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Multi-Target Mechanism of *Ajuga bracteosa* Using Network Pharmacology

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Abstract:

Ajuga bracteosa Wall. ex Benth. is an important medicinal herb belonging to the family Lamiaceae and is widely distributed throughout the Himalayan and sub-Himalayan regions. The plant has been traditionally used in Ayurvedic, Unani, and folk medicine systems for the management of fever, inflammation, respiratory disorders, liver dysfunction, microbial infections, diabetes, neurological disorders, and wound healing. The therapeutic importance of *Ajuga bracteosa* is mainly attributed to the presence of diverse bioactive phytochemicals such as flavonoids, terpenoids, phytoecdysteroids, glycosides, sterols, iridoids, and phenolic compounds. Recent advances in computational biology and systems pharmacology have enabled the application of network pharmacology approaches for understanding the multi-component and multi-target mechanisms of medicinal plants.

The present review comprehensively summarizes the ethnobotanical significance, phytochemical profile, pharmacological activities, toxicity evaluation, and network pharmacology-based therapeutic potential of *Ajuga bracteosa*. Data from published scientific literature, phytochemical databases, and computational prediction platforms were critically analyzed to identify major phytoconstituents and their associated biological targets. Network pharmacology studies suggest that the phytochemicals of *Ajuga bracteosa* interact with multiple proteins and signaling pathways involved in inflammation, oxidative stress, apoptosis, cancer progression, and metabolic regulation. Hub targets including AKT1, TNF, IL6, MAPK1, and NF-κB pathways are strongly associated with the pharmacological effects of the plant.

Several identified compounds demonstrated acceptable drug-likeness properties and low predicted toxicity profiles. Toxicity prediction studies indicated relatively low hepatotoxicity, neurotoxicity, and mutagenicity for most phytoconstituents, although some compounds exhibited moderate cardiotoxicity and immunotoxicity concerns requiring further validation. The review highlights the importance of integrating phytochemistry, bioinformatics, systems biology, and pharmacology to scientifically validate traditional medicinal plants. Overall, *Ajuga bracteosa* emerges as a promising source of multi-target therapeutic agents with potential applications in inflammation-related disorders, cancer, metabolic diseases, and neurodegenerative conditions.

Keywords: *Ajuga bracteosa*, network pharmacology, phytochemicals, medicinal plants, anti-inflammatory activity, antioxidant activity, toxicity prediction, bioactive compounds.

1. Introduction

Medicinal plants have served as an important source of therapeutic agents since ancient times. Traditional systems of medicine such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine rely heavily on plant-derived compounds for the treatment of various diseases. In recent years, scientific interest in medicinal plants has increased significantly due to the growing demand for natural therapeutic agents with fewer side effects compared to synthetic drugs. Among these medicinal plants, *Ajuga bracteosa* Wall. ex Benth. has gained remarkable attention because of its diverse pharmacological activities and rich phytochemical composition.

Ajuga bracteosa belongs to the family Lamiaceae and is commonly distributed in temperate and hilly regions of India, Pakistan, Nepal, and China. The plant is recognized by its creeping habit, hairy stems, bluish-purple flowers, and medicinally valuable aerial parts. Traditionally, the plant has been used to treat respiratory disorders, fever, sore throat, jaundice, digestive disorders, hypertension, inflammatory conditions, and skin diseases.

Modern pharmacological investigations have revealed that *Ajuga bracteosa* possesses antioxidant, anti-inflammatory, antimicrobial, antidepressant, anticoagulant, hepatoprotective, cytotoxic, and wound healing properties. These activities are associated with the presence of bioactive compounds such as flavonoids, phenolic acids, iridoid glycosides, phytoecdysteroids, diterpenoids, sterols, and terpenoids.

Conventional pharmacology usually follows the concept of "one drug–one target–one disease." However, medicinal plants contain multiple compounds capable of interacting with several molecular targets simultaneously. Therefore, understanding the therapeutic mechanism of herbal medicines requires a holistic approach. Network pharmacology has emerged as an advanced systems biology tool that integrates pharmacology, bioinformatics, computational biology, and molecular interaction analysis to understand multi-target drug actions.

The network pharmacology approach is particularly useful for studying medicinal plants because it enables the identification of:

- Bioactive compounds
- Molecular targets
- Protein–protein interactions
- Biological pathways
- Disease associations
- Mechanistic therapeutic actions

This review focuses on the ethnomedicinal significance, phytochemical constituents, pharmacological properties, toxicity profiles, and network pharmacology-based therapeutic mechanisms of *Ajuga bracteosa*. The review also highlights future research opportunities for the development of plant-based therapeutic agents.

2. Botanical Description and Taxonomy

2.1 Taxonomical Classification

Rank	Classification
Kingdom	Plantae
Division	Magnoliophyta

Rank	Classification
Class	Magnoliopsida
Order	Lamiales
Family	Lamiaceae
Genus	*Ajuga*
Species	*Ajuga bracteosa*

2.2 Common Names

- English: Bracted Bugleweed
- Hindi: Nilkanthi
- Sanskrit: Neelkanthi

2.3 Morphological Characteristics

Ajuga bracteosa is a perennial herbaceous plant characterized by:

- Creeping or ascending hairy stems
- Opposite leaves with serrated margins
- Bluish-purple flowers arranged in spikes
- Fibrous root system
- Aromatic medicinal aerial parts

The plant usually grows in temperate climates, open grasslands, forest margins, and hilly slopes.

2.4 Geographical Distribution

The plant is widely distributed in:

- India (Himalayan regions)
- Pakistan
- Nepal
- China
- Afghanistan

Due to overharvesting and habitat destruction, the plant is considered threatened in several regions.

3. Ethnomedicinal Importance of *Ajuga bracteosa*

The therapeutic applications of *Ajuga bracteosa* have been extensively documented in traditional medicine systems. Local healers and tribal communities use different plant parts for treating multiple diseases.

3.1 Traditional Uses

Respiratory Disorders

The plant is traditionally used in the treatment of:

- Asthma
- Bronchitis
- Cough
- Sore throat
- Cold and fever

Gastrointestinal Disorders

Extracts of the plant are used for:

- Dyspepsia
- Indigestion
- Gastric irritation
- Constipation

Inflammatory Conditions

The herb has been used to reduce:

- Joint pain
- Rheumatism
- Swelling
- Arthritis

Liver Disorders

Traditional healers use the plant in:

- Jaundice
- Liver inflammation
- Detoxification therapies

Skin Diseases and Wound Healing

Paste preparations are applied externally for:

- Wounds
- Burns
- Skin infections
- Ulcers

The broad ethnomedicinal use of *Ajuga bracteosa* suggests the presence of multiple biologically active compounds capable of acting through diverse molecular mechanisms.

4. Phytochemical Constituents

Phytochemical studies have demonstrated that *Ajuga bracteosa* contains a wide variety of secondary metabolites responsible for its medicinal properties.

4.1 Major Phytochemical Classes

Flavonoids

Flavonoids are among the most important compounds identified in the plant. They possess:

- Antioxidant activity
- Anti-inflammatory activity
- Anticancer potential
- Neuroprotective effects

Terpenoids and Diterpenoids

Terpenoids contribute to:

- Antimicrobial activity
- Cytotoxic effects
- Anti-inflammatory actions

Phytoecdysteroids

Phytoecdysteroids such as 20-hydroxyecdysone exhibit:

- Adaptogenic effects
- Protein synthesis stimulation
- Antioxidant activity

Phenolic Compounds

Phenolic compounds are known for:

- Free radical scavenging
- Anti-aging effects
- Cytoprotective activity

Sterols and Glycosides

Sterols and glycosides contribute to:

- Immunomodulatory effects
- Cardioprotective activity
- Anti-inflammatory actions

4.2 Important Identified Compounds

Some important compounds isolated from *Ajuga bracteosa* include:

- Daucosterol
- Hexacosan-1-ol
- Triacontan-1-ol-docosanoate
- β-sitosterol
- Stigmasterol
- Ajugarin I
- 8-O-acetylharpagide
- Cyasterone
- 20-hydroxyecdysone

These compounds contribute significantly to the pharmacological properties of the plant.

5. Pharmacological Activities

5.1 Antioxidant Activity

Oxidative stress plays a major role in aging, inflammation, neurodegeneration, and cancer. The flavonoids and phenolic compounds of *Ajuga bracteosa* exhibit strong antioxidant activity by scavenging free radicals and reducing oxidative damage.

Studies have shown that methanolic extracts of the plant demonstrate high reducing power and free radical scavenging activity.

5.2 Anti-inflammatory Activity

Inflammation is associated with numerous chronic diseases including arthritis, cancer, and cardiovascular disorders. *Ajuga bracteosa* extracts inhibit inflammatory mediators such as:

- TNF-α
- IL-6
- COX enzymes
- NF-κB pathways

The anti-inflammatory activity is mainly attributed to flavonoids and terpenoids.

5.3 Antimicrobial Activity

Several extracts of the plant exhibit antibacterial and antifungal properties against pathogenic microorganisms.

Reported microorganisms include:

- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida albicans*

The antimicrobial activity may be associated with phenolic compounds and terpenoids.

5.4 Anticancer Activity

Research studies indicate that phytochemicals from *Ajuga bracteosa* possess cytotoxic and antimutagenic effects.

Mechanisms include:

- Induction of apoptosis
- Cell cycle arrest
- Oxidative stress modulation
- Inhibition of cancer signaling pathways

5.5 Antidepressant Activity

Animal studies have shown reduced immobility time in behavioral tests, suggesting antidepressant potential.

5.6 Hepatoprotective Activity

The plant has shown protective effects against chemically induced liver damage due to antioxidant and anti-inflammatory mechanisms.

5.7 Wound Healing Activity

Experimental studies demonstrated enhanced:

- Collagen synthesis
- Fibroblast proliferation
- Epithelial regeneration
- Angiogenesis

These findings support traditional wound healing applications.

6. Concept of Network Pharmacology

Network pharmacology is an emerging discipline that studies interactions between drugs, genes, proteins, pathways, and diseases at a systems level.

6.1 Principles of Network Pharmacology

Unlike conventional pharmacology, network pharmacology follows:

One drug → Multiple targets → Multiple effects

This concept is particularly relevant to herbal medicines because medicinal plants contain multiple compounds that act synergistically.

6.2 Components of Network Pharmacology

Network pharmacology integrates:

- Pharmacology
- Systems biology
- Bioinformatics
- Computational biology
- Molecular biology

6.3 Steps in Network Pharmacology Analysis

1. Identification of bioactive compounds
2. Drug-likeness screening
3. ADME analysis
4. Target prediction
5. Disease target identification
6. Network construction
7. Protein–protein interaction analysis
8. GO and KEGG enrichment analysis
9. Experimental validation

6.4 Advantages of Network Pharmacology

- Holistic therapeutic understanding

- Identification of synergistic effects
- Cost-effective drug discovery
- Better understanding of herbal medicines
- Identification of novel drug targets

6.5 Limitations

- Requirement for large datasets
- Dependence on computational prediction accuracy
- Need for experimental validation

7. Software and Databases Used in Network Pharmacology

7.1 Dr. Duke's Phytochemical and Ethnobotanical Database

This USDA-supported database provides information about:

- Medicinal plants
- Phytochemical constituents
- Ethnobotanical uses
- Biological activities

7.2 IMPPAT Database

IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) is widely used for:

- Phytochemical identification
- Drug-likeness evaluation
- Therapeutic target prediction
- Pharmacological screening

7.3 SwissADME

SwissADME predicts:

- Absorption
- Distribution
- Metabolism
- Excretion
- Drug-likeness

7.4 SwissTargetPrediction

This platform predicts protein targets of small molecules based on structural similarity.

7.5 STRING Database

STRING is used for:

- Protein–protein interaction analysis
- Functional enrichment
- Network visualization

7.6 ProTox-3.0

ProTox-3.0 predicts:

- LD50 values
- Organ toxicity
- Carcinogenicity
- Mutagenicity
- Cytotoxicity

8. Network Pharmacology of *Ajuga bracteosa*

8.1 Identification of Bioactive Compounds

Bioactive compounds from *Ajuga bracteosa* were identified through literature surveys and phytochemical databases.

Selected compounds included:

- Daucosterol
- Hexacosan-1-ol
- Triacontan-1-ol-docosanoate
- Flavonoids
- Terpenoids
- Sterols

These compounds were selected based on:

- Biological relevance
- Drug-likeness properties
- Pharmacological significance

8.2 Drug-Likeness Evaluation

Drug-likeness screening was performed using Lipinski's Rule of Five.

Parameters Evaluated

- Molecular weight
- Hydrogen bond donors
- Hydrogen bond acceptors
- Lipophilicity (LogP)
- Rotatable bonds

Findings

Flavonoids generally demonstrated favorable drug-likeness profiles, whereas certain sterols and long-chain compounds showed moderate compliance.

8.3 Target Prediction

SwissTargetPrediction and related computational tools identified multiple protein targets associated with the selected compounds.

Major predicted targets included:

- AKT1
- TNF

- IL6
- MAPK1
- CASP3
- EGFR
- VEGFA

8.4 Compound–Target Network

Network construction revealed that individual phytochemicals interact with multiple proteins.
This supports the concept of:

- Multi-target therapy
- Synergistic activity
- Systems-level therapeutic action

8.5 Protein–Protein Interaction Analysis

PPI analysis highlighted hub genes involved in:

- Inflammation
- Apoptosis
- Oxidative stress
- Cancer progression
- Immune regulation

9. Toxicity Prediction and Safety Evaluation

9.1 Daucosterol

Drug-Likeness Score

- 0.5

Predicted Safety Characteristics

- Low hepatotoxicity
- Low neurotoxicity
- Low mutagenicity
- Low carcinogenicity

Concerns

- Cardiotoxicity
- Immunotoxicity
- Nephrotoxicity

Predicted LD50

- 8000 mg/kg

Overall, daucosterol exhibited relatively low acute toxicity with acceptable pharmacological safety.

9.2 Hexacosan-1-ol

Drug-Likeness Score

- -0.92

Predicted Safety Characteristics

- Low organ toxicity
- Low mutagenicity
- Minimal endocrine disruption

Concerns

- Poor drug-likeness
- BBB permeability
- Moderate ecotoxicity

Predicted LD50

- 1000 mg/kg

9.3 Triacontan-1-ol-docosanoate

Drug-Likeness Score

- -0.76

Predicted Safety Characteristics

- Low hepatotoxicity
- Low neurotoxicity
- Minimal CYP450 interaction

Concerns

- Carcinogenicity prediction
- BBB permeability
- Ecotoxicity

Predicted LD50

- 5000 mg/kg

9.4 Overall Toxicity Interpretation

Most compounds demonstrated:

- Low acute toxicity
- Acceptable organ safety
- Minimal mutagenic potential

However, further in vitro and in vivo toxicological studies are essential before therapeutic application.

10. Therapeutic Potential of *Ajuga bracteosa*

The integrated phytochemical and network pharmacology analysis indicates that *Ajuga bracteosa* may have therapeutic potential in:

10.1 Inflammatory Disorders

Through modulation of:

- TNF signaling
- NF-κB pathways
- Cytokine regulation

10.2 Cancer Therapy

Potential anticancer mechanisms include:

- Apoptosis induction
- Cell cycle regulation
- Oxidative stress modulation
- PI3K-Akt inhibition

10.3 Neuroprotection

Antioxidant and anti-inflammatory activities may contribute to neuroprotective effects.

10.4 Metabolic Disorders

The plant may regulate:

- Oxidative stress
- Insulin signaling
- Lipid metabolism

10.5 Antimicrobial Applications

The plant exhibits broad-spectrum antimicrobial potential against bacterial and fungal pathogens.

11. Future Perspectives

Despite significant progress in phytochemical and computational studies, several limitations remain. Future studies should focus on:

- Isolation of novel compounds
- Experimental validation of predicted targets
- Molecular docking studies
- In vitro mechanistic studies
- In vivo pharmacological evaluation
- Clinical safety assessment
- Standardization of herbal formulations
- Sustainable cultivation and conservation strategies

Advanced technologies such as:

- Artificial intelligence
- Multi-omics analysis
- Machine learning-based drug discovery
- Molecular simulation

may further improve understanding of the therapeutic mechanisms of *Ajuga bracteosa*.

12. Conclusion

Ajuga bracteosa is an important medicinal herb possessing significant therapeutic potential due to its rich phytochemical composition and multi-target pharmacological actions. The plant contains diverse biologically active compounds including flavonoids, terpenoids, phytoecdysteroids, sterols, glycosides,

and phenolic compounds that contribute to antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, and wound healing activities.

Network pharmacology provides a scientific framework for understanding the synergistic mechanisms of medicinal plants. Computational studies revealed that phytochemicals from *Ajuga bracteosa* interact with multiple molecular targets and signaling pathways associated with inflammation, apoptosis, oxidative stress, immune regulation, and cancer progression.

Important pathways such as PI3K-Akt, MAPK, TNF, and NF-κB were identified as major therapeutic pathways influenced by the plant constituents. Toxicity prediction studies indicated that most compounds possess relatively low acute toxicity and acceptable safety profiles, although certain compounds require additional toxicological validation.

Overall, the integration of phytochemistry, systems biology, computational pharmacology, and network analysis strongly supports the traditional medicinal importance of *Ajuga bracteosa*. The plant represents a promising natural source for future drug discovery and development of multi-target therapeutic agents. However, additional experimental and clinical investigations are necessary to confirm the computational findings and establish therapeutic efficacy and safety.

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