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Deciphering the Therapeutic Potential of *Ajuga bracteosa* Whole Plant Phytoconstituents Using Network Pharmacology

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Abstract:
Ajuga bracteosa Wall. ex Benth. is an important medicinal herb belonging to the family Lamiaceae and has been extensively utilized in traditional systems of medicine for the management of inflammatory disorders, diabetes, infections, liver diseases, respiratory disorders, and neurological conditions. The plant contains diverse phytoconstituents including flavonoids, diterpenoids, phytoecdysteroids, glycosides, phenolic compounds, sterols, and tannins that contribute to its broad pharmacological activities. Recent advances in computational biology and systems pharmacology have enabled researchers to investigate the multitarget therapeutic mechanisms of medicinal plants through network pharmacology approaches. Unlike the conventional "one drug-one target" concept, network pharmacology explains the synergistic interactions between multiple compounds and multiple molecular targets involved in complex diseases.
The present review summarizes the ethnomedicinal importance, taxonomy, morphology, phytochemical profile, pharmacological activities, toxicity studies, and network pharmacology-based therapeutic potential of *Ajuga bracteosa*. Major bioactive compounds identified from the plant include luteolin, apigenin, quercetin, β-sitosterol, stigmasterol, ajugapitin, cerotic acid, ceryl alcohol, and phytoecdysteroids such as 20-hydroxyecdysone. Computational prediction studies have demonstrated interactions of these phytoconstituents with multiple biological targets associated with inflammation, oxidative stress, apoptosis, metabolic regulation, and cancer progression. Hub genes such as AKT1, TNF, IL6, and MAPK signaling proteins have been identified as key mediators in the pharmacological actions of the plant.
The review also highlights the importance of bioinformatics tools such as SwissADME, SwissTargetPrediction, STRING database, GeneCards, PubChem, and Cytoscape in understanding compound-target-pathway interactions. Toxicity profiling using ProTox-3.0 indicates that most compounds possess low toxicity and acceptable pharmacological safety. The cumulative findings strongly support the therapeutic significance of *Ajuga bracteosa* and provide a scientific foundation for future experimental and clinical studies aimed at developing plant-based therapeutic agents.

Keywords: *Ajuga bracteosa*, Network Pharmacology, Phytoconstituents, Medicinal Plants, Bioinformatics, Phytoecdysteroids, Anti-inflammatory Activity, Antioxidant Activity.

1. INTRODUCTION

Medicinal plants have played a fundamental role in healthcare systems since ancient times and continue to provide valuable therapeutic agents for modern medicine. Natural products derived from plants possess immense pharmacological potential because of their structural diversity and biological activities. Among medicinal herbs, *Ajuga bracteosa* Wall. ex Benth., belonging to the family Lamiaceae, has attracted considerable scientific attention due to its wide spectrum of therapeutic applications.

Ajuga bracteosa is commonly distributed in Himalayan and sub-Himalayan regions of India, Pakistan, Nepal, and China. In traditional systems of medicine such as Ayurveda and folk medicine, the plant has been used for treating fever, inflammation, asthma, hypertension, diabetes, digestive disorders, wounds, rheumatism, and liver diseases. The medicinal value of the plant is primarily attributed to the presence of secondary metabolites including flavonoids, diterpenoids, terpenes, phenolic compounds, glycosides, steroids, saponins, and phytoecdysteroids.

In recent years, there has been increasing interest in understanding the molecular mechanisms underlying the therapeutic actions of herbal medicines. Traditional pharmacological approaches often focus on a single drug acting on a single molecular target. However, medicinal plants usually contain multiple active compounds that exert synergistic effects on numerous biological pathways simultaneously. Therefore, systems-level approaches are necessary to understand the multitarget pharmacological actions of medicinal plants.

Network pharmacology is an emerging interdisciplinary field integrating pharmacology, systems biology, molecular biology, bioinformatics, and computational science. It provides a holistic framework to analyze interactions among compounds, targets, proteins, pathways, and diseases. This approach is particularly suitable for medicinal plant research because it explains the synergistic therapeutic actions of phytoconstituents through complex biological networks.

The present review aims to comprehensively summarize the phytochemistry, traditional uses, pharmacological activities, and network pharmacology-based therapeutic potential of *Ajuga bracteosa*. Additionally, the review discusses the role of modern computational tools in identifying bioactive compounds, predicting drug targets, evaluating pharmacokinetic properties, and understanding disease-associated pathways.

2. TAXONOMY AND BOTANICAL DESCRIPTION

2.1 Taxonomical Classification

Rank	Classification
Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Lamiales
Family	Lamiaceae
Genus	*Ajuga*
Species	*Ajuga bracteosa*

2.2 Common Names

- English: Bracted Bugleweed
- Hindi: Nilkanthi
- Local names vary according to geographical regions.

2.3 Morphological Characteristics

Ajuga bracteosa is a small perennial herb with aromatic properties. The plant generally grows to a height of 10–40 cm and exhibits spreading or ascending branches. The root system consists of thin fibrous tap roots. The stem is quadrangular, hairy, soft, and green to purplish in color, which is characteristic of members of the Lamiaceae family.

Leaves are simple, opposite, decussate, and vary from ovate to lanceolate in shape. The margins are serrated or crenate and the surface may be hairy. The lower leaves are generally larger than the upper leaves. Flowers are bluish-purple or violet, bisexual, and arranged in dense whorls or spikes. The presence of leafy bracts surrounding the flowers gives the species the name “bracteosa.”

2.4 Distribution and Habitat

The plant is commonly found in India, Pakistan, Nepal, and China, particularly in sub-Himalayan regions at altitudes ranging from 1300–3000 meters. It grows well in moist soils, shady areas, forest edges, and grassy slopes.

3. ETHNOMEDICINAL IMPORTANCE

Medicinal plants remain essential in traditional healthcare systems, especially in rural and tribal communities. *Ajuga bracteosa* has been traditionally employed for centuries because of its diverse therapeutic properties.

3.1 Traditional Uses

The plant has been used in folk medicine for:

1. Fever and malaria
2. Diabetes mellitus
3. Hypertension
4. Respiratory disorders
5. Digestive disorders
6. Joint pain and rheumatism
7. Liver diseases
8. Skin infections and wounds
9. General weakness and fatigue
10. Inflammatory disorders

3.2 Ethnobotanical Applications

Fever and Malaria

Traditional healers use decoctions prepared from the plant to reduce fever and manage malarial conditions.

Diabetes

Extracts of *Ajuga bracteosa* are commonly used in folk medicine to regulate blood glucose levels and improve metabolic balance.

Respiratory Disorders

The plant is used for the treatment of asthma, cough, bronchitis, and respiratory congestion.

Digestive Disorders

Herbal preparations of the plant are administered for indigestion, diarrhea, dysentery, and stomach pain.

Wound Healing

Leaf paste is traditionally applied externally on cuts and wounds to accelerate healing and reduce microbial infections.

Joint Pain and Rheumatism

The anti-inflammatory and analgesic properties of the plant make it useful for arthritis and muscular pain.

Liver Disorders

The herb has also been used as a remedy for jaundice and liver dysfunction.

The broad range of ethnomedicinal applications strongly indicates the presence of multiple pharmacologically active constituents in the plant.

4. PHYTOCHEMICAL CONSTITUENTS OF *AJUGA BRACTEOSA*

The medicinal significance of *Ajuga bracteosa* is primarily attributed to its rich phytochemical composition. Secondary metabolites isolated from different parts of the plant include flavonoids, terpenoids, glycosides, phytoecdysteroids, sterols, tannins, saponins, and phenolic compounds.

4.1 Major Phytochemical Groups

4.1.1 Flavonoids

Flavonoids are among the most abundant compounds in *Ajuga bracteosa*. Important flavonoids include luteolin, apigenin, and quercetin. These compounds possess strong antioxidant, anti-inflammatory, anticancer, and neuroprotective properties.

4.1.2 Phenolic Compounds

Phenolic compounds and tannins exhibit significant free radical scavenging activity and protect cells from oxidative damage.

4.1.3 Terpenoids

Terpenoids, particularly diterpenoids and triterpenoids, are responsible for anti-inflammatory and antimicrobial activities.

4.1.4 Steroids and Phytosterols

β-sitosterol and stigmasterol are important sterols isolated from the plant. These compounds contribute to immunomodulatory and anti-inflammatory effects.

4.1.5 Glycosides

Iridoid glycosides are associated with hepatoprotective and cardioprotective properties.

4.1.6 Phytoecdysteroids

Phytoecdysteroids such as 20-hydroxyecdysone and cyasterone are characteristic constituents of the genus *Ajuga*. They exhibit adaptogenic, anabolic, and cytoprotective effects.

4.1.7 Saponins

Saponins possess antimicrobial, expectorant, and immunomodulatory activities.

4.2 Important Bioactive Compounds

The major compounds identified from *Ajuga bracteosa* include:

- Cerotic acid
- Gamma-sitosterol
- Ceryl alcohol
- Ajugapitin
- β-sitosterol
- Stigmasterol
- Luteolin
- Quercetin
- Apigenin
- 20-hydroxyecdysone

These compounds collectively contribute to the multitarget pharmacological effects of the plant.

5. PHARMACOLOGICAL ACTIVITIES

5.1 Anti-inflammatory Activity

Inflammation is a complex biological response associated with numerous chronic diseases. Phytochemicals present in *Ajuga bracteosa* such as flavonoids, diterpenoids, and sterols inhibit inflammatory mediators including TNF-α, IL-6, and cyclooxygenase enzymes.

Experimental studies have demonstrated that methanolic extracts of the plant exhibit significant anti-inflammatory activity. The inhibition of inflammatory pathways may be associated with modulation of MAPK and NF-κB signaling pathways.

5.2 Antioxidant Activity

Oxidative stress plays a crucial role in aging and chronic diseases including cancer, diabetes, and neurodegenerative disorders. Flavonoids and phenolic compounds in *Ajuga bracteosa* exhibit strong antioxidant activity by neutralizing free radicals and preventing cellular damage.

Studies have reported significant ferric reducing antioxidant power and free radical scavenging activity in plant extracts.

5.3 Antimicrobial Activity

Extracts of *Ajuga bracteosa* possess antibacterial and antifungal properties against various pathogenic microorganisms. Terpenoids, tannins, and essential oils contribute to microbial inhibition by disrupting cell membranes and interfering with microbial metabolism.

5.4 Anticancer Activity

Several phytoconstituents isolated from the plant have shown cytotoxic effects against cancer cells. Flavonoids and diterpenoids may inhibit tumor growth by inducing apoptosis and suppressing cell proliferation.

Research studies have also demonstrated antimutagenic activity of isolated compounds such as 14,15-dihydroajugapitin.

5.5 Antidiabetic Activity

The plant exhibits alpha-glucosidase inhibitory activity and improves glucose metabolism. Flavonoids and glycosides are believed to contribute to blood glucose regulation.

5.6 Hepatoprotective Activity

Traditional use of the plant in liver disorders is supported by studies demonstrating hepatoprotective activity against chemically induced liver damage.

5.7 Neuroprotective Activity

Phytoecdysteroids and antioxidant compounds present in the plant may protect neurons from oxidative stress and neurodegeneration.

5.8 Wound Healing Activity

Experimental studies have confirmed significant wound healing activity of *Ajuga bracteosa*. The plant promotes collagen synthesis, fibroblast proliferation, and tissue regeneration.

6. NETWORK PHARMACOLOGY: CONCEPT AND SIGNIFICANCE

Network pharmacology is a systems-level approach that studies interactions among drugs, targets, pathways, and diseases. Unlike conventional pharmacology, which focuses on a single target, network pharmacology explains the multitarget therapeutic actions of herbal medicines.

6.1 Principles of Network Pharmacology

The basic principles include:

1. Drug-target interaction analysis
2. Compound-target network construction
3. Protein-protein interaction analysis
4. Pathway enrichment analysis
5. Disease-gene association studies

This approach is highly relevant to medicinal plant research because herbal extracts contain multiple compounds acting synergistically.

6.2 Applications in Herbal Medicine Research

Network pharmacology helps in:

- Identification of active phytoconstituents
- Prediction of molecular targets
- Understanding synergistic effects
- Discovery of therapeutic pathways
- Development of multitarget drugs

- Personalized medicine approaches

6.3 Advantages

1. Holistic understanding of biological systems
2. Reduced cost and time in drug discovery
3. Identification of multiple therapeutic targets
4. Integration of computational and experimental data
5. Better understanding of herbal medicine mechanisms

6.4 Limitations

Despite its advantages, network pharmacology has certain limitations:

- Dependence on database accuracy
- Requirement of large biological datasets
- Need for experimental validation
- Complexity in data interpretation

7. BIOINFORMATICS TOOLS USED IN NETWORK PHARMACOLOGY

Several computational tools and databases are commonly employed in network pharmacology studies of medicinal plants.

7.1 Dr. Duke's Phytochemical and Ethnobotanical Databases

This database provides information regarding medicinal plants, phytochemicals, biological activities, and ethnobotanical uses.

7.2 IMPPAT Database

IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) is a comprehensive database containing detailed information about Indian medicinal plants and their phytochemical constituents.

7.3 SwissADME

SwissADME predicts pharmacokinetic properties including absorption, distribution, metabolism, and excretion

7.4 ProTox-3.0

ProTox-3.0 predicts toxicity endpoints including hepatotoxicity, carcinogenicity, cytotoxicity, and LD50 values.

8. NETWORK PHARMACOLOGY-BASED THERAPEUTIC ANALYSIS OF *AJUGA BRACTEOSA*

8.1 Identification of Bioactive Compounds

Phytoconstituents identified from *Ajuga bracteosa* through literature surveys and databases include flavonoids, sterols, phenolics, and terpenoids. These compounds were screened for drug-likeness and ADME properties.

8.2 Drug-Likeness Evaluation

Lipinski's Rule of Five was applied to evaluate the drug-likeness of selected compounds.

Most compounds demonstrated:

- Molecular weight less than 500 Da
- LogP values within acceptable range
- Appropriate hydrogen bond donor and acceptor limits
- Favorable pharmacokinetic properties

Flavonoids such as luteolin and apigenin showed excellent compliance with drug-likeness parameters.

8.3 Multi-Target Therapeutic Action

The network pharmacology approach revealed that phytochemicals from *Ajuga bracteosa* exhibit multitarget behavior. Such synergistic interactions are beneficial in complex diseases involving multiple signaling pathways.

9. TOXICITY PREDICTION AND SAFETY EVALUATION

Safety evaluation is a critical aspect of herbal drug development. Computational toxicity studies were performed using ProTox-3.0.

9.1 Cerotic Acid

Cerotic acid showed low toxicity potential with:

- Inactive hepatotoxicity
- Inactive mutagenicity
- Inactive carcinogenicity
- Predicted LD50 of approximately 5000 mg/kg

These findings suggest a favorable safety profile.

9.2 Gamma-Sitosterol

Gamma-sitosterol demonstrated moderate safety with low hepatotoxic and mutagenic risk. Predicted LD50 was approximately 890 mg/kg.

9.3 Ceryl Alcohol

Ceryl alcohol also exhibited acceptable toxicity parameters with a predicted LD50 of approximately 1000 mg/kg.

9.4 Overall Toxicity Assessment

Most compounds identified from *Ajuga bracteosa* belonged to low toxicity classes and showed no major carcinogenic or hepatotoxic effects.

The toxicity profiling strongly supports the potential use of the plant in herbal drug development under controlled therapeutic doses.

10. LITERATURE SURVEY

Several scientific investigations have validated the pharmacological significance of *Ajuga bracteosa*.

10.1 Antimutagenic Activity

Studies on methanolic extracts of the plant reported significant antimutagenic activity against EMS-induced mutagenicity in mice. Compounds such as 14,15-dihydroajugapitin demonstrated strong anticancer potential.

10.2 Antioxidant and Anti-inflammatory Studies

Research investigations confirmed strong antioxidant and anti-inflammatory activities associated with flavonoids and phenolic compounds.

10.3 Wound Healing Studies

Experimental studies demonstrated enhanced collagen synthesis, fibroblast proliferation, and wound contraction following treatment with *Ajuga bracteosa* extracts.

10.4 Ethnopharmacological Reviews

Comprehensive reviews highlighted the ethnobotanical significance of the plant and summarized more than forty isolated chemical constituents.

The collective literature strongly supports the medicinal importance of *Ajuga bracteosa* and justifies further pharmaceutical research.

11. FUTURE PERSPECTIVES

Although considerable progress has been made in understanding the therapeutic significance of *Ajuga bracteosa*, several research gaps remain.

11.1 Clinical Validation

Most studies are limited to in vitro and in silico investigations. Clinical trials are required to validate safety and efficacy in humans.

11.2 Standardization of Herbal Formulations

Standardization of plant extracts is essential to ensure consistent quality and therapeutic activity.

11.3 Advanced Omics Approaches

Integration of genomics, proteomics, metabolomics, and transcriptomics with network pharmacology may provide deeper insights into molecular mechanisms.

11.4 Conservation Strategies

Overexploitation of medicinal plants threatens biodiversity. Sustainable cultivation and conservation practices are necessary to preserve *Ajuga bracteosa*.

11.5 Drug Development

The multitarget pharmacological actions of phytoconstituents make the plant a promising candidate for novel herbal drug discovery.

12. CONCLUSION

Ajuga bracteosa is an important medicinal herb possessing diverse pharmacological properties due to its rich phytochemical composition. The plant contains flavonoids, terpenoids, phenolic compounds, glycosides, phytoecdysteroids, sterols, and other bioactive constituents responsible for anti-inflammatory, antioxidant, antimicrobial, anticancer, antidiabetic, hepatoprotective, neuroprotective, and wound healing activities.

Traditional medicinal applications of the plant are strongly supported by modern pharmacological and computational studies. Network pharmacology has emerged as a powerful tool for understanding the multitarget mechanisms of herbal medicines and identifying key compound-target-pathway interactions.

Computational analysis of *Ajuga bracteosa* phytoconstituents revealed interactions with important molecular targets such as AKT1, TNF, IL6, and MAPK signaling proteins. Pathway enrichment studies further demonstrated involvement in inflammatory, oxidative stress, apoptotic, and metabolic pathways.

Toxicity prediction studies indicate that the majority of compounds possess low toxicity and favorable pharmacokinetic properties, supporting their potential use in therapeutic applications. Nevertheless, further experimental validation, clinical studies, and standardization are essential before translating these findings into pharmaceutical products.

Overall, *Ajuga bracteosa* represents a promising medicinal plant with significant future potential in herbal medicine, pharmaceutical research, and network pharmacology-based drug discovery.

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