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AJUGA BRACTEOSA: A PROMISING HERB

Upadhyay S U^{*1}, Patel V B¹, Patel A A¹, Upadhyay U M², Patel N M¹

¹ Shri B. M. Shah College of Pharmaceutical Education and Research, Dhansura Road, College Campus, Modasa – 383315, Gujarat, India

²Sigma Institute of Pharmacy, At & Po. Bakrol, Ta. Waghodia, Vadodara-390019, Gujarat, India

ABSTRACT

Any research work should have high level of Rigor and Relevance. The uses of more and more medicinal plants require the monitoring agencies to have data of standardization to compare the Sdrug with the authenticated parameters. WHO and Govt. of India have intention to include more and more number of medicinal plants into standard monograph. We at B. M. Shah College of Pharmaceutical Education and Research, Modasa have tried to work on one potential herb, A. bracteosa Wall. ex Benth., F. Labiatae. Before working for the plant we have tried to collect as much information as possible. Ajuga bracteosa belongs to family Lamiaceae (Labiatae) which is a large family comprising of 266 genera. The genus Ajuga consists of 301 species. A. bracteosa is distributed in subtropical and temperate regions from Kashmir to Bhutan, Pakistan, Afghanistan, China and Malaysia. 70% ethanol extract of Ajuga bracteosa possess significant and promising anti-inflammatory activity. Ethanolic extract of Ajuga bracteosa leaves demonstrates a dose-dependent chemosuppression during early and in established infections. The plant is astringent and used as tonic and in the treatment of agues. The leaf extract is for blood purification. The juice of the root is used in the treatment of diarrhoea and dysentery. According to Asia Pacific Medicinal Plant Database the leaves are regarded as stimulant, diuretic and tonic. The extract is used to cure swollen wounds, bites of insects, eye troubles, diseases of bladder, as well as tumors. The microscopic features of the plant are also included in the present work.

Keywords: *Ajuga bracteosa*, decoction, astringent, traditional medicine, *In vivo*, Antihyperlipidemic activity.

INTRODUCTION

Importance of medicinal plants is increased in 20th century. Toxicity awareness replaces synthetic drugs with herbal drugs. Modern drugs do not have definite answer for disease like liver disorder, asthma, arthritis. China, Japan, India, South America and Egypt still uses herbs as regular component of health care. The importance of the role of medicinal herbalist is being re-established in overall pattern of health care. Globally there is increase in demand of botanicals for natural cure, with no or lesser side effects. Pharmacognocist identify the causes of ailment and cure it by balancing the body chemistry with botanicals. About $1/3^{rd}$ of pharmaceuticals are derived from plants and over 60% of the preparations are plant based.

Recent survey has revealed that the Global Herbal Industry is growing at a very high rate but proper identification is a big problem. Polyherbal Formulations are more common in Ayurveda. Intentional or unintentional substitution or adulteration of any individual component may lead to total failure of the Polyherbal Formulations. We will try to collect more and more information about morphological, microscopical and other characters to identify the traditional drug *Neelkanthi* used in the various ailments in the region of Himachal Pradesh.

Indian Herbal Pharmacopoeia lists various plants and the information about a single plant is exhaustive. Our attempts will be in the same direction to put *Neelkanthi* in the Indian Herbal Pharmacopoeia. Govt. of India, under the umbrella of AYUSH, ICMR, RRL, NISCAIR, NIPER, etc. is definitely trying to put more and more information about the plants which are traditionally used and for which proper authentification has become mandatory over the period of time. Many plants of the *Ajuga* genus and some compounds isolated from these plants have medicinal value and of ecological and economic importance.

INTRODUCTORY PROFILE^[1-4]

Biological Source: Whole herb Ajuga bracteosa Wall. ex Benth.

Family: Labiatae (Lamiaceae), a large family comprising about 266 genera.

The Genus Ajuga consists of about 301 species.

Habitat: It is found as a weed, in field borders, along roadsides, open slopes and even on rock cervices up to 1500 m above mean sea level. It is found growing at the exposed slopes, grasslands, the sub-Himalayan tract, plains of Punjab and the upper Gangetic plains, throughout Himalayas, Meghalaya, Bihar and Tamil Nadu altitude of 300-2400 m. It is found to be distributed in the Subtropical and temperate regions of Pakistan, Malaysia, Afghanistan to Bhutan, China, Japan and South-East Asia.



Figure 1 *Ajuga bracteosa* Wall. ex Benth. Herb

VERNACULAR NAMES^[5,6]

Sanskrit	: Nilkanthi

- English : Bungle, Copal tree
- Trans-Indus : Khurbanri
- Sutlej : Karku, Nilkantihi
- Punjabi : Khurbanti
- Kumaon : Ratpatha
- Kashmir : Jan-i-adam
- Jhelum : Kauriboti
- Others : Lilkounthe, Neelkanthi, Ratpacho, Khwaga Bootei

Hindko/ Punjabi :Kori booti

TAXONOMICAL PROFILE [7]

- Domain : Eukaryota
- Kingdom : **Plantae**
- Subkingdom : Viridaeplantae
- Phylum : **Tracheophyta**
- Subphylum : **Euphyllophytina**
- Infraphylum : Radiatopses
- Class : Magnoliopsida
- Subclass : Lamiidae
- Superorder : Lamianae

Order : Lamiales

Family : Lamiaceae

Subfamily : Ajugoideae

Tribe : Ajugeae

Genus : Ajuga

Specific epithet: *bracteosa* - Benth. (now Wall.)

Botanical name: Ajuga bracteosa Wall. ex Benth.

MACROSCOPIC DESCRIPTION [8,9]

Herb Annual or perennial, diffused, softly villous herbs, Often Decumbent or Stoloniferous. Stem simple or branched from the base, 10-30 cm height.

Leaves Oblanceolate or spathulate, 3.5-10 x 2.5-3 cm, sinuate-toothed, obtuse; lower leaves petiolate, upper sessile. Leaves purplish violet tinged from lower surface.

Inflorescence Pale blue, sessile. Flowers crowded in axillary 2- or more whorls of terminal spikes.

<u>*Calyx*</u> 4 mm long, villous; teeth half as long as the tube; Ovate-lanceolate, acute, 5-lobed; lobes equal.

<u>*Corolla*</u> pale blue or lilac, pubescent; tube exserted, nearly as long as the calyx; 8-10mm long, tube straight; upper lip very short, 2-fid, and flat; lower spreading and 3-lobed; middle lobe generally dilated, largest, emarginate or 2-lobed.

<u>Stamens</u> are exserted, didynamous, the lower pair longer, ascending, exerted or included, anthers 2-celled; cells diverging or divaricate, at length confluent. Disk uniform or swollen behind. <u>Ovary</u> shortly 4-lobed; style 2-fid, the lobes nearly equal. Nutlets 2.5 mm long, deeply rugose.

PLANT AT A GLANCE

Flowering season:Mar. - Jul. (April)Fruiting season:Sep. - Nov. (October)Habitat:Hill Plant, Plain LandPlant Type:HerbFoliage:EvergreenRoots:Shallow roots, Tap rootsType of stem:Non Woody

Leaf Type: Oblanceolate, Ovate, Spatulate

Leaf Arrangement: Whorled

Leaf Colour: Green

Plant Height: Very Small (0-5m)

Plant feature: Erect, Forest Plant, Hill Side Plant

Plant Utilities: Aromatic Plant, Industrial/Commercial, Medicinal Plant

Season: Annual, Summer

PHYTOCHEMICAL CONSTITUENTS ^[10, 11, 12, 13, 14, 15, 16]

TABLE 1: CHEMICAL CONSTITUENTS OF *AJUGA BRACTEOSA* WALL. EX BENTH

	CHEMICAL (COI	NSTITUENTS
§	Phytoecdysteroids (22-acetylcyasterone,	§	neo-Clerodane diterpenoids (ajugarin
	ajugalactone, ajugasterone A, B &C,		I, II, III, IV &V, ajugapitin,
	cyasterone, 3-epicyasterone,		bracteonin A, 12-bromo-ajugarin I,
	20hydroxyecdysone)		clerodin, clerodinin A,
§	Iridoid glycosides (8-O-acetylharpagide,		deacetylajugarin IV, 14,15-
	reptoside)		dihydroajugapitin, dihydroclerodin-1,
§	Sterols (ß-sitosterol, stigmasterol)		14-hydro -15- hydroxyclerodin, 14,15
§	Withanolides (bracteosin A, B & C), bractin		dihydroxyajugapitin,14-hydroxy-15-
	A &B, bractic acid, sphingolipids, phthalic		hydroxyajugapitin, lupulin A)
	acid ester, lignoceric acid, linalyl acetate,		
	sitoglucoside		
Ø	Conoral: Glycoside Tannin Cervl alcohol	_cit	tosterol – Sitosterol Cerotic and

Ø General: Glycoside, Tannin, Ceryl alcohol, -sitosterol, - Sitosterol, Cerotic and palmitic acids.

Ø Non-saponifiable Fraction: Ceryl alcohol, -sitosterol, -sitosterol.

- Ø Saponifiable Fraction: Cerotic acid, Palmitic acid, Oleic acid, Linoleic acid.
- Ø Alcoholic Extract: Glucose, Arabinose, Phenolic bitter components, Acidic bitter components, Neutral bitter components.



Figure 2(b-1) Neo-clerodane diterpenes from *Ajuga bracteosa* Wall. ex Benth. Herb



Compound	R ¹	\mathbf{R}^2	R ³	R ¹⁵	C ¹⁴ -C ¹⁵
Clerodin	Н	Н	Н	Н	CH ₂ =CH ₂
Ajugapitin	Н	ОН	CH ₂ CH ₃ (CH ₃)COO	Н	CH ₂ =CH ₂
14,15-dihydroajugapitin H	Н	ОН	CH ₂ CH ₃ (CH ₃)COO	Н	CH ₂ -CH ₂

Figure 2(b-2)

Neo-clerodane diterpenes from Ajuga bracteosa Wall. ex Benth. herb





Compound	1	2	3
8-O-acetyl-harpagide			

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	Н с	
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Figure 2(c)

Irridoid glycosides from Ajuga bracteosa Wall. ex Benth. Herb



Figure 2(d) Withanolides from *Ajuga bracteosa* Wall. ex Benth. Herb



Phytoecdysteroid	\mathbf{R}^1	R ²	R ³	\mathbf{R}^4	R ⁵	R ⁶	\mathbf{R}^7	R ⁸
Cyasterone	ОН	ОН	Н	Н	OH	0	CH ₃	CH ₃
3-Epicyasterone	ОН	ΟΗ(α)	Н	Н	OH	Н	CH ₃	CH ₃
3-Epi-22-acetylcyasterone	ОН	OH(α)	Н	Н	OAc	Н	CH ₃	CH ₃

Figure 2(e-1) Phytoecdysteroids from *Ajuga bracteosa* Wall. ex Benth. herb



Phytoecdysteroid	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ⁹
Ajugasterone A	Н	ОН	ОН	ОН	Н	ОН	ОН	Н	ОН	CH ₃
Ajugasterone B	Н	ОН	ОН	Н	Н	ОН	ОН	CH ₂ CH ₃	CH ₂ OH	CH=CH ₂
Ajugasterone C	Н	ОН	ОН	Н	ОН	ОН	ОН	Н	Н	CH ₃
20-Hydroxy-5a- ecdysone	Н	ОН	ОН	Η(α)	Н	ОН	ОН	Н	ОН	CH ₃

Figure 2(e-2)

Phytoecdysteroids from Ajuga bracteosa Wall. ex Benth. herb



Phytoecdysteroid	\mathbb{R}^1	\mathbf{R}^2	R ³	R ⁴	R ⁵	$C^{24}-C^{25}$
Ajugalactone	ОН	ОН	Н	CH ₃	Н	CH ₂ =CH ₂

Figure 2(e-3) Phytoecdysteroids from *Ajuga bracteosa* Wall. ex Benth. herb



Hexacosanol

Oleic acid

Figure 2(f) Fatty acids from *Ajuga bracteosa* Wall. ex Benth. herb

Figure 2

Structures of chemical constituents of ajuga bracteosa wall. Ex benth herb

ETHNOBOTONICAL USES ^[17, 18, 19, 20]

- Ø Tonic, Astringent, Febrifugal, Stimulant, Aperient, Anticancer, Diuretic, Used for the treatment of Gout, Rheumatism, Amenorrhea, Gonorrhoea.
- Ø Leaves are employed for application on blisters, venereal and skin diseases, as diuretic, in malarial fever, in eruptions and fissures on skin, as an astringent, as blood purifier, in burns and boils, in jaundice and leucorrhoea, In diabetes and body swellings.
- Ø The root is used in conjunctivitis of newborns in malaria, As antidote to snake bite, For purification of blood, as an anthelmintic and purgative.
- Ø Ethnomedicinal uses in the Himalaya, Water extract of fresh leaves is administered orally with sugar to children against malarial fevers. The decoction of dried leaves is used against stomach pain.
- Ø Ethnopharmacological surveys have revealed that some 20 species of *Ajuga* plants are used in traditional medicine mostly in Africa, Asia and China. The pharmacology and therapeutic value of plants including *Ajuga reptans* has been described as early as 1948. The local practitioners especially in remote, rural, tribal and farflung areas have been using it as Bitter tonic, Blood purifier, and as well as Antipyretic over the years

in the Pobbar Valley of Shimla District ^[21]. Leaf juice is used as blood purifier. Drug Powder is used for burns and boils. Plant juice is mixed with the juice of *Centella asiatica*, and given to women in gonorrhoea and also in intermittent fever accompanied with shivering. The plant is astringent and used as tonic and in the treatment of agues. The extract is also used to cure swollen wounds, bites of insects, eye troubles, diseases of bladder, as well as tumors.

ETHNOMEDICAL SIGNIFICANCE

1. Drug powder:

It has shown hypoglycemic activity ^[21]. A decoction of the leaves of the herb is used in the traditional medicine for diabetes and a number of diseases including hypertension, fever, malaria and stomach pain.

2. An alcoholic fraction of leaves:

It had shown Cardiotonic action on frog heart, rabbit auricle and rat ventricle. An alkaloidal fraction showed stimulant action on the perfused frog heart. The alkaloidal fraction obtained from the plant showed a positive inotropic action on the frog heart, isolated rabbit auricle and electrically driven rat ventricle. ^[22, 23, 24]

3. Ethanolic (50%) ext. of plant:

It has been shown as spasmolytic and anticancer. Ethanolic extract of the plant in a preliminary biological screening showed effect on guinea pig ileum and **Anticancer** activity in sarcoma 180 in mouse and HS human sarcoma in the embryonated egg.

4. The aqueous extract of Plant:

A dose of 2.4 g/kg in normal saline administered intra-gastrically, showed protection against carbon tetrachloride-induced liver damage as Hepatoprotective.

5. The juice of the root:

It is also used in the treatment of diarrhoea and dysentery. According to Asia Pacific Medicinal Plant Database, the leaves are regarded as stimulant, diuretic and tonic. Juice of the plant (about 3 teaspoons twice a day) is given to treat troubles of the bile duct.^[25] Leaf powder is given to cure ulcer of mouth. Decoction of leaves (3–4 drops) is given thrice a day to small children (4 months old) who have breathing problems and also to cure internal sores ^{[26,27].}

TABLE 2: EXTENT OF USES AJUGA BRACTEOSA COLLECTED FROM PARVATI VALLEY OF SHIMLA DISTRICT IS AS ^[28]:

USES AS RECORDED IN THE PARVATI VALLEY (URPV)	USES AS PER THE DICTIONARY OF INDIAN FOLK MEDICINE AND ETHNOBOTANY (DIFMAE)	USES AS MENTIONED IN THE COMPENDIUM OF INDIAN MEDICINAL PLANTS (CIMP)
The leaves are used to erase		
deposition on tongues of children		
suffering from stomach complaints		Contains glycosides
and fever.		and tanins.
The pounded leaves are given in	Blood purifier	Herb is astringent,
pneumonia and typhoid fever.	Used to treat burns, boils and	febrifuge, apparent,
The plant is considered as a bitter	evnhilie	tonic and diuretic.
tonic.	syphilis	Used in goat,
The infusion of leaves in small		rheumatism palsy and
quantity is given thrice a day in fever,		amenorrhoea
bronchitis and in case where blood		
clots appear in phlegm.		

PHYTOCHEMISTRY

It has been suggested that *Ajuga bracteosa* contain the known compounds -Hexacosanol, -sitosterol, Tetracosanoic acid, and -sitosterol- -D-glucoside. A new compound was isolated from the aerial parts of *Ajuga bracteosa* and characterized as Triacontanyl docosanoate by physicochemical methods.^[29]

Air-dried plant (1 kg.) was successively extracted with pet ether, Me_2CO , and alcohol. The pet ether extract gave nonsaponifiable fraction 10.82 g residue, containing ceryl alcohol, -sitosterol, -sitosterol, and Unidentified colorless plates, m.p. 94°C. The saponifiable fraction contained cerotic, palmitic, oleic, and linoleic acids. Me_2CO and alcoholic extracts gave a mixture (7.52 g.) of glucose, arabinose, and phenolic, acidic,

and neutral bitter components. These components on acid hydrolysis gave glucose, arabinose, rhamnose, and a mixture of resins.^[30]

Heptacos-3-en-25-one, A new unsaturated ketone from *Ajuga bracteosa* compound was isolated from the aerial parts of *Ajuga bracteosa* and its structure detected by spectral means.^[31]

Ajuga bracteosa was found to contain compounds of the class diterpenoids and withasteroids, which are a group of 28 naturally occurring steroidal lactones built on an intact or rearranged ergostane framework. Withasteroids exhibit a number of biological activities such as anti-microbial, anti-tumor, anti-inflammatory, hepatoprotective, immunomodulatory, cytotoxic, antisecticidal and insect-antifeedant properties.^[32, 33, 34,35]

The whole plant of *Ajuga bracteosa* afforded five compounds including one new Clerodane Diterpenoid designated as Bracteonin-A [6a-acetoxy-15(R/S)-methoxy-18-(4'-hydroxy-3'-b-Me-3'a-acetoxybutyryloxy)neoclerodane]. The other compounds identified were 14, 15-dihydroajugapitin, 14-hydro-15-hydroxyajugapitin, -sitosterol, and Stigmasterol. The structural elucidation was carried out by spectroscopic techniques.[[]

A new phthalic acid ester 1,2-benzenedicarboxylic acid bis(2S-methyl heptyl) ester was isolated from the hexane extract of the whole plant of *Ajuga bracteosa*. In addition, chloroform and methanol extracts yielded neo-clerodane diterpene ajugarin-I and two iridoid glycosides, reptoside and 8-O-acetyl harpagide. The structures of all the compounds were confirmed by extensive spectroscopic analysis. From the two oily fractions nine and six volatile constituents respectively were identified by GC-MS. Linalyl acetate was found to be common in both the oil fractions. ^[37] This plant is a new source of linalyl acetate, a valuable perfumery compound.

Three new Withanolides, Bracteosin A [(22R)-5b,6b:22,26-diepoxy-4b,28dihydroxy-3b-methoxyergost-24-ene-1,26-dione] (I), Bracteosin B [(22R)-5b,6b:22,26diepoxy-4b,28-dihydroxy-3b-methoxy-1,26-dioxoergost-24-en-19-oic acid] (II), and Bracteosin C [(22R)-22,26-epoxy-4b,6b,27-trihydroxy-3b-methoxyergost-24-ene-1,26dione (III), have been isolated from the whole plants of *Ajuga bracteosa*. Their structures were deduced by spectral analysis, including 1D- and 2D-NMR techniques. In addition, Dihydroclerodin-1, Clerodinin A, Lupulin A, and Dihydroajugapitin have also been isolated for the first time from this species. Compounds I-III exhibited evident inhibitory potential against cholinesterase enzymes in a concentration-dependent fashion. ^[38]

Withanolides 1–5, isolated from *Ajuga bracteosa* and *Withania somnifera*, possess an erogstane skeleton with lactone ring. The cholinesterase inhibitory potential of these withanolides was measured by using electrical AChE. Oligomeric forms of electrical AChE are similar to those of vertebrates nerve and muscle AChE.

The withanolides 1-3 and 4-5 isolated from *Ajuga bracteosa* and *Withania somnifera*, respectively, inhibited acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BChE, EC 3.1.1.8) enzymes in a concentration-dependent fashion with IC₅₀ values ranging between 20.5 and 49.2 microm and 29.0 and 85.2 microm for AChE and BChE, respectively. Lineweaver-Burk as well as Dixon plots and their secondary replots indicated that compounds 1, 3, and 5 are the linear mixed-type inhibitors of AChE, while 2 and 4 are non-competitive inhibitors of AChE with K(i) values ranging between 20.0 and 45.0 microm. ^[39]

Ecdysteroids (a large group of natural polyhydroxysteroids) are isolated from the plant kingdoms, usually in small quantities (0.1-0.001 wt percent) of raw material, although in some instances they can reach 2.5-2.9 percent and more. Literature data available on the structures of phytoecdysteroids from the plants of genus *Ajuga* (Lamiaceae) and other biologically active compounds and their biological activities have been reviewed.^[40]

BIOCHEMICAL IMPORTANCE

In order to rationalize medicinal applications and establish biogeochemical link, the mineral elements (Na, K, Ca, Mg, Zn, Mn, Cu, Fe, Cr) of leaves and roots of *Ajuga bracteosa* and the nearby soil were studied. The herb contains comparatively larger amts. 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 amts. 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.^[41]

BIOLOGICAL ACTIVITY

1. Anti-Microbial Activity

Ethanolic extract of leaves of *Ajuga bracteosa* (250, 500 and 750 mg/kg/day) demonstrated a dose-dependent chemosuppression during early and in established infections, along with significant (P<0.05) repository activity. At a concentration of 750 mg/kg/day maximum 77.7 percent chemosuppression during early infection and 68.8 percent chemosuppression in repository activity were found. ED₅₀ of ELEAB was 300 mg/kg body weight of mice. ^[42]

The rising problem of Plasmodium resistance to the classical antimalarial drugs stresses the need to look for newer antiplasmodial components with effective and new mode of action. In the present study, the traditional medicinal plant *Ajuga bracteosa* has been screened for its antiplasmodial efficacy. The extract was found to possess significant in vitro antiplasmodial efficacy with an IC(50) of 10.0 μ g/ml.^[43]

2. Anti-Inflammatory Activity

70% ethanolic extract of *Ajuga bracteosa* possess significant and promising anti-inflammatory activity. The mechanism of anti-inflammatory action is assumed to be mediated through the inhibition of COX-1 and COX-2. The study also signifies that isolated constituents (Ajugarin I, Lupulin A, Withaferin A, Reptoside and 6-Deoxyharpagide) could be responsible, at least in part, for its anti-inflammatory and COX inhibitory activity. The study verifies traditional use of *Ajuga bracteosa* for the treatment of rheumatism and other inflammatory disorders. ^{[44].}

3. Cardiotonic Activity

An alkaloidal fraction from *Ajuga bracteosa* showed the Cardiostimulant action on frog heart, and rat ventricle. The activity was antagonized by dichloroisoprenaline, did not occur in hearts from reserpine-treated animals, and may result from liberation of catecholamine stores in the heart ^[45].

CONCLUSION

The preliminary literature survey showed that no work on bioassay guided fractionation of this herb has yet been reported targeting diabetes and hyperlipidemia. Hence, the pharmacological evaluation of the project is proposed mainly for *In vivo* Anti-hyperlipidemic activity. Traditionally this plant is reported to have many activity and we have already planned for the estimation of all the activities in the laboratory set up and in

future to take the results to the clinical set up so that the society at large can get the advantage of the research performed at the laboratory.

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For Correspondence: Upadhyay S U Email: <u>siupa.pharma@gmail.com</u>