the antiinflammatory mechanism of the extracts of *C. rotundus* is due to HO-1 induction and inhibition of inducible nitric oxide synthase. They established that the sesquiterpenes (+)-nootkatone and (+)-valencene present in the extract were particularly active.<sup>[34]</sup>

Similar results were obtained by Korean investigators who observed that the hexane soluble portion of the hydro-alcoholic extract of *C. rotundus* inhibited nitric oxide formation induced by lipopolysaccharides in

RAW264.7 cells. Once again, sesquiterpenes were shown to be responsible for the activity.<sup>[35]</sup> The same authors also established that in the same cell line the sesquiterpene cyperone present in *C. rotundus*, inhibited lipopolysaccharide induced COX-2 expression and PGE-2 production through negative regulation of NF- $\kappa$ B signaling.<sup>[36]</sup>

The extracts of *C. rotundus* were tested in rodents for antiinflammatory, analgesic and antigenotoxic activity, and positive results were obtained in each case. The activities were attributed to the flavonoids, tannins and polyphenols present in the extract.<sup>[37]</sup>

The wide spectrum of antiinflammatory activity displayed by *C. rotundus* in the above mentioned examples establishes it as a useful drug in keeping with its role as a *shottha bara* (antiinflammatory) drug in traditional medicinal systems.

#### Antimicrobial activity

In 2004, antimicrobial studies were done using the essential oil of *C. rotundus* rhizomes prepared by hydro distillation. From the antimicrobial study, it was concluded that essential oil was active against gram positive micro-organisms but completely inactive against gram negative species, the test used being the disc agar diffusion method.<sup>[38]</sup> Similarly, sequential cold extraction of *C. rotundus* rhizomes was done by Sini *et al.* using hexane, chloroform and water and the extracts tested for antibacterial activity against *Bacillus pumilis* and *E. coli* by the disc diffusion method. The hexane and water extracts of *C. rotundus* showed inhibition against *B. pumilis* but not *E. coli*.<sup>[39]</sup>

*Streptococcus mutans* is known as the primary causative bacteria in the formation of dental plaque and dental caries. *S. mutans* multiplies in plaque and generates organic acids such as lactic, propionic, formic and butyric acids which demineralize the tooth surfaces and thereby induce dental caries. Studies by Yu *et al.* in 2007 showed that the ethanol extract of *C. rotundus* tubers repressed the growth of *S. mutans* and also inhibited the production of organic acids by the bacteria. Thus, it shows good anticariogenic properties.<sup>[40]</sup>

In their work on rhizomes of *C. rotundus* sourced from Tunisia, Kilani *et al.* reported on the antibacterial activity of the extracts against food related bacteria. The strains used were: *Staphylococcus aureus*, *Enterococcus faecalis*, *E. coli*, *Salmonella enteritidis*, and *Salmonella typhimurium*. Various levels of antibacterial effect were seen against all strains tested. The total oligomers flavonoids (TOFs) enriched extract was the most effective against *S. enteritidis* and *S. aureus*. The ethyl acetate extract showed remarkable activity against the gram positive bacteria *S. aureus* and *E. faecalis*.<sup>[41]</sup>

Antibacterial, antifungal and analgesic activities of ethanolic extract of *C. rotundus* rhizomes were reported by several authors.<sup>[42-44]</sup> Bisht *et al.* reported good activity of the oil as compared to the standard chloramphenicol especially against *Bacillus subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa*, while, on eight fold dilution, inhibition of *S. aureus* alone was seen. Good antifungal activity as compared to the standard drug nystatin was observed against *C. parapsilosis* and *A. fumigatus* while inhibition of spore formation was seen in *F. oxysporum* and *A. flavus*.<sup>[45]</sup> Similar results were also obtained by Biradar *et al.*, who showed that the essential oil of *C. rotundus* was active against *S. aureus*, *Staphylococcus albus*, *P. aeruginosa*, *E. coli*, *Candida albicans* and *Aspergillus niger*.<sup>[46]</sup>

Sharma and Singh examined the effect of various extracts of the rhizomes of *C. rotundus* in order to evaluate their antimicrobial activity. Different gram positive (*Staphylococcus epidermidis*, *Bacillus cereus*) and gram negative (*P. aeruginosa*, *E. coli*) bacteria along with fungal strains (*C. albicans*, *A. niger*) were used in this study. It was found that none of the extracts exhibited antifungal activity against the strains used. However, the ethanolic extract was found to be most effective against the gram positive as well as one of the gram negative (*P. aeruginosa* – nosocomial diarrhea causing agent) bacteria though it was ineffective against *E. coli*.<sup>[47]</sup>

Extracts of the aerial parts of *C. rotundus* showed antibacterial activity against *S. aureus*, *E. faecalis*, *Salmonella enteridis* and *S. typhimurium*.<sup>[48]</sup>

Essential oil of *C. rotundus* exhibited anthelmintic activity against *P. postuma* and *Ascaridia galli*.<sup>[49]</sup>

*C. rotundus* has a broad spectrum antimicrobial activity corresponding to its classification as a *krimihara* in Ayurveda. It is more effective against gram positive bacteria than gram negative species. In addition, it also displays antifungal and anthelmintic properties.

### Cytotoxic activity

The essential oil of *C. rotundus* obtained from the rhizomes by hydro distillation was also tested for cytotoxic activity against human tumor cell lines (U 251 and Hela), and Ehrlich ascites carcinoma cells. A positive result was obtained against Ehrlich ascites carcinoma cells with 100% inhibition at all concentrations tested. Negative results were seen when tested against human tumor cell lines.<sup>[38]</sup> However, the phytoconstituents responsible for this action was not recognized.

### Antioxidant activity

Several studies established the antioxidant potential of *Musta*. Using *in vitro* models Nagulendran *et al.* showed that *C. rotundus* hydro-alcoholic extracts exhibit free radical scavenging,

reducing power and metal chelating activity. Their study on the superoxide anion scavenging activity and hydroxyl radical scavenging activity gave good results namely IC<sub>50</sub> values of 0.031–0.021 mg/ml respectively. They did not, however, identify the constituents responsible for the activities.<sup>[49]</sup>

The TOF (total oligomeric flavonoids) and ethyl acetate extracts of *C. rotundus rhizomes* have strong antimutagenic and antigenotoxic activities. The same extracts are potent radical scavengers, display cytotoxic effects and induce apoptic DNA fragmentation.<sup>[50]</sup>

The antioxidant activity of the extract of *C. rotundus* has also been correlated to its anticataract activity.<sup>[51]</sup>

Several antioxidant assays such as xanthine oxidase inhibition, superoxide anion inhibition and protection against hydrogen peroxide/UV induced DNA damage were correlated with the ability of *C. rotundus* rhizome extracts to exert an antiproliferative effect toward K 562 erythroleukemia cells. Flavonoids were shown to be important for this activity.<sup>[52]</sup>

In their search for novel antioxidants, Dutta and Pal in 2006 investigated the rhizomes of *C. rotundus*. They carried out the evaluation by nonenzymatic glycosylation of hemoglobin measured colorimetrically and found that at concentrations of 1 mg/ml the extracts displayed inhibition with ethanol showing maximum activity at 35.3% followed by aqueous (14.1%), chloroform (12%) and petroleum ether (7.9%).<sup>[53]</sup>

Bashir *et al.* compared the activity of methanolic and ethanolic extracts of *C. rotundus* rhizomes. The percentage yield, as well as total phenolic and flavonoid content, were found to be more in roots followed by leaves and then stem. Furthermore, the methanolic extracts were found to be better in terms of activity and yield as compared to ethanolic extracts, suggesting that it is a better solvent for extraction. The tests used for determination of antioxidant activity were 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and inhibition of linoleic acid lipid peroxidation.<sup>[54]</sup>

It is well known that the presence of reactive oxidation species (ROS) causes a number of undesirable effects on the body including ischemia and reperfusion. The effect of this can be studied by the damage to the stomach tissues. In Turkey, Guldur and others studied the effect of the extracts of *C. rotundus* rhizomes on gastric mucosal damage induced in rats. They reported that the treatment with the extracts showed a significant decrease in the mucosal damage and suggested that the effective free radical scavenging activity of the *C. rotundus* extracts helped in the protection against damage caused by free radicals.<sup>[55]</sup>

Extracts of the aerial parts of *C. rotundus* reduced genotoxicity induced by nifuroxazide and aflatoxin B1.<sup>[48]</sup>

*C. rotundus*, therefore, has widely distributed antioxidant activity and its use for this purpose deserves more attention.

#### Antiallergic activity

Release of histamine and  $\beta$ -hexosaminidase by degranulation during an allergic reaction can be used as a biomarker of allergic response of mast cells. Furthermore, inhibition of 5-LOX (lipoxygenase) enzyme which produces the mediators of allergic reactions; leukotrienes (LT) can be used as a measure of antiallergic action. Jin *et al.* carried out *in vitro* tests for immediate-type hypersensitivity by inhibition of  $\beta$ -hexosaminidase and 5-LOX enzyme as well as *in vivo* study examining the delayed-type hypersensitivity (DTH). Jin worked on the ethanol extracts of *C. rotundus* rhizomes as well as isolated sesquiterpenes, monoterpenes and 4-cymene. In the case of 5-LOX inhibition, the extract inhibited LT production by 66–91% at 30–300  $\mu\text{g/ml}$ . At 100  $\mu\text{M}$ , the sesquiterpenes valencene, nootkatone and caryophyllene  $\alpha$ -oxide showed 60%, 93%, and 99% inhibition while the monoterpenes and 4-cymene did not show any effect. Furthermore, at the same concentration, valencene, nootkatone, and caryophyllene  $\alpha$ -oxide showed 88%, 44% and 28% inhibition of  $\beta$ -hexosaminidase while the monoterpenes and 4-cymene showed less than 15% inhibition. In the case of *in vivo* studies also, the sesquiterpenes showed the most significant activity.<sup>[56]</sup>

#### Activity on central nervous system

The first report on the central nervous system (CNS) activity of *C. rotundus* rhizome was by Pal, who studied the action of the extracts of this plant against different activities. Preliminary work showed that the ethanol extract displayed marked CNS depressant action compared to the other extracts. They studied the ethanol extract in detail including the chemical constituents. Toxicity study, effect on sleeping time and analgesic activity study using different models, were carried out. The results showed that the extract enhanced sleeping time, has analgesic and anticonvulsant activities and reduced different behavioral reflexes. The researchers thereby concluded that the extract exhibited strong CNS depressant action.<sup>[57]</sup>

Sunil *et al.* carried out a detailed investigation into the neuroprotective effects of the TOFs obtained from rhizomes of *C. rotundus*, a nootropic and nervine tonic according to traditional medicine. There was a significant improvement in excitotoxicity, oxidative stress, neurological, and behavioral alterations in male Sprague Dawley rats subjected to middle cerebral artery occlusion and reperfusion. These findings led the researchers to suggest

that TOFs should be studied further for development of drugs for the treatment of cerebral stroke.<sup>[58]</sup>

The ethanolic extract of *C. rotundus* rhizomes exhibited neuroprotective activity as shown by inhibition of peroxynitrite induced neurotoxicity in human neuroblastoma SH-SY5Y cells.<sup>[59]</sup> It was also reported to ameliorate hydrogen peroxide induced human neuronal cell damage via its antioxidative and antiapoptotic activity. High content of phenolics and flavonoids in rhizomes of *C. rotundus* is related to this activity. In this context, Kumar and Khanum also suggest the possibility to develop *C. rotundus* as preventive therapy against neurodegeneration.<sup>[60]</sup> The above research indicates that *C. rotundus* is a potent neuroprotective agent. Further research in this direction may bring out a herbal nootropic drug, which is the need of the hour.

#### Antiplatelet activity

Seo *et al.* in 2011 studied the antiplatelet effects of *C. rotundus* rhizome ethanolic extract as well as some of its components especially nootkatone. Their *in vitro* and *in vivo* studies showed that the extract inhibited platelet aggregation, thereby exhibiting antiplatelet activity. This was further confirmed by *in vivo* studies showing prolongation effects in bleeding time in rats. Of the different constituents examined, nootkatone in particular was found to inhibit platelet aggregation as well as prolong bleeding time in *in vivo* studies. The studies suggest that the extract and nootkatone in particular can be useful in the treatment of atherothrombotic diseases in which inhibition of platelet aggregation plays an important role.<sup>[61]</sup>

#### Antiobesity and the antihyperlipidemic activity

Ayurveda claim *Musta* to reduce muscle fat (*meda*). It has been categorized under *lekhaneeya gana* (group of drugs able to scrape off excess fat and *kapha*) in Caraka Samhita.<sup>[1]</sup> Studies using obese Zucker rats showed that supplementation of the diet with the hexane extracts of *C. rotundus* rhizomes at 220 mg/kg body weight reduced weight gain by 10%.<sup>[62]</sup> It was suggested that the effect was due to activation of the  $\beta$ 3-AR (adrenoreceptor) by the extract, supporting “*lekhaneeya*” property indicated in Ayurveda.

Raut *et al.* reported the antihyperglycemic effect of the hydro-alcoholic extract of *C. rotundus* rhizomes on alloxan induced hyperglycemia in rats. The results showed that the extract at a dosage of 500 mg/kg was as effective as metformin standard at 450 mg/kg.<sup>[63]</sup> Similarly, studies by Ardestani on advanced glycation end products formation as a result of persistent hyperglycemia showed that *C. rotundus* extracts have protein glycation inhibitory and antioxidant activity.<sup>[64]</sup>

The methanolic extract of *C. rotundus* rhizomes showed inhibitory activity against alpha-glucosidase and alpha-amylase, enzymes involved in carbohydrate digestion. Compounds responsible for the activity were identified as a new flavone, namely (2RS, 3SR)-3,4',5,6,7,8-hexahydroxyflavone as well as the known stilbene dimers cassigerol E and scirpusins A and B.<sup>[65]</sup>

*C. rotundus* has been mentioned as very effective in the treatment of lipid disorders that is, hyperlipidemia. Chandratre's research group has studied the lipid lowering activity of the aqueous as well as alcoholic extracts of the rhizomes of *C. rotundus* in rats. In acute toxicity studies, the two extracts were found to be safe up to a dosage of 2000 mg/kg. They found significant lowering of total cholesterol, triglyceride and low density lipoprotein levels in serum, although the effect on high density lipoprotein was found to be statistically insignificant. It was concluded that the studies validated the claims made in traditional medicine regarding the use of *C. rotundus* in hyperlipidemia although the specific constituents responsible for the activity were not identified.<sup>[66,67]</sup>

Ayurvedic literature including *brhattra* (Caraka, Susruta and Vagbhata samhita) and *nighantus* (lexicons) and practices use *Musta* as a *medohara* (antilipidemic) drug. The studies mentioned above support the traditional usage of *Musta* as a lipid lowering drug.

#### **Insecticidal and plasmodicidal activity**

The essential oil of *C. rotundus* showed ovicidal and larvicidal activities against *Aedes albopictus* (Skuse) (the "Asian tiger mosquito").<sup>[68]</sup> Similarly, Singh *et al.* in 2009 reported that the hexane extract of *C. rotundus* had repellent activity against three mosquito species (two malaria vectors and one filarial vector). It showed comparatively better activity than that of DEET (N, N diethyl- 3-methylbenzamide). Therefore, the extract can be an effective and safe personal protective measure against mosquito bites.<sup>[69]</sup>

The hexane extract of *C. rotundus* rhizomes also exhibited high potency against *Plasmodium falciparum*, a malarial parasite. Qualitative assessment of the antimalarial activity *in vitro* was determined by means of microculture radioisotope technique.<sup>[70]</sup>

The toxicity of different constituents of *C. rotundus* against the German cockroach *Blattella germanica* L was examined by Chang *et al.* in 2012. The encouraging results obtained suggest *C. rotundus* as a potential alternative to widely used synthetic insecticides.<sup>[71]</sup> Green insect repellants, safe for use in indoor environments are highly desired.

#### ***Cyperus scariosus* R. Br.**

*Cyperus scariosus* is known as *Nagaramusta* in Ayurveda. It is used in various traditional systems of medicine to cure fever, diarrhoea, thirst and burning sensation all over the body. The essential oil of *C. scariosus* has hypotensive, antiinflammatory, antimicrobial as well as CNS stimulating properties while the rhizome is used as a diuretic, stomachic and antidiarrheal.<sup>[27,72,73]</sup>

In Bangladesh, *C. scariosus* is used in tribal areas as a phytotherapeutic agent against dysentery, prompting Rahman *et al.* to investigate the ethanol extract of the rhizomes of this herb for antibacterial and cytotoxic activity. The petroleum ether extract showing high antimicrobial activity was subjected to fractionation using column chromatography. One of the fractions showing high antibacterial and high antifungal activity was subjected to various spectroscopic analyses, and a key compound was identified as longiverbenone, a sesquiterpene. Specifically, against *Vibrio cholerae* it showed minimum inhibitory concentration at 20 µg/ml and minimum bactericidal concentration at 80 µg/ml. In the brine shrimp assay for cytotoxic activity, the LC<sub>50</sub> of longiverbenone was found to be 14.38 µg/ml.<sup>[74]</sup>

Gupta *et al.* studied the antiinflammatory activity of the essential oil of *C. scariosus*. They used 3 different techniques in their studies: Carrageenan-induced edema, cotton-pellet granuloma pouch test and adjuvant-induced arthritis. The oil at 100 mg/kg, i.p., dose showed 66.2% inhibition in the carrageenan-induced edema study and significant inhibition of granulation tissue formation comparable to that of hydrocortisone in the cotton-pellet induced granuloma pouch test and also suppressed adjuvant-induced arthritis. Thus, the studies indicated that *C. scariosus* oil possesses potent antiinflammatory activity against the exudative and proliferative phases of inflammation.<sup>[75]</sup>

Hepatoprotective activity of the aqueous-methanolic extract of *C. scariosus* against acetaminophen and carbon tetrachloride induced liver damage in rats was studied by Gilani and Janbaz. They found that pretreatment of rats with the plant extract at a dosage of 500 mg/kg was able to restore to normal the serum levels of alkaline phosphatase, oxaloacetate transaminase and glutamate pyruvate transaminase and reduced morbidity by 70%.<sup>[76]</sup>

Bhagwat investigated the immune-modulation potential of the aqueous-alcoholic extract of rhizomes of *C. scariosus* and its therapeutic potential as an antiinflammatory agent. *C. scariosus* inhibited Th1 cytokines suggesting its immunosuppressive potential. This indicates its potential use as an antiinflammatory agent and also in the treatment of rheumatoid arthritis.<sup>[77]</sup>

The methanolic extract of *C. scariosus* leaves showed significant antinociceptive and antihyperglycemic activity. The antinociceptive activity was determined using the model of acetic acid induced gastric pain in mice. At a dose of 200 mg/kg the extracts gave results comparable to that of aspirin at the same dose. Antihyperglycemic activity determined through glucose tolerance test in mice showed that a dose of 400 mg/kg extract was as effective as 10 mg/kg of glibenclamide.<sup>[78]</sup>

*Cyperus scariosus* is not used as extensively as *C. rotundus* and deserves to be investigated in greater detail.

***Cryptocoryne spiralis* (Retz.) Fisch ex Wydler**

*Cryptocoryne spiralis* (Indian Ipecacuanha) is used widely in Sri Lanka as a traditional remedy for infantile vomiting and cough, and in adults for the treatment of abdominal complaints and fever.<sup>[27]</sup> However, a search of the literature has not revealed any studies carried out on the bioactivity of this plant. It is used as a substitute for Ipecacuanha

root in the treatment of dysentery.<sup>[79]</sup> Usually, larger doses of Ipecacuanha are administered in the case of drug intolerance, but only after alkaloids have been removed from the drug (de-emetised Ipecacuanha). *Cryptocoryne spiralis*, which does not contain emetine and cephaeline, is often used as a substitute. It is interesting to observe that *C. rotundus*, which is used in the treatment of diarrhea, contains only trace amount of alkaloids.

**DISCUSSION**

This review shows that both *A. heterophyllum* and *C. rotundus* have several similar pharmacological activities such as antiinflammatory, antipyretic, antibacterial and antidiarrheal. *C. scariosus* also possesses antiinflammatory and antibacterial activities.

Table 2 present the summary of the phytochemical and pharmacological activities of the reviewed species.

**Table 2: Summary of the reported phytochemical and pharmacological profiles of *Ativisha*, *Musta* and related species**

Parameter of comparison	<i>A. heterophyllum</i>	<i>Cryptocoryne spiralis</i>	<i>C. rotundus</i>	<i>C. scariosus</i>
Chief functional groups of chemical constituents				
Alkaloids	+	-	+	-
Terpenoids	+	-	+	+
Fatty acids and esters	-	+	-	-
Hydrocarbons	-	+	-	+
Glycosides	-	-	+	+
Phenolics and flavonoids	-	-	+	-
Keto-alcohol	-	-	+	-
Tannins and coumarins	-	-	+	-
Steroids	-	-	+	-
Chemical markers				
	Atisine	Ethyl 14-oxotetracosanoate	Cyperene	Cyperenone
	Hetisine	Hentriacontane	Mustakone	Cyperotundone
	Heteratisine		Nootkatone Rotundone α-cyperone	
Pharmacological activities and models used				
Anti-inflammatory	+	-	+	+
	Cotton pellet induced granuloma <sup>[18]</sup>		Carrageenan-induced paw edema in Swiss albino rats <sup>[33]</sup> RAW264.7 cell-lines <sup>[34-36]</sup>	Carrageenan-induced oedema, cotton-pellet granuloma pouch test and adjuvant-induced arthritis <sup>[75]</sup>
Antipyretic	+	-	+	-
	Yeast induced pyrexia in rats <sup>[80]</sup>		Yeast induced pyrexia in rats <sup>[29]</sup>	
Antibacterial	+	-	+	+
	Agar diffusion method <sup>[20]</sup>		Disc diffusion method <sup>[39-47]</sup>	Disc diffusion method <sup>[74]</sup>
Antifungal	-	-	+	+
			Disc diffusion method <sup>[45-47]</sup>	Disc diffusion method <sup>[74]</sup>

Table Contd...

**Table 2: Continued...**

Parameter of comparison	<i>A. heterophyllum</i>	<i>Cryptocoryne spiralis</i>	<i>C. rotundus</i>	<i>C. scariosus</i>
Immunological	+	-	-	-
	Delayed type hypersensitivity, humoral responses to sheep red blood cells, skin allograft rejection and phagocytic activity in mice <sup>[22]</sup>			
Anthelmintic	+	-	-	-
	Evaluated against <i>Pheritema postuma</i> (earthworm) <sup>[25]</sup>			
Hypolipidemic and Anti-obesity	+	-	+	-
	Diet induced obese rat <sup>[26]</sup>		Obese Zucker rats, <sup>[62]</sup> diet induced obesity in Wister albino rats <sup>[65-67]</sup>	
Antidiarrheal	+	-	+	-
	Castor oil induced diarrhea in mice <sup>[27]</sup>		Castor oil induced diarrhea in mice <sup>[27,32]</sup>	
Antigenotoxic	-	-	+	-
			Hydrogen peroxide/UV induced DNA damage in K 562 erythroleukemia cells, <sup>[52]</sup> nifuroxazide and aflatoxin B <sub>1</sub> induced genotoxicity <sup>[48]</sup>	
Cytotoxic	-	-	+	+
			Human tumor cell lines (U 251 and HeLa) and Ehrlich ascites carcinoma cells <sup>[39]</sup>	Brine shrimp assay <sup>[74]</sup>
Insecticidal	-	-	+	-
			Larvicidal against <i>Aedes albopictus</i> <sup>[68]</sup>	
Mosquito repellent	-	-	+	-
			Repellent of mosquito <sup>[70]</sup>	
Antimalarial	-	-	+	-
			<i>In vitro</i> microculture radioisotope technique <sup>[69]</sup>	
Toxicity against cockroach	-	-	+	-
			Repellent of <i>Blatella germanica</i> L <sup>[71]</sup>	
Antioxidant	-	-	+	-
			Anti-cataract activity, <sup>[51]</sup> nonenzymatic glycosylation of haemoglobin, <sup>[53]</sup> DPPH assay inhibition of linoleic acid lipid peroxidation, <sup>[54]</sup> gastric mucosal damage in rats <sup>[55]</sup>	
Antiallergic	-	-	+	-
			<i>In vitro</i> tests for immediate-type hypersensitivity by inhibition of β-hexosaminidase and 5 – LOX enzyme and <i>in vivo</i> DTH <sup>[56]</sup>	
CNS depressant	-	-	+	-
			Pentobarbitone sodium, diazepam, and meprobamate induced sleeping, and behavioral reflexes in mice <sup>[57]</sup>	
Neuroprotective	-	-	+	-
			Middle cerebral artery occlusion and reperfusion in Sprague Dawley rats, <sup>[58]</sup> peroxynitrite induced neurotoxicity in human neuroblastoma SH-SY5Y cells <sup>[59]</sup>	
Antiplatelet	-	-	+	-
			Platelet aggregation and bleeding time <sup>[61]</sup>	

Table Contd...

**Table 2: Continued...**

Parameter of comparison	<i>A. heterophyllum</i>	<i>Cryptocoryne spiralis</i>	<i>C. rotundus</i>	<i>C. scariosus</i>
Immune-suppression	-	-	-	+ Th1 cytokines suppression <sup>[77]</sup>
Antinociceptive	-	-	-	+ Acetic acid induced gastric pain in mice <sup>[78]</sup>
Anti-hyperglycemic	-	-	+ Alloxan induced hyperglycemia in rats <sup>[63]</sup>	+ Glucose tolerance test in mice <sup>[78]</sup>

+: Reported event; -: No reports available; *A. heterophyllum*: *Aconitum heterophyllum*; *C. rotundus*: *Cyperus rotundus*; *C. scariosus*: *Cyperus scariosus*; LOX: Lipoxygenase; DPPH: 1,1-di-phenyl-2-picrylhydrazyl; DTH: Delayed-type hypersensitivity

It is a well-known fact that alkaloids like morphine have antidiarrheal activity, and alkaloids may be the key constituents responsible for the activity in the case of *A. heterophyllum* as well. While modern studies have shown that *A. heterophyllum* has good antimicrobial activity against gram-negative bacteria (diarrhea causing), the same does not seem to be the case with gram positive and other microbes.

In *C. rotundus*, especially, the mode of action studies carried out suggest that its antidiarrheal activity may be due to the effect on cell adherence and toxin production rather than by antimicrobial. The alkaloids reported as present by Jeong<sup>[81]</sup> are in such miniscule amounts that it is very unlikely that they are wholly responsible for the antidiarrheal action of the plant. Not much work has been done on the remaining two species on the antidiarrheal activity thus leaving a big lacuna as far as our understanding of their mode of activity and scientific legitimacy of substitution.

Report of the presence of alkaloids in *C. rotundus* in 2000<sup>[81]</sup> was the first hint of any possible similarities in the constituents of the two species. However, no comparative studies have been reported bringing out any possible similarities between the plants except for the experimental work based on *abhava dravya* initiated by Venkatasubramanian *et al.* Phytochemical studies and preliminary HPLC showed some similarities in the constituents of *A. heterophyllum* and *C. rotundus*. They have also reported the antidiarrheal activity of both drugs.<sup>[17]</sup>

The fact that *C. rotundus* and *C. scariosus* belong to the same Cyperaceae family could account for their substitution along with the fact that just visual observation makes their differentiation difficult for the uninformed user. *Cryptocoryne spiralis* shows presence of tannins which are known to be used in the treatment of diarrhea. The prominent South Indian name *Naattu Athividayam* for *Cryptocoryne* hints at the possibility of a potential and genuine substitute for *A. heterophyllum*, which needs to be further supported with scientific studies.

Comparative studies between the four species are warranted to throw more clarity on any commonalities in the phytoconstituents and bioactivities of the four species. This could pave the way for understanding the concept of *abhava-pratinidhi dravya* and also help identify legitimate substitutes for unavailable species. It is indeed striking that despite differences in morphological, botanical, phytochemical details, there are similarities in Ayurvedic pharmacologic classification and bioactivities of *Ativisha* and *Musta* [Table 2].

## CONCLUSION

Identification of the substitute species appears to be mainly based on *dravya karmukatva* (pharmaco-dynamics) and *karma* (*pharmacological action*). There are striking similarities in the *rasa* (taste), *guna* (properties), *vipaka* (taste after digestion), *doshakarma* (action on *dosha*) and *rogaghната* (therapeutic indications) of *Ativisha* and *Musta* [Table 1]. The difference in their *veerya* (potency), do not seems to alter the therapeutic actions. This indicates that similar bioactivities could be obtained from unrelated species even when the chemical composition and botanical identities may not be the same. This way of classification of materials based on the biological effect on the body could be called as pharmaco-taxonomy or functional taxonomy.

Many questions remain unanswered since details are not available in Ayurvedic literature about the drug/substitute identification processes. E.g, in formulations like *chaturbhadra churna* that contain both the *abhava* (*Ativisha*) as well as the *pratinidhi* (*Musta*) *dravya*, it is not clear if it is permitted to use *Musta* alone in excess as a substitute for *Ativisha*. Systematic research on *abhava-pratinidhi dravya* is still in its fledgling stage. Probing deeper into the Ayurvedic way of classifying a drug can help understand the pharmaco-dynamics of drugs and also how to identify new drugs.

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