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An Update on Chemical Composition and Bioactivities of *Acorus* Species

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Abstract: Medicinal and pharmacological significance of the *Acorus* species is steadily increasing. Several species mainly *Acorus calamus*, *A. christophii*, *A. tatarinowii* and *A. gramineus* have been investigated for their chemical compositions and bioactivities. Perhaps, *A. calamus* has been most extensively studied plant among others. A number of active constituents from leaves, rhizomes and essential oils of *Acorus* spp. have been isolated and characterized. The major active constituents identified were α-and β-asarones and held responsible for most of the bioactivities of *Acorus* species. Besides, more new active constituents possessing important bioactive properties are being isolated and identified from *Acorus* spp. A number of reports published have documented many new useful bioactivities of *Acorus* spp. whole plant extract, leaves and rhizome extracts, essential oils and α- and β-asarones such as, anti-inflammatory/ immunosuppressive, anti-adipogenic, antimicrobial, fungicidal, insulin sensitizing/anti-diabetic, neuro-protective, wound healing, mitogenic, insecticidal, anthelmintic, allelopathic, antiepileptic, antispasmodic activities and inhibitor of acetylcholine esterase. In the present article we have discussed recently recognized many newer bioactivities and chemical composition of *Acorus* spp. This study would be very useful for those conducting researches on bioactivity screening in *Acorus* spp. and similar other less studied species of the plants.

Key words: *Acorus*, asarones, anti-inflammatory, anti-adipogenic, insulin sensitizing, neuroprotective

INTRODUCTION

The genus *Acorus* comprises 40 species, however, only few species like *Acorus calamus* (Linn.), *A. christophii A. tatarinowii* (Schott.) and *A. gramineus* (Solandin Ait.) have been investigated for their chemical composition and bioactivities. Perhaps, *A. calamus* has been most extensively investigated plant sp. among others. It is reported as a good source of active constituents possessing several useful bioactive properties. *Acorus calamus* (L.) commonly known as sweet flag is a native of Central Asia and Eastern Europe (Gilani *et al*., 2006). The plant grows worldwide wildly along swamps, rivers and lakes (Kim *et al*., 2009). It is widely used in traditional folk medicine of America and Indonesia for gastrointestinal disorders such as, colic pain, diarrhea and the radix in the therapy of diabetes (Gilani *et al*., 2006; Si *et al*., 2010). Also, *A. calamus* has been an integral part of Indian and Chinese systems of medicine for hundreds of years (Wu *et al*., 2009; Lee *et al*., 2011). The other species *A. gramineus* is native to eastern Asia and commonly known as Japanese sweet flag is an aquatic or wetland perennial plant with semi evergreen grass like foliage. It has narrow, 6 to 14 in (15-35.6 cm) glossy leaves and looks like thick, lush grass.

Many previous studies have reported chemical compositions and bioactivities of *A. calamus* whole plant, different parts like rhizome, leaves and essential oil obtained from steam-distillation of rhizome material (Namba, 1993; Wang *et al*., 1998). Reports have revealed that *A. calamus* rhizomes, roots and essential oils of rhizomes possess important bioactivities *viz*., antimicrobial (McGaw *et al*., 2002; Lee, 2005; Phongpaichit *et al*., 2005; Devi and Ganjewala, 2009), allelopathic (Nawamaki and Kuroyanagi, 1996), anticellular and immunosuppressive (McGaw *et al*., 2002). Essential oils of *A. calamus* have been reported to demonstrate antigonadal activities in insects (Mathur and Saxena, 1975; Koul *et al*., 1977a, b; Saxena *et al*., 1977; Schmidt and Streloke, 1994). Aromatic oils obtained by alcoholic extraction of the rhizome are used in the pharmaceutical and oenological industries (Du *et al*., 2008). Studies of chemical composition of *Acorus* spp. have revealed α- and β-asarones as the major active components in the extracts of different plant parts and essential oils (Raina *et al*., 2003; Venskutonis and Dagilyte, 2003; Lee *et al*., 2010; Geng *et al*., 2010). Some other constituents like caryophyllene, isoasarone, methyl isoeugenol and safrol present in lesser amounts have also been identified in the extracts of rhizomes and roots

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(Namba, 1993; Wang *et al*., 1998). Geng *et al*. (2010) have found that β-asarone showed beneficial effects in cognitive impairment associated disorders such as, Alzheimer's Disease (AD). The lectins found in the rhizomes of *A. calamus* and *A. gramineus* have mitogenic activity (Bains *et al*., 2005).

Until few years back the *Acorus* spp. comparatively less has been a studied species of the plant However, after realizing its pharmacology and medicinal significance a steadily increasing progress has been witnessed towards investigating chemical composition and bioactivities of this species and the present study discusses new developments on investigation of chemical compositions and bioactivity screening of *Acorus* spp. highlights its rapidly growing pharmacological and medicinal significance. The information complied in the present article have been derived from the analysis of the research articles and reports published on chemical composition and bioactivities of *Acorus* spp. during 2002-2011.

Chemical compositions: Chemical compositions of *Acurus* spp. mainly of *A. calamus* have been investigated thoroughly. Several studies and reviews have documented chemical compositions of *Accorus* spp. whole plant, plant parts viz., leaves and rhizomes as well as of essential oils of rhizomes. Du *et al*. (2008) have investigated chemical composition of *A. gramineus* leaves and rhizome and found that these materials were highly rich in methylchavicol (49%) which gives an unusual anisic odor, whereas chemical investigation of *A. christophii* leaf and rhizome have revealed β-asarone (43%) as the major compound. Twenty eight chemical constituents were identified in *A. calamus* rhizome tissues. Of the 28 compounds identified three were new sesquiterpenes (1 beta, 7 alpha (H)-cadinane-4 alpha, 6 alpha, 10 alpha-triol, 1 alpha, 5 beta-guaiane-10 alpha-O-ethyl-4 beta, 6 beta-diol and 6 beta, 7 beta (H)-cadinane-1 alpha, 4 alpha, 10 alpha-triol (Dong *et al*., 2010a). Dong *et al*. (2010b) have also reported the presence of two new sesquiterpenes, cadinane with a propan-2-ylidene in the ethanol extract of *A. calamus* rhizome tissues. Seven new compounds namely, 1-hydroxy-7, 9-guaiadien-8-one, calamenone, cis-asarone, chrysophanol, physcion, emodin, (+)-galbacin were isolated and identified in the petroleum ether fraction of ethanolic extract of *A. tatarinowii* (Zhu *et al*., 2010). Previously, two novel spiroalkaloids namely acortatarins A and B with a naturally unusual morpholine motif were reported from the rhizome of *A. tatarinowii* (Tong *et al*., 2010a). A cortatarins-A has potential of inhibiting reactive oxygen species production in high-glucose-stimulated mesangial cells in a dose-and time-dependent manner (Tong *et al*., 2010a). Another study by Tong *et al*. (2010b) has revealed the presence of a new cadinane-type sesquiterpenoid, tatarinowin-A, two phenylpropanoids, tatarinoids A and B and a trinorlignan, tatarinoid C along with other 15 known compounds in the *A. tatarinowii* rhizome tissue. Chemical structures of some of these compounds are presented in Fig. 1.

Important bioactivities

Anti-inflammatory and immunosuppressive activities: Anti-inflammatory properties of many plants species have been known for a long time. The fact that the plants and their products may be implicated in alleviating diseases *via* modulation of immune responses has directed researchers for screening of plants for anti-inflammatory properties. Several studies have recognized anti-inflammatory potential of *Acurus* spp. A study by Mehrotra *et al*. (2003) has revealed that ethanolic extract of *A. calamus* rhizome display anticellular and immunomodulatory properties. The extract inhibits proliferation of mitogen (phytohaemagglutinin; PHA) and antigen (purified protein derivative; PPD)-stimulated human Peripheral Blood Mononuclear Cells (PBMCs). Kim *et al*. (2009) have studied anti-inflammatory activity of *A. calamus* leaf extract and elucidated the mechanism of action of the extract using human keratinocyte HaCaT cells. The anti-inflammatory properties of the extract have been studied using RT-PCR, ELISA, immunoblotting and immunofluorescence staining techniques which revealed that *A. calamus* leaf extract inhibits the production of pro-inflammatory cytokines through multiple mechanisms (Kim *et al*., 2009).

Anti-adipogenic activity: Researchers investigating anti-adipogenic properties of *Accorus* spp. for past few years have found that *A. calamus* demonstrate hypolipidemic activity in rats (Parab and Mengi, 2002). The saponins found in ethanolic extract of *A. calamus* apparently have hypolipidemic properties. The water extract of *A. calamus* at high concentration have also demonstrated hypolipidemic activity (Parab and Mengi, 2002).

Ethanol extract devoid of β-asarone has been reported to enhance differentiation in adipocytes in mouse (Wu *et al*., 2007). Differentiations in adipocytes were measured as a function of triglyceroids and protein expression of the glucose transporter in adepocytes. The property of *A. calamus* to enhance differentiations in adipocytes is most likely very useful in the treatment of type 2 diabetes. Interestingly, β-asarone present in the

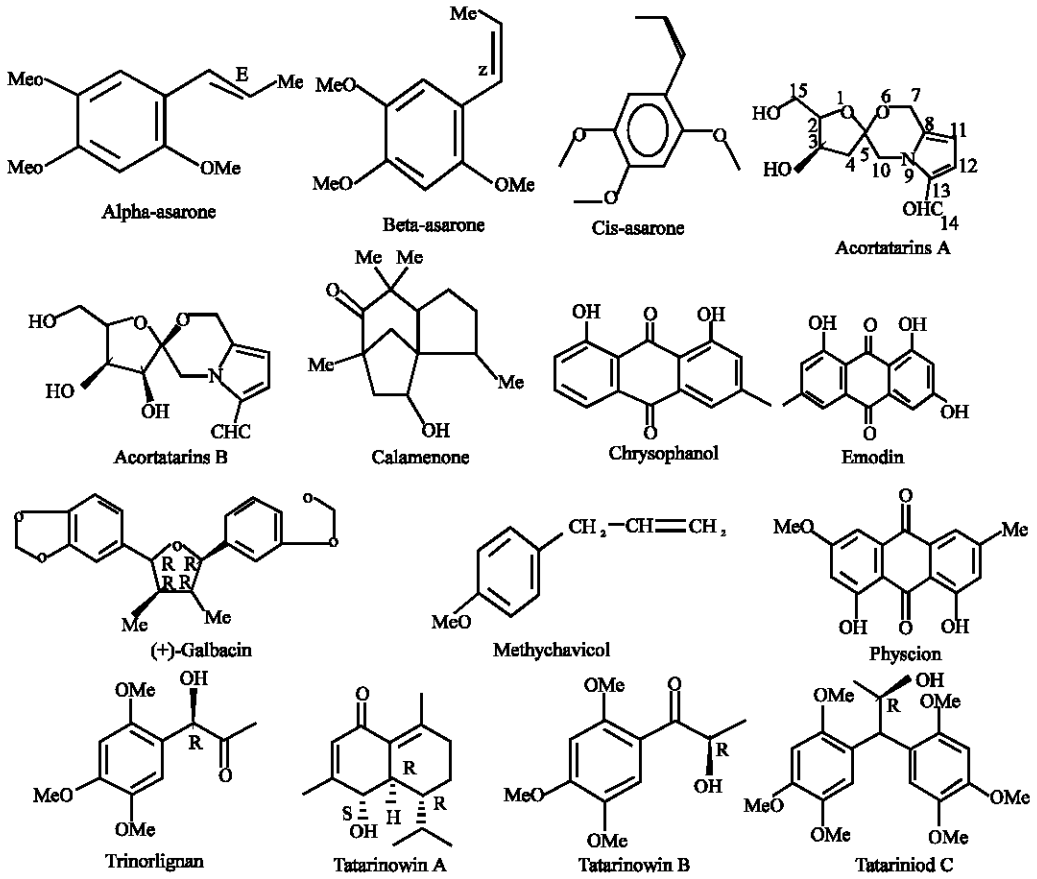

Fig. 1: Structures of some chemical constituents isolated from *Acorus* species

essential oil of *A. calamus* has shown inhibitory effect on adipogenesis in 3T3-L1 cells (Lee *et al*., 2011). As a plausible mechanism of action it has been suggested that β-asarone might have suppressed the expression of adipogenic transcription factors (Lee *et al*., 2011). Earlier, this group has reported that asarones from *A. calamus* have properties of inhibiting adipogenesis and stimulating lipolysis in 3T3-L1 adipocytes (Lee *et al*., 2010). Asarone tend to reduces intracellular triglyceride levels by stimulating the phosphorylation of hormone-sensitive lipase which triggers lipolysis in adipocytes.

Antimicrobial and fungicidal properties: Comparatively, antimicrobial properties of *Acorus* spp. have been studied in more detail. We have studied antibacterial and antifungal properties of petroleum ether, chloroform, hexane and ethyl acetate extract of leaf and rhizome tissues of *A. calamus* as well as commercial α- and β-asarone. Results of the study have shown that leaf and rhizome extract demonstrated marked antifungal activity but no antimicrobial activity observed except against *Escherichia coli* (Devi and Ganjewala, 2009). Moreover, commercial α- and β-asarones were found to be more effective than the leaf and rhizome extracts (Devi and Ganjewala, 2009). Anti-microbial properties of *A. calamus* leaf and rhizome extracts have been attributed to α- and β-asarone. Phongpaichit *et al.* (2005) have reported significant antimicrobial activity of crude methanolic extract of *A. calamus*. The active constituent β-asarone has also possessed antibacterial as well as anthelmintic properties (McGaw *et al*., 2002).

Lee *et al.* (2004) for the first time have reported that β-asarone (cis-2,4,5-trimethoxy-1-propenylbenzene) isolated from *A. gramineus* rhizomes demonstrated antifungal activity against phytopathogens like *Magnaporthe grisea* and *Cladosporium orbiculare*. Further, Lee (2007) has studied the fungicidal property of hexane extract of *A. gramineus* rhizome-derived materials against *Botrytis cineria*, *Erysiphe graminis*, *Phytophthora infestans*, *Puccinia recondita*, *Pyricularia grisea* and *Rhizoctonia solani* and found that β-asarone and asaronaldehyde present in rhizome has fungicidal properties against selected pathogens.

The plant of *A. calamus* biosynthesizes and accumulates haem peroxidase enzymes which serves as part of antifungal defense system during the pathogenesis (Ghosh, 2006). Their synthesis, however, is triggered by the pathogenesis. The haem peroxidase of *A. calamus* has been classified as class III peroxidase and it significantly inhibits growth of phytopathogens such as *M. phaseolina*, *Fusarium moniliforme* and *Trichosporium vesiculosum* (Ghosh, 2006). Later, this enzyme was isolated and purified from the leaf epidermal cells and lumen tissues of xylem. Several reports published previously have reported that a number of plant species synthesize and accumulate such types of enzymes/proteins to protect themselves from the attack of phytopathogens. At present, knowledge of synthesis and accumulation of the heam perxidase or similar proteins in other members of *Acorus* spp. is completely lacking. Therefore, future studies in this direction may provide further, details regarding the biosynthesis and regulation of defense enzymes/proteins and their mechanism of action in *Acorus* sp. during the pathogenic attack.

Insulin sensitizing/Antidiabetic activities: Recent studies have shown anti-diabetic potential of *Acorus* spp. For long time, the radix of *A. calamus* is being used in the therapy of diabetes in traditional folk medicine of America and Indonesia. A new study reports that *A. calamus* improves postprandial hyperglycemia and cardiovascular complications (Si *et al*., 2010). The study found that ethyl acetate fraction of *A. calamus* had insulin releasing and α-glucosidase inhibitory activities *in vitro* HTT-T15 cell line and *in vivo* fasted and glucose/amylum challenged normal mice (Si *et al*., 2010). Certainly, the hypoglycemic effects are due to insulin releasing and α-glucosidase inhibitory properties of *A. calamus* extract. Previously, Wu *et al.* (2009) have reported similar insulin sensitizing properties of ethyl acetate fraction of *A. calamus in vitro* and *in vivo*. Although these preliminary reports have clearly indicated the potential of *A. calamus* for its application in the treatment of diabetes and cardiovascular complications, more research efforts needed for the investigation of other members of the species for their anti-diabetic or insulin sensitizing properties and elucidation of exact mechanism of action.

Protective effects: Protective roles of *Acorus* spp. have been studied against free radicals and other Reactive Oxygen Species (ROS). The protective effects of *Acorus* spp. have augmented its implication in neurodegenerative diseases. *A. calamus* leaves and rhizomes are already known for a long time to be used for the treatment of various neurological disorders. Commercial asarones as well as those isolated from *A. gramineus* have been evaluated for their neuroprotective properties and their mechanism of action in the primary cultured rat cortical cells (Cho *et al*., 2002). Commercially obtained α- and β-asarone and asarone isolated have been found to inhibit the excitotoxicity induced by the N-Methyl-D-Aspartate (NMDA) in primary cortical cultures but the commercial α- and β-asarone exhibited more potent inhibitions of the NMDA-induced excitotoxicity. Furthermore, the excitotoxicity induced by glutamate has also been inhibited, but with much less potency than the toxicity induced by NMDA (Cho *et al*., 2002). The study based on the receptor-ligand binding using a use-dependent NMDA receptor-channel blocker [^{3}H]MK-801 revealed that asarone inhibited the specific bindings in a concentration-dependent fashion (Cho *et al*., 2002). Asarone exhibited neuroprotective action against the NMDA- or Glu-induced excitotoxicity through the blockade of NMDA receptor function. *Acorus calamus* rhizome extract prepared with ethanol:water (1:1) has demonstrated neuroprotective effects in the middle cerebral artery occlusion-induced ischaemia in rats (Shukla *et al*., 2006). Application of *A. calamus* rhizome extract has resulted in a significant improvement in neurobehavioural performances such as, rota-rod performance and grid walking in the experimental rats.

Free radicals and other ROS have been recognized as an important causative factor in the development of neurodegenerative disorders. In the past several years, a number of reports have been published revealing antioxidant potential of many medicinal plants which has been implicated in minimizing harmful effects of free radicals. Several research groups have evaluated antioxidant potential of plants of *Acosrus* spp. and validated their protective roles in free radical and ROS generated disorders. In our recently published study we have reported antioxidant activities of methanolic extract of *A. calamus* leaves and rhizomes (Devi and Ganjwala, 2011). The properties of scavenging free radical of *A. calamus* has been found to be useful to overcome excess production of oxygen free radicals generated due to continuous exposure to loud noise which pose a serious health problem (Manikandan and Devi, 2005). Protective effect of ethyl acetate and methanolic extract of *A. calamus* against noise stress induced changes in the rat brain have also been reported (Manikandan *et al*., 2005). These extracts have protected most of the changes induced by noise-stress in the rat brain. The protective effects were substantiated by measurement of the activities of enzymes superoxide dismutase, catalase, glutathione peroxidase, reduced glutathione as well as the level of vitamin C, E, protein thiols and lipid peroxidation

(Manikandan *et al*., 2005). The antioxidant property of β-asarone found in *A. calamus* is believed to be responsible for counteracting the stress in the rat brain due to continuous exposure to noise. Though these studies have favored implication of β-asarone against noise-stress induced changes perhaps further studies involving clinical trials would be required for validation of efficacy of β-asarone in noisy environment in human subjects (Manikandan *et al*., 2005). A study by Hazra *et al.* (2007) has revealed that *A. calamus* helped preventing the development of ferric chloride-induced epileptogenesis in rats by modulating antioxidant enzymes. Thus, this property of *A. calamus* could be exploited for the development of an effective anti-epileptic drug in future.

A recent study has provided preliminary insight into the radioprotecting potential of *A. calamus* (Sandeep and Nair, 2010). The study *in vitro* carried out has shown that extract of *A. calamus* safeguarded DNA and membrane damages in murine cells and human peripheral blood leukocytes caused due to γ-radiation (Sandeep and Nair, 2010). The radioprotective effects were evaluated by measuring the degree of lipid peroxidation caused using thiobarbituric acid reacting substances. *In vitro* DNA damage was measured by assessing the radiation induced relaxation of supercoiled plasmid DNA (pBR322) whereas alkaline single cell gel electrophoresis or comet assay was used to monitor any damage to cellular DNA induced by γ-radiation (Sandeep and Nair, 2010). The properties of *A. calamus* extract scavenging free radicals have been attributed for radioprotective effects studied.

Extract of *A. calamus* has also displayed protective effects on nickel chloride induced renal oxidative stress, toxicity and cell proliferation response in male Wistar rats (Prasad *et al*., 2006). Nickel, is a major environmental pollutant known for its clastogenic, toxic and carcinogenic properties. Beside protective roles of *A. calamus* against nickel chloride induced renal oxidative stress, the rhizome extract of *A. calamus* are reported to have protective roles against acrylamide induced neurotoxicity in rats (Shukla *et al*., 2002).

In recent years search for new drugs for Alzheimer's disease from medicinal plants has been rapidly increased. In this context several research groups are investigating *Acorus* spp. Geng *et al.* (2010) have published first report describing anti-Alzheimer's potential of the β-asarone isolated from *A. tatarinowii*. Their study revealed that the β-asarone suppressed neuronal apoptosis in the β-amyloid hippocampus injection rats (Geng *et al*., 2010). They also studied the mechanism of action of β-asarone which indicated that β-asarone attenuates β-amino acid peptide (1-42 amino acid long) induced neuronal apoptosis in hippocampus by reversal down-regulation of Bcl-2, Bcl-w, caspase-3 activation and c-Jun N-terminal kinase phosphorylation (Geng *et al*., 2010).

Other useful bioactivities: The list of important bioactivities of the *Acorus* spp. is steadily increasing. In this section we have discussed several important but less studied bioactivities of *Acorus* species. Interestingly, pharmacological as well as ecological significance of *A. calamus* and its active chemical constituent α- and β-asarone and essential oil obtained from rhizomes have been impressively increased in the past few years. Ethanolic extracts of *A. calamus* leaves possess wound-healing activity in an excision and incision-based wound model in both male and female rats (Jain *et al*., 2010). Treatment of wound in male and female rats induced by an excision and incision with ethanolic extract has been found to be promising for healing. Novel lectins isolated from the rhizomes of *A. calamus* and *A. gramineus* have shown potent mitogenic activity towards mouse splenocytes and human lymphocytes whereas inhibitory activities towards murine cancer cell lines (Bains *et al*., 2005). These lectins have molecular weight 55-56 kDa and stable up to 55°C. They did not require metal ions for their activity however affected by high concentrations of denaturants like urea, thiourea and guanidine hydrochloric acid (Bains *et al*., 2005).

Park *et al.* (2003) have studied insecticidal activities of asarones present in *A. gramineus* rhizome against three stored product pests *Sitophilus oryzae*, *Callosobruchus chinensis* and *Lasioderma serricorne*. Two research groups have documented allelopathic activities of *A. tatarinowii* and *A. calamus* on algae and water-bloom forming algal species (He and Wang, 2001; Hu *et al*., 2009a). The root system of *A. tatarinowii* excretes some chemical substances which arrest the algal growth. These substances tend to destroy some chlorophyll-A molecules thereby inhibit photosynthesis in algae. Their effects on algae were dose dependent; at low concentration they promoted algal growth whereas at high concentration they inhibited the algal growth (He and Wang, 2001). Water extracts of *A. calamus* has also demonstrated allelopathic effects on the growth of two water bloom-forming algal species *Microcystis aeruginosa* and *Chlorella pyrenoidosa* (Hu *et al*., 2009a). Shah and Gilani (2009) based on their findings that *A. calamus* extract has properties of lowering blood pressure and vascular modulator mediated through multiple pathways have suggested their application for the treatment of cardiovascular disorders. Essential oil of *A. calamus* rhizome is reported to cause injuries to Plasmatocytes (Pls) and Granular hemocytes (GRs) and affects the hemogram of the tobacco armyworm, *Spodoptera litura* (Sharma *et al*., 2008). A study has

shown beneficial effects of *A. tatarinowii* on ultra structure and permeability of blood-brain barrier in rats (Hu *et al*., 2009b) while another study has reported its antiepileptic effect (Liao *et al*., 2005). The rhizome extract and volatile oil of *A. tatarinowii* display anticonvulsive effects in pentylenetetrazol kindling models. Also, both extracts prevents convulsion-related GABAergic neuron damage in the brain in the prolonged pentylenetetrazol kindling model (Liao *et al*., 2005). The essential oil of *A. calamus* and its major constituent β-asarone has been found to inhibit activity of acetylcholine esterase (Mukherjee *et al*., 2007). Extract of *A. calamus* contains chemical constituents with properties to block calcium channel which has been held responsible for spasmolytic activity (Gilani *et al*., 2006). Crude extract and ethyl acetate and n-hexane fractions of the extract have been evaluated for spasmolytic effects in the isolated rabbit jejunum preparation (Gilani *et al*., 2006).

In recent times usefulness of *A. calamus* extract has been tested to develop environment friendly control measures. A study by Ghosh *et al*. (2010) has highlighted the efficacy of *A. calamus* extract against cattle tick *Rhipicephalus microplus*. They have tested large number of extracts prepared with ethanol, hydroethanol and hot water against the cattle tick (Ghosh *et al*., 2010). These extract have been found to be safe and did not show any reaction in animals treated even with 50% of the concentration.

CONCLUSION

In the present study, we have discussed the chemical composition and bioactivities of less studied *Acorus* spp. However, several recently published reports on bioactive potential of the *Acorus* spp. have indicated their rising pharmacological and medicinal significance. The genus *Acorus* comprises 40 species but only 3-4 species, *A. calamus*, *A. christophii*, *A. tatarinowii* and *A. gramineus* have been considerably investigated for their chemical composition and bioactivities. In the past few years many promising bioactivities such as, anti-inflammatory/immunosuppressive, anti-adipogenic, antimicrobial, fungicidal, insulin sensitizing/antidiabetic, neuroprotective of *Acorus* spp. plants have been reported. The most striking activity realized is anti-Alzheimer's of β-asarone from *A. tatarinowii*. Also, for the first time bioactive potential of *Acorus* species as wound healing, mitogenic, insecticidal, anthelmintic, allelopathic, antiepileptic, antispasmodic and inhibitor ofacetylcholinesterase have been realized. Of course it is due to these bioactive properties pharmacological and medicinal significance of *Acorus* species is gradually increasing. Perhaps, thorough studies involving clinical trials in human subject remains to be performed. Therefore, these are high times for investigations of chemical composition and bioactivities of unexplored plants of the *Acorus* and devote more efforts towards understanding the mechanism of action of bioactive constituents present therein.

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