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Review Article

Ajuga parviflora: A Comprehensive Review on Botanical, Phytochemical, and Pharmacological Aspects

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Abstract

Ajuga parviflora Benth. (*Lamiaceae*) is a herbaceous medicinal plant that has a rich tradition of use in various regions of Uttarakhand, India, for treating a range of human ailments, including cough, vaginal discharge, muscle aches, and stomach problems. This plant exhibits diverse pharmacological properties, including antifungal, antibacterial, insecticidal, hypoglycemic, and hepatoprotective activities. Numerous compounds have been isolated from *A. parviflora*, demonstrating a wide array of biological and pharmacological effects. This comprehensive review offers scientific insights into the bioactive components of the medicinal plant *A. parviflora*, its pharmacological attributes, and its applications in pharmaceuticals and medicine.

Keywords: *Ajuga parviflora*; Medicinal Plant; Bioactive Compounds; Pharmaceuticals; Medicine

Introduction

The genus Ajuga comprises evergreen, clump-forming, rhizomatous perennial or annual herbaceous flowering plants, belonging to the larger family Lamiaceae, which includes 266 genera. There are over 301 species within the Ajuga genus, exhibiting a wide range of variations. These plants are distributed across Asia, Europe, Africa , North America, and Australia, and they are often utilized in gardens as ground cover or for bordering because of their lovely foliage and flowers [16].

Many species of Ajuga have a history of traditional medicinal use for various purposes, including treating malaria, fever, toothaches, dysentery, high blood pressure, gastrointestinal disorders, and diabetes, also serving as diuretic, anthelmintic, and antifungal agents. They are also known for their anti-inflammatory and antimycobacterial properties, and they act as insect growth inhibitors [7,12,17].

The Ajuga plant yields a variety of bioactive compounds that have been isolated, encompassing diterpenoids, phytoecdysteroids, neo-clerodane diterpenes, withanolides, anthocyanidin-glucosides, triterpenes, sterols, flavonoids, triglycerides, iridoid glycosides, and essential oils [9,14,25,36]. These compounds have a diverse range of pharmacological, biological, and therapeutic characteristics, including anti-inflammatory, analgesic, antibacterial, anabolic, antileukemic, antiestrogenic, cytotoxic, antifungal, antimycobacterial, antihypertensive, antimalarial, antioxidant, antipyretic, vasorelaxing, cardiotonic, and hypoglycemic, activities [12,14]. Additionally, they serve as antifeedants and possess properties that inhibit insect growth. Consequently, the genus Ajuga holds substantial significance both in terms of its medicinal properties and economic value [16].

In this review, we provide insights into the multifaceted attributes of *A. parviflora*, encompassing its botanical characteristics, phytochemical composition, and pharmacological implications.

Botanical characteristics

A. parviflora is described as an annual or short-lived perennial plant. Its characteristics include stems that are spreading or ascending, typically measuring 10-25 cm in length. These stems are usually unbranched and covered with a sparse to dense layer of

long villous multicellular hairs, which lack glands. The leaves of *A. parviflora* can form a rosette or not, and they vary in size, ranging up to 45 by 25 mm. They are shaped as obovate-spathulate to elliptic, with entire to crenate margins. The leaves narrow into petioles and have multicellular eglandular hairs. The basal leaves may have petioles up to 20 mm, while the cauline leaves are smaller and decrease in size as they go up the stem. The plant produces an unbranched inflorescence that can consist of up to 18 distant or approximately 8-12-flowered verticillasters. The calyx is 2.5-4 mm in size and shares a similar indumentum with the stem. It may or may not have sessile oil globules and has a campanulate shape. The calyx teeth are triangular-lanceolate and acute, measuring as long as the tube. As nutlets mature, the calyx teeth may become basally enlarged. The corolla of *A. parviflora* can be pink, bluish white, or white, measuring 5-6 (sometimes up to 8) mm, and it is covered in pilose hairs. The corolla tube is slender and is shortly exserted from the calyx lobes. The stamens are typically included within the corolla tube. The nutlets are pale brown, transversely rugose, with prominent ridges, and they are about 1.5 by 1 mm in size. This species is found in Eastern Afghanistan, Pakistan, Kashmir, and Northwestern India and typically blooms from March to June [21].

Figure 1: Ajuga Parviflora Benth. (Neelkanti) from Uttarakhand Pauri Garhwal.

Ethnomedicinal uses

A. parviflora is used as a diuretic and purgative in Jammu and Kashmir, as well as for the treatment of piles, gonorrhoea, intestinal infections, indigestion, stomach disorders, malaria, cough, and fever [13]. It has been reported that the whole plant that belongs to *A. parviflora* can be utilized to treat a variety of illnesses and nanoparticle synthesized by utilising its leaf extracts can act as a potent medication. The biological activities of this herb include dermatological, antibacterial, antidiabetic, antimicrobial, antiviral, antifungal, antioxidant, insecticidal, and brine shrimp toxicity. Considering factors such as its availability, collection methods, growth patterns, and the parts of the plant used, the calculated preservation status of this herb has been categorized as "vulnerable." This suggests that there is a need for careful management and preservation efforts to ensure its continued availability and sustainability [11,15,31]. The study conducted by Rana., *et al*. in 2010 highlights the medicinal significance of plants found in Nanda Devi National Park in Uttarakhand, India, for treating various ailments. Here are some of the traditional uses includes a Mixture of *A. parviflora* leaves, Aconitum heterophyllum roots, and Podophyllum hexandrum roots combination is dried in the shade and powdered. It is administered as a half-teaspoonful twice a day, in the morning and at night after meals, for up to three months. It is used to treat conditions such as diabetes, leucorrhoea (vaginal discharge), and as a carminative (relieving flatulence. Aqueous extract of *A. parviflora* root in a concentration of 5-10 ml dose is given twice a day, in the morning on an empty stomach and at night after meals. This extract is used for 7 to 28 days to address chronic fever, diarrhea, and as a remedy for the common cold. *A. parviflora* leaf powder mixed with Aconitum heterophyllum tuber powder; a quarter teaspoon of this mixture is administered twice a day for an extended period. It is employed in the treatment of leucorrhoea, high fever, colic, and diabetes. Mixture of Podophyllum hexandrum root powder with Ajuga parviflora with a 2.5 g dose is given twice a day for three months to manage diabetes and chronic fever. Also *A. parviflora* root paste is used in External application. The paste made from these medicinal plant roots is applied externally on wounds, cuts, and skin ailments. Rhizome powder of *A. parviflora* with a 2.5 g dose is administered twice a day, in the morning before meals and at night after meals, for 14 to 28 days. It is used to address bile complaints, act as a carminative, and treat leucorrhoea [32].

Phytochemistry

Methanolic extract of *A. parviflora* Benth. was assessed for its ability to screen for phytochemicals (the plant extract revealed the presence of tannins, polyphenols, quinines and dions, flavonoids, alkaloids, aminophenols, steroids/sterols, and terpenoids), as well as its antimicrobial properties against a variety of bacterial and fungal strains.

Newly discovered neo-clerodane diterpenoids such as, 3fl-acetoxyclerodinin C, deoxyajugarin-I, and ajugarin-I chlorohydrin have been isolated from Ajuga parviflora collected near Nainital, India. Also there was presence of clerodinins C and D, ajugarin-I and II, dihydroclerodin-I, ajugamarin F4, and 15-α-ethoxy- and 15-β-ethoxy-14-hydroajugapitin [3].

Pharmacology

Chemical constituents of the genus *Ajuga L.* have been the focus of comprehensive research since the early 1950s. One of the initial phytochemical investigations on the genus Ajuga, dating back to 1976, reported the isolation of neo-clerodane diterpenes with insect antifeedant properties [20]. In recent years, there has been a growing interest in the pharmacological activities of *Ajuga L.* species. Modern pharmacological studies have revealed that Ajuga species are involved in various activities, including, antinociceptive, antitumor, anti-inflammatory, antidiabetic effects and antioxidant activities, among others. These findings indicate a broad range of potential pharmacological activities associated with the genus *Ajuga L.*

Anti-hepatotoxic activity

S. No.	Bioactive compounds	Activity	Reference
Withanolides			
	Withanolide (1)	Antifungal activity against *T. Schoeneinii*	[29]
	Withanolide (2)	antifungal activity against *R. solani*	
	Ajugin E	Antidiabetic	[23,28,34]
	Ajugin F	Antimicrobial, antidiabetic	
	Ajugin C	Antimicrobial, antidiabetic	[18,34]
	Ajugin D	Antimicrobial, antidiabetic	
Neo-clerodane diterpenes			
	Ajugarin I	Antifeedant Antimalarial Cytotoxicity Antimycobacterial	[3,8,22]
	Ajugrain II	Antifeedant, antimalarial Cytotoxicity, Antimycobacterial	[3,8,22]
	Deoxyajugarin-I	Antimicrobial, antioxidant	[3,26]
	Ajugarin-I chlorohydrin	Antimicrobial	[3,26]
	Ajugamarin F4	Antifeedants	[3,4]
	Dihydroclerodin-I	Antifeedant	[3,10]
	Clerodinins C	Growth inhibition, feeding stimulant	[3,19]
	3β Acetoxyclerodinin D	Feeding stimulant	[3,19]
	15α Ethoxy-14-hydroajugapitin	---	[3]
Quinols			
	4-acetyloxy-4- methylenecarboethoxy -cyclohexa-2,5-dienone (1)	--	[27]
	4-acetyloxy-4- (methylenecarbomethoxy) -cyclohexa-2,5-dienone (2)	---	[27]

	4-hydroxy-4- methylenecarboethoxy -cyclohexa-2,5-dienone (3)	--	[27]
	4-hydroxy-4- methylenecarbomethoxy -cyclohexa-2,5-dienone (4)	Cytotoxic activity	[27,30]
Flavonoids			
	Lupeol	Treatment of damaged skin and burns	[24,27]
	Oleanolic acid	Chronic disease treatment, hepatoprotective, anti-inflammatory, antiparasitic, antidiabetic, antihypersensitive, antioxidant	[1,27]
Sterols			
	Stigmasterol	Antidiabetic	[2,27]
	Beta sitosterol	Antidiabetic, antioxidant	[27,33]

Table 1: Chemical Constituents isolated from *A. parviflora.*

In a study conducted by Burki., *et al*. in 2020, it was observed that the crude methanol extract derived from *A. parviflora* demonstrated hepatoprotective properties by mitigating the toxicity induced by isoniazid and rifampicin (INH and RFP) in healthy animals. The notable hepatoprotective effects of *A. parviflora* are likely attributed to the compounds contained within the crude extract. When animals were pre-treated with *A. parviflora* at doses of 200 and 300 mg/kg, it was observed that the epithelium of the central portal vein remained intact, with a sufficient presence of glucagon. This prior treatment with *A. parviflora* effectively shielded the liver from INH and RFP-induced hepatotoxicity. The outcomes of pre-treated animals with *A. parviflora* at doses of 200 and 300 mg/kg notably reversed the severe disturbances in parameters such as cytolysis, lymphoid aggregates in the portal vein, lymphocytic infiltration and hydropic degeneration. Moreover, the decreased expression of peroxisome proliferator-receptor activator-δ (PPAR-δ) gene induced by INH and RFP was substantialy upregulated by *A. parviflora* extract in pre-treated animals at doses of 200 and 300 mg/kg. These findings establish the foundational pharmacological applications of *A. parviflora* in the context of liver disorders [5].

Burki., *et al*. in 2021 reported that an LC/MS analysis confirmed the presence of various essential pharmacological compounds in the methanolic leaf extract of *A. parviflora*. The noteworthy bioactive compounds included pyocyanin, zonisamide, D Saccharic acid, altretamine, carbocyclic thromboxane A2, Sinapyl alcohol, and vitamin C. Additionally, crucial polypeptides identified comprised Lys-Tyr-Lys, His-His-Lys, Met-Asp-Arg, Phe-Val-Arg, and PyroGlu-Val-Arg. The LD50 (lethal dose for 50% of subjects) of *A. parviflora* was found to be greater than 1000 µg/mL. Administration of *A. parviflora* significantly alleviated CCl4-induced toxicity in rats, resulting in the reduction of elevated levels of RBCs, pus, and epithelial cells. Abnormally elevated specific gravity, creatinine, urobilinogen, urea, and albumin levels were also returned to normal physiological levels. Moreover, urinary protein and pH were normalized. Serum urobilinogen, urea, and total bilirubin levels were likewise restored to normal, and diminished albumin and total protein levels returned to normal as well. The levels of important phase I and II enzymes were also reversed in rats administered with *A. parviflora*. Levels of H2O2, thiobarbituric acid reactive substances (TBARS), and nitrite were significantly reduced. Furthermore, damaged DNA and histopathological changes in rats exposed to CCl4 were highly significantly reversed after the administration of *A. parviflora* [6].

Antiviral activity

In a study reported by Yousaf., *et al*. 2018 methanol extracts of *A. parviflora* showed 70% reduction in the Hepatitis C virus growth resulted in possible treatment of HCV infections with medicinal plants [37].

Insecticidal activity

For its insecticidal properties, the plant extract was applied to red flour beetles (*Tribolium castaneum*) and grain weevils (*Sitophilus granaries*), as well as their larvae. Different concentrations of the medicinal herb *A. parviflora* methanolic extract (10, 100, and 1000 ug/ml) were used for the brine shrimp lethality bioassay. Using probit analysis, the percent mortality and LD50 value were determined after 24 hours. The LD50 value of extract was 321.42µg/

ml while that of standard drug cyclophosphamide was 16.09ug/ml [31].

Antidiabetic

In the foothills of the Himalayas in India, the leaves of Ajuga parviflora Benth. (Lamiaceae) are commonly employed for managing hyperglycemia. Suryavanshi., *et al*. 2021 evaluated the inhibitory potential of hexane and hydroalcoholic leaf extracts of *A. parviflora* against carbohydrate-hydrolyzing enzymes associated with hyperglycemia, specifically α-glucosidase and α-amylase. They also assessed the impact of these extracts on glucose uptake by yeast cells through in-vitro experiments. The IC50 values obtain for both hexane and hydroalcoholic extracts indicated their significant potency for scavenging free radicals with ABTS (128.2 ± 1.71 µg/mL and 156.67 ± 6.76) and DPPH (206.8 ± 9.43 µg/mL and 113.13 ± 1.4) respectively. Additionally, both extracts exhibited noteworthy inhibitory effects on α-amylase (5116.34 ± 2.08 and 103.55 ± 2 µg/mL.) and α-glucosidase (74.76 ± 0.29 and 61.38 ± 0.25 µg/mL). Furthermore, these extracts significantly improved the rate of glucose uptake into yeast cells. These results suggest that the leaves of *A. parviflora* possess both antidiabetic and antioxidant properties, supporting their traditional use in the treatment of diabetes [35].

Future Perspective and Conclusion

This review provides a comprehensive and current overview of the diverse ethnomedicinal applications, phytochemistry, and pharmacological properties of *A. parviflora* and its active compounds. Given the potential medicinal value of Ajuga species, there has been a growing body of research in this area. *A. parviflora* is rich in various compounds, including diterpenoids and neo-clerodane diterpenes quinols, flavonoids, and sterols. Neo-clerodane diterpenes, in particular, hold promise for the development of drugs aimed at addressing antitumor and anti-inflammatory activities. Furthermore, several other species within the Ajuga genus have exhibited diverse pharmacological activities, with studies on crude extracts revealing potential bioactivities. These encompass anti-inflammatory, antinociceptive, antifungal antitumor, anti-hepatotoxic antioxidant, antifungal, hypoglycemic, antidiabetic, hypolipidemic, immunomodulatory, and vasodilating. There is a growing interest in establishing the connection between the traditional uses of *A. parviflora* and its pharmacological effects. However, it's worth noting that research on this species remains relatively limited, with a predominant focus on *A. parviflora*. Although some studies have attempted to bridge the gap between traditional uses and pharmacological activities, there is still a need for more research. Most pharmacological investigations of the *Ajuga L*. genus have primarily concentrated on the activity of crude extracts, particularly aqueous and ethanol extracts. The precise mechanisms of action of bioactive components in treating various ailments remain largely unexplored. More studies are required to isolate and elucidate the compounds found in *A. parviflora* and uncover their potential mechanisms in validating the plant's traditional significance in disease management.

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Conflict of Interest

There is no conflict of interest to declare.

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