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Der Pharmacia Sinica, 2011, 2 (2): 1-10

Der Pharmacia Sinica

ISSN: 0976-8688
CODEN (USA): PSHIBD

Ajuga bracteosa wall: A review on its ethnopharmacological and phytochemical studies

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ABSTRACT

The aim of the study is an attempt to investigate out Phytochemical and ethnopharmacological application of Ajuga bracteosa wall benth. to treat cancer, diabetes, gastrointestinal disorders, worm infestations, urinary disorders , fungal infections, inflammation and tuberculosis in folk medicines. Data was collected from various internet websites and libraries of Council of Scientific and Industrial Research Institutes as CIMAP (Central Institutes of Medicinal and aromatic plant) Lucknow, CDRI (Central Drug Research Institute) Lucknow, NBRI (National Botanical Research Institute) Lucknow, NML (National Medical Library) New Delhi and Pharmacy Department, GGDU, Bilaspur, India. Various plant parts such as leaves, bark, stem and roots of Ajuga bracteosa have been used in ethno medicine to exploit its medicinal properties including astringent, hypoglycemia, gastrointestinal disorders, as anthelmintic, diuretic, antifungal, anti-inflammatory and antimycobacterial agents. Chemical compounds isolated from Ajuga bracteosa wall Ex. Benth have been proven to be pharmacological active against several major diseases including cancer, hypoglycemia and protozoal diseases. Preclinical studies indicate the therapeutic potential of crude extracts of Ajuga bracteosa wall Ex. Benth in the treatment of many microbial diseases, spasmodic activity and gastric ulcer. This review covers the pharmacological activities of some isolated chemical constituents of Ajuga bracteosa and preclinical studies on some crude extracts and pure compounds to explore novel bioactive compounds for therapeutic application.

Keywords: *Ajuga bracteosa*, Anticancer, Hypoglycemic activity, Antifungal, Antimalarial.

INTRODUCTION

Recently there has been a shift in universal trend from synthetic to herbal medicine, which we can say ‘Return to Nature’. Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. Nature has bestowed our country with an enormous wealth of medicinal plants;

therefore India has often been referred to as the Medicinal Garden of the world. Countries with ancient civilizations such as China, India, South America, Egypt, etc. are still using several plant remedies for various conditions. In this regard India has a unique position in the world, where a number of recognized indigenous systems of medicine viz., Ayurveda, Siddha, Unani, Homeopathy, Yoga and Naturopathy are being utilized for the health care of people. No doubts that the herbal drugs are popular among rural and urban community of India. The one reason for the popularity and acceptability is belief that all natural products are safe. The demand for plant based medicines, health products, pharmaceuticals, food supplement, cosmetics etc are increasing in both developing and developed countries, due to the growing recognition that the natural products are non-toxic, have less side effects and easily available at affordable prices [1].

World Health Organization (WHO) defines The World Health Organization (WHO) estimates that 4 billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care and WHO notes that of 119 plant-derived pharmaceutical medicines, about 74 percent are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures [2].

Ajuga bracteosa Wall Ex. Benth (Neelkanthi) is another Indian herbal plant, which has enormous traditional uses and also in Ayurvedic prepration. *Ajuga bracteosa* is perennial family (Labiatae), erect or ascending hairy herb, often prostrate with oblanceolate or sub-spathulate. Flowers are white or purplish-violet tinged from lower surface in distant, axillary whorls in spike. Its allied species *A. parviflora* is also found sporadically [3].

The genus *Ajuga* consists of about 40- 50 species. *A. bracteosa* is distributed in subtropical and temperate regions from Kashmir to Bhutan, Pakistan, Afghanistan, China and Malaysia. In Pakistan it is found in northern hilly areas, where in local Hindko/Punjabi language it is called *kori booti* owing to its bitter taste [4]. Many compounds including γ-sitosterol, β-sitosterol, triacontanyl docosanoate and tetracosanoic acid have been isolated from aerial part [5]. Other constituents like phenolic components, bitter components, arabinose, cerotic acid, palmitic acid along with glucosidic constituents, D-glucosideand anthocynidin-glucosides have been found [6].

Various crude extracts of this plant have shown activities including antidiabetic, antioxidant, antibacterial, diuretic, stimulant [7], astringent, rheumatism, febrifuge, blood purifier effects [8] on various animal models. All the compounds present in the extracts responsible for these activities have not been identified so far. Therefore, in this article, a brief but all encompassing discussion has been presented on the bioactive compounds isolated from this plant, their pharmacological activities and preclinical studies.

This article will enhance the existing knowledge of the *Ajuga bracteosa wall Ex. Benth*, and also create the awareness of possible new therapeutic uses for the development of pharmaceutical entities or dietary adjuncts for better health care in the future.

1. Phytochemical investigations

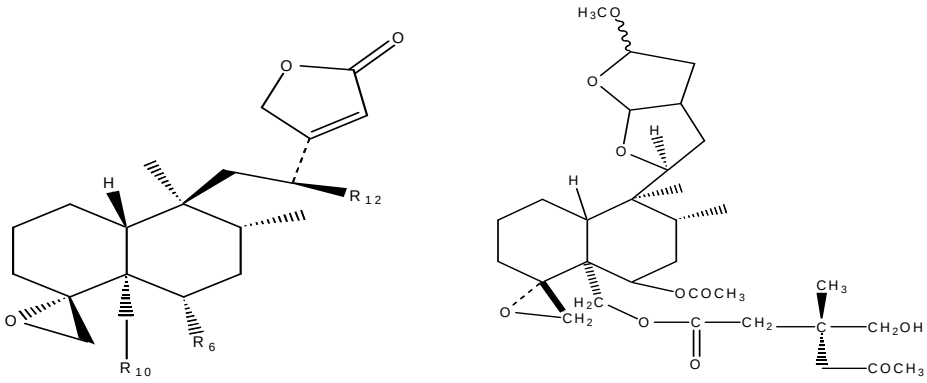
A large number of compounds have been isolated from various species of the *Ajuga* herb and few of them have been studied.

Table 1 Bioactive compounds (steroids) isolated from genus Ajuga species

Name of compounds	Name of source	Ref. no
Ecdysone	*A.reptanse*	9
20-hydroxyecdysterone	*A. reptanse*	9
Polypodine	*A. reptanse*	9
Cyasterone	*A. reptanse*	9
29-Norcyasterone	*A. reptanse*	9
29-Norsengosterone	*A. reptanse*	9
Ajugalactone	*A. reptanse*	9
Ponosterone	*A.japonica*	10
Ajugasterone C	*A. japonica*	10
Makisterone	*A. japonica*	10
Makisterone D	*A. japonica*	11
Ajugasterone-B	*A.incisa*	11
Ajugasterone tetracetate	*A. incisa*	11
Beta-sitosterol	*A.bracteosa*	12,13
y-sitosterol	*A.bracteosa*	12,13
Turkesterone	*A.turkistanica*	14
Ecdysterone	*A.decumbanse*	15
Makisterone-A	*A.decumbanse*	16
22-oxocyasterone	*A.decumbens*	17
Sengosterone	*A.reptanse, A.incisa*	18
Ajugasterone-A	*A.reptanse, A.incisa*	18
Ajugasterone-D	*A.reptanse, A.incisa*	18
Cyasterone	*A.turkistanica*	19

Chemical Stucture

1. *neo*-Clerodane diterpenoids

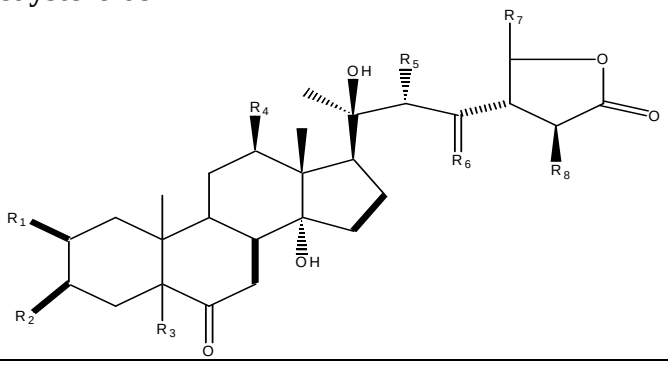


Bracteonin A

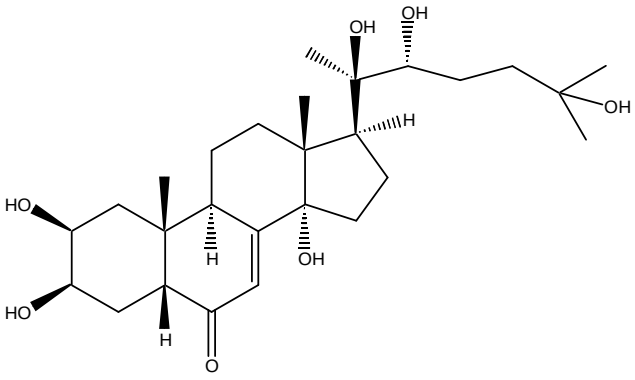
Compound	R6	R12	R19
Ajugarin I	OAc	H	OAc
Ajugarin II	OH	H	OAc
Ajugarin V	OAc	H	H

Ac = acetyl

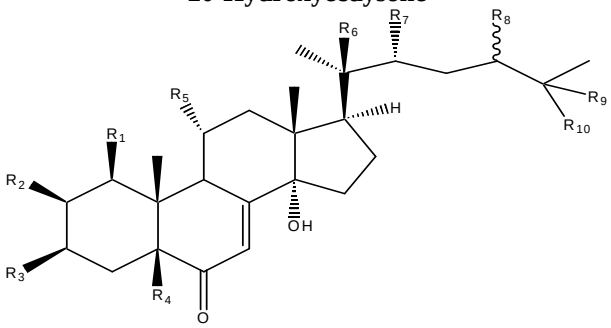
2. Phytoecdysteroids



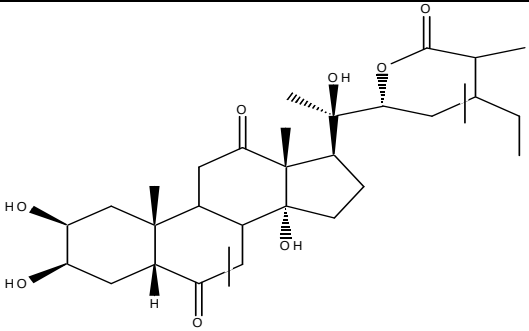
Phytoecdysteroid	R1	R2	R3	R4	R5	R6	R7	R8
Cyasterone	OH	OH	H	H	OH	H	CH3	CH3
Cyasterone-22-OAc	OH	OH	H	H	OAc	H	CH3	CH3
3-Epicyasterone	OH	OH (α)	H	H	OH	H	CH3	CH3



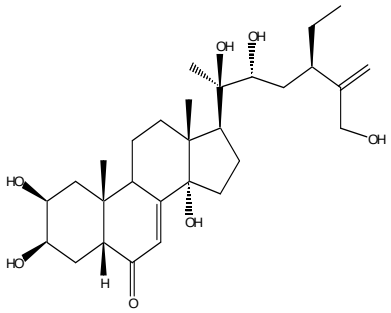
20-Hydroxyecdysone



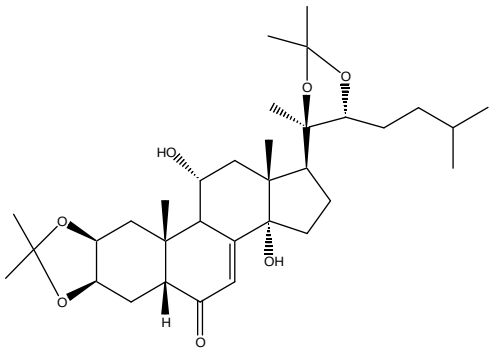
Phytoecdysteroid	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10
Ajugasterone A	H	OH	OH	OH	H	OH	OH	H	OH	CH3
Ajugasterone B	H	OH	OH	H	H	OH	OH	CH2CH3	CH2OH	C=CH2
Ajugasterone C	H	OH	OH	H	OH	OH	OH	H	H	CH3



Ajugalactone

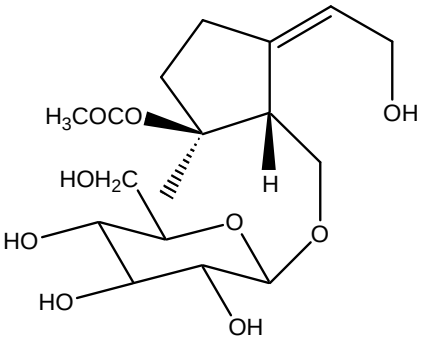


Ajugasterone B

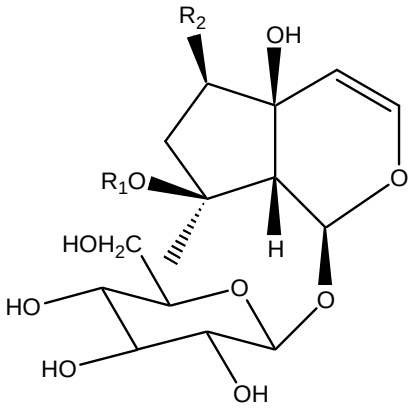


Ajugasterone C

3. Iridoid glycosides



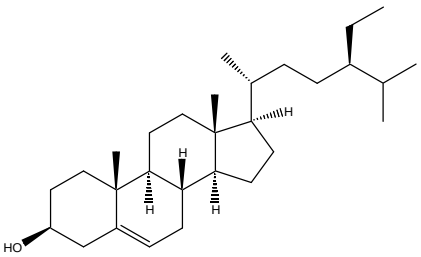
Str-1



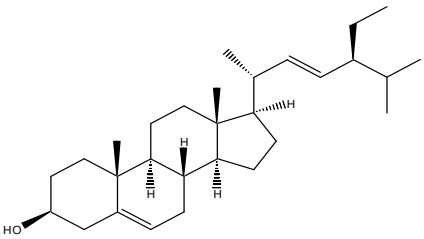
Str-2,3,4

1. Ajureptoside
2. Reptoside; R_1=Ac,R_2=H
3. Herpagide; R_1=H,R_2=OH
4. 8-acetylherpagide; R_1=Ac,R_2=OH

3. Sterols

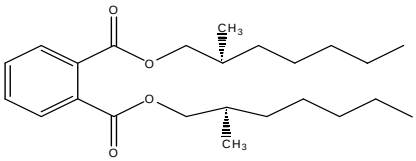


β-Sitosterol

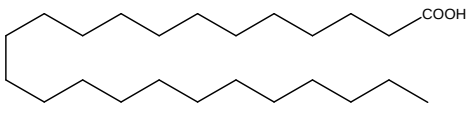


Stigmasterol

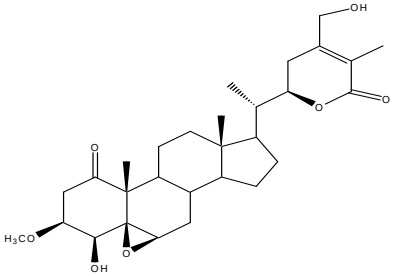
Withanolides



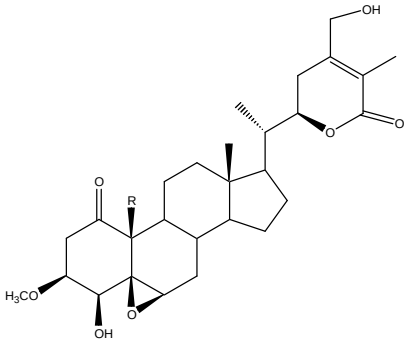
Phthalic acid ester



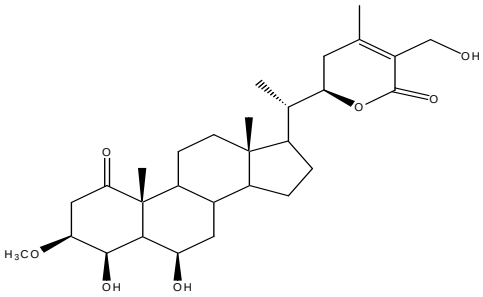
Lignoceric acid



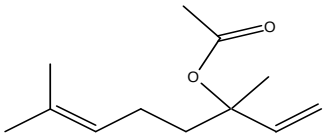
Bracteosin A



Bracteosin B; R=COOH



Bracteosin C



Linalyl acetate11, 21-28

2.1. Leaf

Several compounds such as glycoside, tannin, ceryl alcohol, cerotic acid, have been isolated from *Ajuga bracteosa* leaves. The aqueous extract of leaves shows diuretic, stimulant action, aperient and febrifugal [20]. The presence of alkaloids, flavonoids, steroids, triterpenoids, saponins and tannins like phenolic compounds. Although mechanism of action of these secondary metabolites has not been evaluated in the present study, some of these metabolites have been found to exert their antiplasmodial effect against plasmodium berghei, either by elevating red blood cell oxidation or by inhibiting protein synthesis [21]. A decoction of the leaves of the herb is used in the traditional medicine for a number of diseases including diabetes, hypertension, fever, malaria and stomach pain [22].

2.2. Bark

Among the important bioactive compounds isolated from bark is a clerodane diterpenoid. The bark after decoction is useful for curing jaundice and sore throat in experimental animal model [23].

2.3. Root

The bioactive compounds isolated from *Ajuga bracteosa* are steroids, palmitic acid and heptacos-3-en-25-one [24]. The roots of *Ajuga bracteosa* contains comparatively larger amounts of chromium (leaves 25 mg and roots 20 mg per 100 g) which may be correlated to its use as remedy for diabetes. The considerably larger amounts of potassium (leaves 139 mg, roots 159 mg per 100 g) than sodium (leaves 21 mg, roots 29 mg per 100 g) may have some correlation with the use of the herb in hypertension [25].

2.4. Whole plant

Crude extracts from multiple parts of the *Ajuga bracteosa* plant are used to treat various disorders in different Indian traditional systems. The whole plant of Ajuga bracteosa afforded five compounds including one new clerodane diterpenoid designated as Bracteonin-A (1) 6alpha-acetoxy, 15 (R&S)-methoxy, 18-(4'-hydroxy, 3'-beta-methyl, 3'-alpha-acetoxy, butyryloxy) neoclerodane. The other compounds identified were 14, 15-dihydroajugapitin, 14-hydro-15-

hydroxy ajugapitin, beta-sitosterol, and stigmasterol [26]. Bractin A (¼(2S,3S,4R,5E)-2-{[(2R)-2-hydroxydodecanoyl]amino}triacont-5-ene-1,3,4-triol; **1**) and bractin B (¼(2S,3S,4R,5E,8E)-2-{[(2R)-2-hydroxyhexacosanoyl]amino}pentadeca-5,8-diene-3,4,15-triol-1-O-b-glucopyranoside; **2**), new sphingolipids, and bractic acid (¼(5Z,10Z,15Z)-2-decyl-4,7,8,12,13,17,18-heptahydroxy-20,23-dioxopentacosa-5,10,15-trienoic acid; **3**), a long-chain polyhydroxy-acid, were isolated from the whole plant *Ajuga bracteosa*. Compounds **1–3** displayed inhibitory potential against enzyme lipoxygenase Lipoxygenases (LOX; EC 1.13.11.12) constitute a family of non-heme ironcontaining dioxygenases that are widely distributed in animals and plants. It has been found that these LOX products play a role in a variety of disorders such as bronchial asthma, inflammation [27] and tumor angiogenesis [28]. LOXs are, therefore, a potential target for the rational drug design and discovery of mechanism-based inhibitors for the treatment of bronchial asthma, inflammation, cancer, and autoimmune diseases. Compounds 1 – 3 showed significant inhibitory activity against LOX with IC50 values ranging between 10.0 and 33.0 mm. Cholinesterase enzymes are implicated as key biological players in AlzheimerLs disease (AD), which makes them logical targets for inhibitory therapeutics. The most important and well-documented function of acetylcholinesterase (ACHE) is the hydrolysis of the neurotransmitter acetylcholine [29]. According to the cholinergic hypothesis, the memory impairment in the patients with senile dementia of Alzheimer's type results from a deficiency in cholinergic function in the brain [30]and the whole plant is used Internal colic, pimples [31].

3. Pharmacological activity

3.2. Hypoglycemic activity

In order to rationalize its medicinal applications and establish biogeochemical link, the mineral elements (Na, K, Ca, Mg, Zn, Mn, Cu, Fe and Cr) of leaves and roots of *Ajuga bracteosa* and the nearby soil were studied. The herb contains comparatively larger amounts of chromium (leaves 25 mg and roots 20 mg per 100 g) which may be correlated to its use as remedy for diabetes as per Ahmed et al. Chromium is another essential mineral that human require in trace amounts. It is an important component of many body building strategies to and in the development of lean muscle mass, as well as in the treatment of diabetes and for weight loss. Chromium increases the metabolism of proteins, fats and carbohydrates. Significantly, it enhances the efficiency of insulin to regulate blood sugar levels [32-34].

3.3. Antihypertensive activity

Hypertension is the most common cardiovascular disorder which has a major contribution in coronary artery disese, heart failure, renal- insufficiency, stroke and dissecting aneurysm of the aorta. The Renin-angiotensin system (RAS) plays an important role in the control of cardiovascular homeostasis, affecting both blood pressure and fluid volume and is one of the most important ethiological candidates in hypertension. [35]. 8-*O*-Acetyl harpagide was isolated and characterized from *Ajuga bracteosa* Wall, cardiotonic effects elicited by the compound [36]. Sodium is the common mineral determined in *Ajuga bracteosa* for which Estimated Safe and Adequate Dietary Intake varies from 1100-3300 mg which is 1875-5625 mg for potassium. The ions of these metals are electrolytes which maintain "body water balance" and carry out nerve functions. The requirement of K+ for daily intake is obviously quite higher in concentration within body cells, while Na+ (along with Cl-) ions are found in excess especially in extra cellular fluids such as blood plasma. Larger amounts of potassium (leaves 139 mg, roots 159 mg per 100 g) than sodium (leaves 21 mg, roots 29 mg per 100 g) may have some correlation with the use of the herb in hypertension [37].

3.4. Anti-inflammatory activity

Anti-inflammatory activity of 3β-hydroxy-2, 3-dihydrowithanolide F [38] by testing subacute models of inflammation and claimed its effect to be comparable to that of hydrocortisone. The compound has been, reported to be superior to hydrocortisone in its activity as hepatoprotective agent against CCl4 induced liver damage [39]. Physangulide and 24, 25-epoxywithanolide D [40] have also been reported to produce anti-inflammatory effects.

3.5. Anticancer activity

Withaferin-A [41] and withacanistin [42] showed cytotoxic against KB cell cultures [43]. Significant inhibitory activity against sarcoma 180 tumor in mice and walker intramuscular carcinoma 256 in rats was also shown by withaferin- A. It exhibited significant growth retardation of Ehrlich ascites carcinoma in mice; i.p. administration of a single dose of withaferine-A (25-40 mg/kg) 24 hr. after Ehrlich ascites implantation decreased the growth of the tumor which subsequently disappeared in 80% of the mice [44,45]. Besides, withaferinA and withacnistin several other structurally related withanolides have been reported to exhibit cytotoxic activity.

The inhibition of the growth of mouse leukemia L5178Y cells in-vitro by AB ring analogus of withaferin- A have antitumor activity [46].

3.6. Antibacterial activity

Various extracts of *Ajuga bracteosa* leaves, roots and bark have been reported to be active against many bacterial strains. [47] studies the antibacterial activity of withaferin A and its compound reported that this constituent active against gram positive bacteria. Ali et al was reported, the 20-deoxywithanolide-D to possess the highest activity among the compound tested.

3.7. Immunomodulatory activity

Withanolides have also been shown to possess both immunosuppressive and immunostimulanting properties [48]. The immunosuppressive activity of withaferin A is evident from its ability to inhibit adjuvant arthritis in rats and the graft versus host reaction in chicks [49]. The substance A [50] was demonstrsted [51]. They study its ability to inhibit proliferation of murine spleen cell culture.

The glucowithanolides, sitoindoside [52] were shown to exhibit adaptogenic and immunostimulating activities.

3.8. Antispasmodic activity

Spasms are colic, an episodic pain due to spasms of smooth muscle in a particular organ (e.g. the bile duct). Shafi et al. studies, 8-O-acetylharpagide offers antispasmodic effect of *Ajuga bracteosa.*

3.9. Miscellaneous activities

The petroleum-ether extracts of *Ajuga bracteosa* contantining glucosidic constituents. The withasteroids comprise one such group of natural products many of which exhibit hepatoprotective activity. The aerial part of the plant shows insecticidal and insect-antifeedant properties due to nine clerodane diterpenoids. The plant also to cure the fever, swollen wounds and diseases of bladder. The external use of this plant as syphilis. The plants of this genus have also been used in female's menstrual disorders [53-55].

CONCLUSION

It is quite evident that *Ajuga bracteosa* contains several important bioactive compounds and some have already shown their therapeutic potential. Unfortunately, most of the compounds have not properly been evaluated for the exploration of new lead molecule or pharmacophore. Moreover, mechanisms of action of a few bioactive compounds have been identified so far. Hence, extensive research is required to find out the mechanisms of action as well as bioactivity of other compounds in crude extracts and to exploit their therapeutic potential to combat various diseases. A drug development programme can be developed through extensive investigation of the bioactivity of various compounds, their mechanism of action, pharmacotherapeutics, toxicity, standardization and clinical trials. Thus in near future *Ajuga bracteosa wall Ex. benth* may play a very important role in modern system of medicine.

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