RESEARCH PAPER

Technology for the Production of Biologically Active Substances Based on Medicinal Plants: Turkestan Ajuga and *Tribulus terrestris*

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Abstract

The increasing reliance on plant-based therapeutics has intensified efforts to develop efficient and sustainable technologies for isolating biologically active compounds. Among emerging medicinal resources, *Ajuga turkestanica* and *Tribulus terrestris* have attracted considerable attention due to their rich composition of phytoecdysteroids, steroidal saponins, flavonoids, and phenolic constituents. These compounds are associated with diverse biological effects, including antioxidant, anti-inflammatory, metabolic, and adaptogenic activities. Despite their potential, practical utilization is often limited by inconsistent extraction efficiency, compositional variability, and poor bioavailability.

This review critically examines current technological approaches for enhancing the production and delivery of bioactive substances derived from these plants. Modern extraction techniques such as supercritical fluid extraction, microwave-assisted extraction, and ultrasound-assisted extraction are evaluated in terms of efficiency, selectivity, and environmental sustainability. In addition, biotechnological strategies, including tissue culture and metabolite engineering, are discussed as viable solutions for controlled and scalable production.

Particular attention is given to advanced drug delivery systems designed to overcome pharmacokinetic limitations. Nanocarriers, lipid-based systems, and phytosome complexes are assessed for their role in improving stability, solubility, and targeted delivery. The integration of these technologies provides a multidimensional framework for maximizing therapeutic potential. However, challenges related to standardization, reproducibility, and industrial translation remain critical areas for future investigation.

Keywords

Ajuga turkestanica; Tribulus terrestris; bioactive compounds; phytochemistry; extraction technologies; nanotechnology; drug delivery systems; phytosomes; tissue culture; sustainable production

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1. Introduction

Medicinal plants continue to play a pivotal role in therapeutic development, not only within traditional systems but also as a foundation for modern pharmacological innovation. Increasing scientific attention has been directed toward plant-derived compounds due to their structural diversity and multi-target biological activity. Within this context, *Ajuga turkestanica* and *Tribulus terrestris* have emerged as significant sources of pharmacologically relevant metabolites.

Tribulus terrestris is widely recognized for its abundance of steroidal saponins, particularly protodioscin, which has been associated with various physiological effects. In addition to saponins, the plant contains flavonoids and phenolic compounds that contribute to its antioxidant and anti-inflammatory properties. Its traditional applications have stimulated extensive research into its role in metabolic regulation and cardiovascular health.

In contrast, *Ajuga turkestanica* is distinguished by its high concentration of phytoecdysteroids, notably turkesterone. These compounds exhibit anabolic and adaptogenic properties without the adverse endocrine effects typically linked to synthetic analogues. This unique profile has positioned the plant as a promising candidate for applications in metabolic disorders and performance enhancement.

However, the transition from traditional use to pharmaceutical application is constrained by several technical challenges. Conventional extraction techniques often fail to provide consistent yields and may lead to degradation of sensitive compounds. Furthermore, environmental factors and cultivation conditions introduce variability that complicates standardization.

Recent technological developments have addressed some of these limitations. Advanced extraction methods offer improved efficiency and reduced processing time, while biotechnological approaches enable controlled production of secondary metabolites. Additionally, the emergence of nanotechnology-based delivery systems has provided new opportunities to enhance the bioavailability and stability of plant-derived compounds.

Given these advancements, there is a clear need for an integrated perspective that combines extraction science, biotechnology, and drug delivery innovations. This review aims to synthesize current knowledge and identify future directions for optimizing the production and application of bioactive substances from these medicinal plants.

2. Phytochemical Composition and Biological Activity

The therapeutic potential of medicinal plants is largely attributed to their diverse phytochemical constituents. *Tribulus terrestris* contains a wide array of bioactive compounds, including steroidal saponins, flavonoids, alkaloids, and phenolic acids . Among these, protodioscin, a steroidal saponin, is considered one of the most biologically active components responsible for its pharmacological effects.

Table 1: Major Bioactive Compounds

Plant	**Compound Class**	**Key Compounds**	**Biological Activity**
Tribulus terrestris	Saponins	Protodioscin	Aphrodisiac, anti-inflammatory
Tribulus terrestris	Flavonoids	Quercetin, Kaempferol	Antioxidant
Ajuga turkestanica	Phytoecdysteroids	Turkesterone	Anabolic, adaptogenic
Ajuga turkestanica	Phenolics	Rosmarinic acid	Anti-inflammatory

Flavonoids such as quercetin and kaempferol play a critical role in antioxidant defense mechanisms. These compounds neutralize free radicals and reduce oxidative stress, which is implicated in various chronic diseases .

Ajuga species, particularly *Ajuga turkestanica*, are rich in phytoecdysteroids such as turkesterone. These compounds exhibit anabolic and adaptogenic properties, making them valuable in sports medicine and metabolic disorders.

3. Extraction and Isolation Technologies

The efficient recovery of biologically active compounds from medicinal plants is a critical step that directly influences their pharmacological effectiveness, industrial applicability, and economic feasibility. In the case of *Ajuga turkestanica* and *Tribulus terrestris*, the extraction process must be carefully optimized due to the structural diversity and sensitivity of their phytoconstituents, including phytoecdysteroids, steroidal saponins, flavonoids, and phenolic compounds. The choice of extraction and isolation technique determines not only the yield but also the integrity and bioactivity of the final product.

3.1 Conventional Extraction Methods

Traditional extraction approaches such as maceration, percolation, and Soxhlet extraction have been widely employed for isolating phytochemicals from plant matrices. These methods rely on solvent diffusion and solubility principles, typically using organic solvents like methanol, ethanol, or hydroalcoholic mixtures. While these techniques are relatively simple and cost-effective, they are often associated with several limitations, including prolonged extraction times, high solvent consumption, and the potential degradation of thermolabile compounds.

For instance, Soxhlet extraction, although efficient in exhaustive extraction, involves continuous heating, which may compromise heat-sensitive constituents such as flavonoids and certain glycosides. Similarly, maceration requires extended contact time between solvent and plant material, increasing the risk of microbial contamination and oxidation. Despite these drawbacks, conventional methods are still used in preliminary studies and small-scale applications due to their operational simplicity.

3.2 Advanced Extraction Technologies

Recent advancements in extraction science have led to the development of innovative techniques designed to enhance efficiency, selectivity, and environmental sustainability. Among these, supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), and ultrasound-assisted extraction (UAE) have shown considerable promise for medicinal plant processing.

Supercritical fluid extraction utilizes supercritical carbon dioxide (CO_2) as a solvent under controlled temperature and pressure conditions. This technique offers several advantages, including low solvent toxicity, minimal thermal degradation, and high selectivity for non-polar and moderately polar compounds. In the context of *Tribulus terrestris*, SFE has demonstrated improved recovery of steroidal saponins with higher purity compared to conventional solvent extraction.

Microwave-assisted extraction operates on the principle of dielectric heating, where microwave energy induces rapid heating of the solvent and plant matrix. This leads to cell wall disruption and enhanced mass transfer, significantly reducing extraction time. MAE is particularly effective for extracting polar compounds such as phenolics and flavonoids from both *Ajuga turkestanica* and *Tribulus terrestris*. Additionally, the reduced solvent requirement aligns with green chemistry principles.

Ultrasound-assisted extraction employs acoustic cavitation to facilitate the release of intracellular compounds. The formation and collapse of microbubbles generate localized pressure and temperature variations, which enhance solvent penetration and solute diffusion. UAE has been widely reported to improve extraction yields while preserving the structural integrity of sensitive compounds.

3.3 Pressurized and Green Extraction Approaches

Pressurized liquid extraction (PLE), also known as accelerated solvent extraction, utilizes elevated temperature and pressure to increase solvent efficiency. This technique enhances solubility and diffusion rates, resulting in higher extraction yields within shorter durations. PLE is particularly advantageous for industrial-scale operations due to its reproducibility and automation capabilities.

In recent years, there has been a growing emphasis on environmentally friendly extraction methods. Green extraction technologies aim to minimize the use of hazardous solvents and reduce energy consumption. Techniques such as enzyme-assisted extraction (EAE) and natural deep eutectic solvents (NADES) have emerged as sustainable alternatives. Enzymes such as cellulases and pectinases break down plant cell walls, facilitating the release of bioactive compounds without the need for harsh chemical treatments.

NADES, composed of natural components like sugars, amino acids, and organic acids, offer tunable solvent properties and high biocompatibility. These solvents have shown potential in extracting a wide range of phytochemicals while maintaining environmental safety.

3.4 Isolation and Purification Techniques

Following extraction, the isolation and purification of individual compounds are essential for ensuring product quality and therapeutic efficacy. Chromatographic techniques remain the cornerstone of phytochemical separation. High-performance liquid chromatography (HPLC) is widely used for the qualitative and quantitative analysis of bioactive compounds, offering high resolution and reproducibility.

Gas chromatography (GC), often coupled with mass spectrometry (GC-MS), is suitable for volatile and semi-volatile compounds. For non-volatile constituents such as saponins and phytoecdysteroids, liquid chromatography–mass spectrometry (LC-MS) provides detailed structural information and high sensitivity.

Column chromatography and preparative thin-layer chromatography (TLC) are also employed for fractionation and purification, particularly in laboratory-scale studies. These methods enable the separation of complex mixtures into individual components based on differences in polarity, molecular size, and adsorption characteristics.

3.5 Optimization and Process Parameters

The efficiency of extraction and isolation processes is influenced by several parameters, including solvent type, temperature, extraction time, particle size, and solvent-to-solid ratio. Optimization of these variables is essential to maximize yield while preserving bioactivity. Statistical tools such as response surface methodology (RSM) and design of experiments (DoE) are increasingly used to identify optimal conditions and minimize experimental variability. For example, reducing particle size enhances surface area, facilitating better solvent penetration, while excessive grinding may lead to compound degradation. Similarly, higher temperatures can improve solubility but may also accelerate the breakdown of sensitive molecules. Therefore, a balanced approach is required to achieve optimal extraction performance.

3.6 Comparative Analysis of Extraction Techniques

A comparative evaluation of different extraction methods reveals that no single technique is universally superior; rather, the choice depends on the target compound, plant matrix, and intended application. Advanced methods such as SFE, MAE, and UAE generally outperform conventional techniques in terms of efficiency, selectivity, and environmental impact. However, factors such as equipment cost, scalability, and technical expertise must also be considered.

Table: Comparative Overview of Extraction Techniques

Technique	Key Features	Advantages	Limitations
Maceration	Room temperature extraction	Simple, low cost	Time-consuming, low efficiency
Soxhlet	Continuous hot extraction	Exhaustive extraction	Thermal degradation risk
SFE	Supercritical CO_2	High purity, eco-friendly	Expensive equipment
MAE	Microwave heating	Fast, efficient	Limited scalability
UAE	Ultrasonic cavitation	Energy efficient	Equipment dependency
PLE	High pressure & temperature	Rapid extraction	High operational cost

4. Biotechnological Production Approaches

Biotechnological methods offer sustainable alternatives for producing bioactive compounds without overexploiting natural plant resources. These include:

- Plant tissue culture
- Cell suspension culture
- Hairy root culture
- Metabolic engineering

Hairy root cultures, induced by *Agrobacterium rhizogenes*, have shown promising results in enhancing secondary metabolite production.

Table 2: Biotechnological Methods

Method	**Advantages**	**Limitations**
Tissue culture	Controlled environment	High cost
Hairy root culture	High yield	Technical complexity
Cell suspension	Scalable	Genetic instability

These technologies allow continuous production of phytochemicals with consistent quality, which is essential for pharmaceutical applications.

5. Drug Delivery Technologies

The successful therapeutic application of plant-derived bioactive compounds largely depends not only on their pharmacological properties but also on their effective delivery within biological systems. Despite the rich phytochemical composition of *Ajuga turkestanica* and *Tribulus terrestris*, many of their active constituents exhibit limitations such as poor aqueous solubility, low permeability, rapid metabolic degradation, and reduced systemic availability. These challenges significantly restrict their clinical translation. Consequently, the development of advanced drug delivery technologies has become essential to enhance the stability, bioavailability, and targeted delivery of these phytochemicals.

5.1 Limitations of Conventional Delivery

Traditional dosage forms, including powders, decoctions, and crude extracts, often result in inconsistent therapeutic outcomes due to variability in absorption and metabolism. Compounds such as phytoecdysteroids and steroidal saponins may undergo rapid degradation in the gastrointestinal environment or exhibit poor membrane permeability. Additionally, first-pass metabolism in the liver can further reduce the effective concentration of these compounds in systemic circulation. These factors necessitate the use of innovative delivery strategies capable of protecting bioactive molecules and facilitating controlled release.

5.2 Nanotechnology-Based Delivery Systems

Nanotechnology has emerged as a transformative approach in the field of drug delivery, offering solutions to many of the limitations associated with conventional formulations. Nanocarriers, typically ranging from 10 to 200 nanometers in size, provide a large surface area and enhanced interaction with biological membranes, leading to improved absorption and distribution.

Nanoparticles formulated from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and chitosan are widely used for encapsulating plant-derived compounds. These systems protect sensitive molecules from environmental degradation while enabling sustained release. For example, encapsulation of flavonoids from *Tribulus terrestris* in polymeric nanoparticles has been shown to enhance antioxidant activity and prolong systemic circulation time.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) represent another class of nanocarriers that combine the advantages of lipid-based systems with improved stability. These carriers are particularly suitable for lipophilic compounds such as saponins and phytoecdysteroids, improving their solubility and bioavailability.

5.3 Liposomes and Phytosomes

Liposomes are spherical vesicles composed of phospholipid bilayers capable of encapsulating both hydrophilic and lipophilic compounds. Their structural similarity to biological membranes allows efficient fusion with cell membranes, facilitating intracellular delivery. Liposomal formulations of plant extracts have demonstrated enhanced therapeutic efficacy due to improved cellular uptake.

Phytosomes, a specialized form of lipid-based delivery system, involve the complexation of phytochemicals with phospholipids to form stable molecular complexes. Unlike simple encapsulation, phytosomes improve the bioavailability of plant constituents by enhancing their lipid compatibility. This approach has been particularly effective for flavonoids and phenolic compounds, which otherwise exhibit limited absorption.

5.4 Nanoemulsions and Self-Emulsifying Systems

Nanoemulsions are thermodynamically stable systems consisting of oil, water, surfactant, and co-surfactant, with droplet sizes typically below 200 nm. These systems provide enhanced solubilization of hydrophobic compounds and improved gastrointestinal absorption. Nanoemulsions prepared from extracts of *Ajuga* *turkestanica* have shown increased stability and improved pharmacokinetic profiles.

Self-emulsifying drug delivery systems (SEDDS) further enhance oral bioavailability by forming fine oil-in-water emulsions upon contact with gastrointestinal fluids. These systems are particularly useful for delivering poorly soluble phytochemicals and ensuring consistent drug release.

5.5 Controlled and Targeted Drug Delivery

Controlled release systems are designed to deliver bioactive compounds at a predetermined rate over an extended period. This approach minimizes dosing frequency and maintains therapeutic drug levels. Polymer-based matrices and hydrogels are commonly used for this purpose.

Targeted drug delivery systems aim to direct bioactive compounds to specific tissues or cells, thereby increasing therapeutic efficacy while reducing side effects. Surface modification of nanoparticles with ligands such as antibodies or peptides enables selective binding to target receptors. Although still in early stages for plant-derived compounds, this strategy holds significant promise for future applications.

5.6 Comparative Evaluation of Delivery Systems

Different drug delivery systems offer distinct advantages depending on the nature of the bioactive compound and the intended therapeutic application. Nanoparticles and lipid-based carriers generally provide superior protection and controlled release, whereas nanoemulsions offer simplicity and ease of formulation. The selection of an appropriate system requires careful consideration of factors such as stability, scalability, toxicity, and cost-effectiveness.

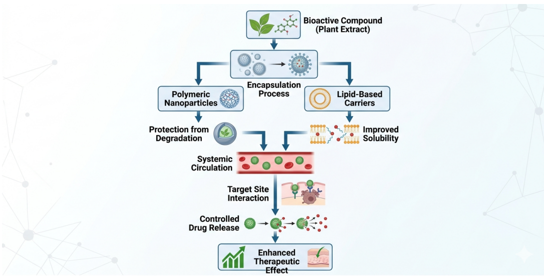

Figure: Nanotechnology-Based Drug Delivery System

6. Pharmacological Applications

The pharmacological relevance of *Ajuga turkestanica* and *Tribulus terrestris* is primarily attributed to their diverse array of secondary metabolites, including phytoecdysteroids, steroidal saponins, flavonoids, and phenolic compounds. These constituents exhibit a broad spectrum of biological activities, making these plants valuable candidates for the development of therapeutic agents. The integration of modern extraction and drug delivery technologies has further enhanced the efficacy and applicability of these bioactive compounds.

6.1 Antioxidant Activity

Oxidative stress is a key contributing factor in the pathogenesis of numerous chronic diseases, including cardiovascular disorders, neurodegenerative conditions, and cancer. Bioactive compounds present in *Tribulus terrestris*, particularly flavonoids and phenolic acids, play a crucial role in neutralizing reactive oxygen species (ROS). These compounds act as free radical scavengers, thereby reducing cellular damage and preventing lipid peroxidation.

Similarly, *Ajuga turkestanica* contains significant amounts of antioxidant constituents, including rosmarinic acid and phytoecdysteroids, which contribute to its protective effects against oxidative stress. Experimental studies have demonstrated that extracts from these plants can enhance endogenous antioxidant enzyme systems such as superoxide dismutase and catalase, thereby strengthening cellular defense mechanisms.

6.2 Anti-inflammatory Properties

Inflammation is a complex biological response that plays a central role in various pathological conditions. The anti-inflammatory effects of *Tribulus terrestris* are largely associated with its steroidal saponins, which modulate inflammatory pathways by inhibiting the production of pro-inflammatory cytokines. These compounds have been shown to suppress mediators such as tumor necrosis factor-alpha (TNF-α) and interleukins, thereby reducing inflammatory responses.

In the case of *Ajuga turkestanica*, phytoecdysteroids exhibit significant anti-inflammatory activity by regulating signaling pathways involved in immune responses. These compounds can attenuate the activation of nuclear factor kappa B (NF-κB), a key transcription factor responsible for the expression of inflammatory genes. As a result, both plants demonstrate potential in managing inflammatory disorders with reduced risk of adverse effects.

6.3 Anticancer Potential

The exploration of plant-derived compounds for anticancer therapy has gained considerable attention due to their ability to target multiple pathways involved in tumor progression. Extracts of *Tribulus terrestris* have shown inhibitory effects on various cancer cell lines, including breast, prostate, and liver cancers. The mechanism of action involves the induction of apoptosis, inhibition of cell proliferation, and disruption of cancer cell signaling pathways.

Phytoecdysteroids from *Ajuga turkestanica* have also demonstrated anticancer properties, particularly through their ability to regulate cell cycle progression and promote programmed cell death. These compounds may interfere with the growth of malignant cells without causing significant toxicity to normal tissues, highlighting their potential as adjuncts in cancer therapy.

6.4 Antidiabetic and Metabolic Effects

Metabolic disorders, including diabetes mellitus, are characterized by impaired glucose regulation and insulin resistance. Bioactive compounds from *Tribulus terrestris* have been reported to improve glycemic control by enhancing insulin sensitivity and promoting glucose uptake in peripheral tissues. Additionally, these compounds may inhibit enzymes involved in carbohydrate digestion, thereby reducing postprandial blood glucose levels.

Ajuga turkestanica also exhibits promising antidiabetic properties, primarily through its influence on metabolic pathways. Phytoecdysteroids have been associated with improved protein synthesis and energy metabolism, which may contribute to better glucose utilization and reduced metabolic stress. These effects suggest potential applications in managing metabolic syndrome and related conditions.

6.5 Cardioprotective Activity

Cardiovascular diseases remain a leading cause of mortality worldwide, and the role of natural products in cardioprotection has been widely explored. The antioxidant and anti-inflammatory properties of *Tribulus terrestris* contribute to its cardioprotective effects by reducing oxidative damage and improving vascular function. Studies have indicated that its bioactive compounds may help regulate blood pressure, lipid profiles, and endothelial function.

Similarly, *Ajuga turkestanica* may support cardiovascular health through its adaptogenic and metabolic effects. By enhancing cellular resilience and reducing oxidative stress, its compounds may help protect cardiac tissues from damage and improve overall cardiovascular performance.

6.6 Adaptogenic and Anabolic Effects

One of the distinctive features of *Ajuga turkestanica* is its high content of phytoecdysteroids, which are known for their adaptogenic and anabolic properties. These compounds enhance the body’s ability to cope with physical and physiological stress while promoting protein synthesis and muscle growth. Unlike synthetic anabolic steroids, phytoecdysteroids exhibit these effects without significant hormonal disruption, making them attractive for therapeutic and nutraceutical applications.

Tribulus terrestris is also commonly associated with adaptogenic effects, particularly in relation to energy metabolism and physical performance. Its bioactive compounds may contribute to improved endurance and recovery, although the underlying mechanisms require further investigation.

6.7 Neuroprotective Potential

Emerging evidence suggests that phytochemicals from these plants may offer neuroprotective benefits. The antioxidant properties of flavonoids and phenolic compounds help mitigate neuronal damage caused by oxidative stress. Additionally, anti-inflammatory effects may reduce neuroinflammation, which is implicated in neurodegenerative diseases such as Alzheimer’s and Parkinson’s disorders.

Phytoecdysteroids from *Ajuga turkestanica* may also influence neuronal signaling pathways, supporting cognitive function and neural health. Although research in this area is still evolving, the preliminary findings indicate promising therapeutic potential.

7. Conclusion

The advancement of plant-based therapeutics increasingly depends on the ability to efficiently produce, stabilize, and deliver bioactive compounds. *Ajuga turkestanica* and *Tribulus terrestris* represent promising botanical sources due to their diverse chemical composition and wide-ranging biological activities. Compounds such as phytoecdysteroids, flavonoids, and steroidal saponins contribute to their therapeutic relevance across multiple physiological systems.

Progress in extraction technologies has significantly improved the recovery and quality of these compounds. Modern techniques, including ultrasound-assisted and supercritical fluid extraction, offer enhanced efficiency while reducing environmental impact. At the same time, biotechnological methods provide controlled production systems that minimize variability and support large-scale applications.

Equally important is the role of advanced drug delivery systems in addressing inherent limitations of phytochemicals. Nanocarriers, lipid-based formulations, and molecular complexes have demonstrated the capacity to improve solubility, protect against degradation, and enable controlled release. These developments are essential for translating phytochemicals into clinically viable products.

Despite these advancements, several challenges remain unresolved. Standardization of plant material, reproducibility of extraction processes, and regulatory considerations continue to limit widespread commercialization. Furthermore, the lack of large-scale clinical validation restricts the transition from experimental studies to therapeutic use.

Future research should prioritize the integration of multidisciplinary approaches, combining green extraction methods, molecular characterization, and advanced delivery technologies. Such efforts will be crucial in establishing reliable, effective, and sustainable phytopharmaceutical systems. Overall, the convergence of traditional knowledge with modern technological innovation offers a strong pathway for the development of next-generation plant-based therapeutics.

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