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PHYTOCHEMICAL PROFILE, EXTRACTION DYNAMICS AND MULTIFUNCTIONAL BIOACTIVITY OF *BERBERIS VULGARIS* L. ALKALOIDS: A COMPREHENSIVE PHARMACOGNOSTIC AND THERAPEUTIC ASSESSMENT

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Annotation: This article presents a comprehensive analysis of the phytochemical composition, extraction-dependent variability, and multifunctional biological activities of isoquinoline alkaloids found in *Berberis vulgaris* L. Drawing upon extensive literature, the review highlights berberine, palmatine, jatrorrhizine, berbamine, and magnoflorine as the principal bioactive constituents responsible for the plant's pharmacological potential. The findings demonstrate that alkaloid concentration is strongly influenced by ecological conditions, plant organ, growth stage, and extraction parameters such as solvent polarity, temperature, pH, and extraction duration. Advanced analytical studies confirm that different extraction techniques (Soxhlet, ultrasound-assisted, microwave, maceration, supercritical CO_2 extraction) yield distinct chemical profiles.

Keywords: *Berberis vulgaris*; berberine; isoquinoline alkaloids; phytochemistry; extraction methods; antioxidant activity; antimicrobial effect; Nrf2 pathway; AMPK signaling; phytotherapy; nutraceuticals; synergistic bioactivity.

INTRODUCTION

The isoquinoline alkaloids present in *Berberis vulgaris* L. hold significant scientific importance in pharmacognosy, natural products chemistry, and modern phytotherapy. Species belonging to the *Berberis* genus are particularly rich in alkaloids such as berberine, palmatine, jatrorrhizine, berbamine, and magnoflorine, which have stimulated extensive research into the pharmacological potential of these raw plant materials. These compounds exhibit notable antioxidant, antimicrobial, anti-inflammatory, metabolic-modulating, and cytotoxic properties. Among them, berberine has been the focus of numerous studies due to its effects on intracellular signaling pathways, oxidative stress markers, microbial proliferation, and metabolic homeostasis.

The biological activity of these alkaloids is closely linked to their chemical structure, including functional groups and conformational features, as well as extraction methodology, solvent characteristics, and various technological parameters. Consequently, the qualitative and quantitative composition of *Berberis vulgaris* alkaloids is strongly affected by plant part, growth stage, ecological conditions, drying techniques, and extraction parameters such as temperature, pH, solvent polarity, and extraction time. Different extraction protocols-including Soxhlet, ultrasound-assisted extraction, maceration, microwave extraction, and supercritical CO_2 extraction, can yield fractions with markedly distinct chemical profiles. These variations are attributed to differences in solvent affinity, alkaloid ionization state, and membrane permeability.

Understanding the correlation between the chemical composition of *Berberis* alkaloids and their biological activity is critically important from both pharmacological and technological perspectives. Synergistic or antagonistic interactions among components significantly shape the overall bioactivity of the extracts. For instance, the antimicrobial potency of berberine has been

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shown to increase when co-present with phenolic compounds or other benzylisoquinoline alkaloids. Likewise, flavonoids enhance the oxidative stability of alkaloids, while phenolic acids can potentiate antimicrobial effects through membrane destabilization. Detailed investigation of these interaction mechanisms not only enriches fundamental phytochemical knowledge but also enables the development of novel nutraceutical formulations, phytocomplexes, and therapeutic preparations.

Currently, *Berberis*-based phytopreparations are being used as adjunctive therapies for inflammatory conditions, bacterial infections, metabolic syndrome, insulin resistance, and gastrointestinal dysfunctions. Within this context, elucidating the relationship between the chemical structure of *Berberis vulgaris* L. alkaloids, their stability under various extraction conditions, and their biological activity remains a highly relevant scientific objective in contemporary plant chemistry.

LITERATURE REVIEW

Research on the alkaloid composition and pharmacological activity of plants belonging to the *Berberis* genus has expanded significantly over the past decade. Early investigations primarily focused on the chemical nature of berberine and its antimicrobial and anti-inflammatory properties. However, more recent studies have shifted toward elucidating molecular mechanisms, metabolic modulation, and complex phytochemical interactions, reflecting the growing scientific interest in the multifunctional therapeutic potential of *Berberis* species.

1. Chemical Composition of *Berberis* Alkaloids. The major bioactive constituents of *Berberis vulgaris* L. are isoquinoline alkaloids, among which berberine, palmatine, magnoflorine, jatrorrhizine, berbamine, and columbamine are the most prevalent. Numerous scientific sources indicate that alkaloid content varies substantially depending on the plant organ (root, bark, leaf, fruit), vegetative stage, agroclimatic conditions, and extraction methodology. Several studies report that the bark and root fractions contain the highest levels of berberine, reaching 5–7%, which is markedly greater than in leaves or fruits.

Advanced analytical techniques, including HPLC, UHPLC, LC–MS/MS, FTIR, and NMR, have been widely applied to characterize the alkaloid profile. Literature data emphasize that each method offers specific advantages related to detection sensitivity, structural elucidation, and fragmentation patterns. LC–MS/MS studies, for example, clearly characterize the ionization pattern of berberine (m/z 336) and its fragment ions with high accuracy.

Influence of Extraction Conditions on Alkaloid Composition. The extraction of *Berberis* alkaloids is highly sensitive to technological parameters. Studies consistently show that solvent polarity, pH, temperature, and extraction duration significantly influence both yield and chemical profile: Soxhlet extraction enhances alkaloid yield at high temperatures but may degrade thermolabile compounds. Ultrasound-assisted extraction: ensures high efficiency at low temperatures with shorter processing time. Microwave-assisted extraction: markedly increases berberine recovery when used with polar solvents. Supercritical CO_2 extraction: exhibits high selectivity but often requires co-solvents for ionic alkaloids like berberine. Multiple sources identify ethanol–water mixtures (50-70%) as the most effective solvents for optimal berberine extraction. A mildly acidic environment (pH 3–5) stabilizes the protonated form of the alkaloids, thereby improving extraction efficiency.

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Biological Activity of *Berberis* Alkaloids. The biological activity of *Berberis* alkaloids is closely linked to their chemical structure and functional groups. Literature findings highlight several key mechanisms associated with berberine: Antioxidant Activity. Berberine not only directly scavenges reactive oxygen species but also activates the Nrf2 signaling pathway, enhancing the expression of endogenous antioxidant enzymes such as SOD, GPx, and CAT. Additionally, it reduces mitochondrial oxidative stress, contributing to cellular redox homeostasis.

Antimicrobial Properties-Most studies confirm the strong activity of *Berberis* alkaloids, especially berberine, against Gram-positive bacteria, with measurable inhibitory effects on Gram-negative species as well. Mechanisms include disruption of microbial cell membranes, inhibition of nucleic acid synthesis, and interference with microbial metabolic pathways. Metabolic Modulation-Berberine demonstrates potent effects on metabolic regulation, including improvement of insulin sensitivity, enhancement of glucose uptake via AMPK activation, and reduction of lipid accumulation. These findings support its role as a natural metabolic modulator.

Integrated Findings from Comparative Studies- Comparative analyses of extracts obtained using Soxhlet, ultrasonic, or maceration techniques reveal consistent patterns: High-temperature extraction increases total alkaloid yield. Mild extraction preserves phenolic compounds important for synergistic bioactivity. Solvent polarity strongly influences berberine concentration. Biological studies further demonstrate that *Berberis* alkaloids possess notable antioxidant, antimicrobial, and metabolic regulatory effects. Many authors emphasize that berberine's bioactivity is significantly enhanced through synergistic interactions with phenolic acids, flavonoids, and related isoquinoline alkaloids. General Conclusion from Literature- Overall, the literature supports a strong correlation between: the chemical diversity of *Berberis* alkaloids, their sensitivity to extraction parameters, and their multifunctional biological activities.

The integrated evidence confirms that *Berberis vulgaris* extracts constitute a chemically rich and pharmacologically potent natural source, highly suitable for the development of nutraceuticals, phytocomplexes, and therapeutic formulations.

DISCUSSION

The analysis of the literature enables several important theoretical conclusions regarding the properties of *Berberis vulgaris* alkaloids. First, chemical and pharmacognostic studies consistently demonstrate that the concentration and ratio of alkaloids are strongly influenced by ecological conditions, harvesting period, drying technique, and extraction technology. These factors represent critical technological determinants that must be standardized to ensure consistent chemical profiles in *Berberis*-derived preparations.

A second key observation is the close relationship between chemical composition and biological activity. Numerous studies report that complex extracts exhibit considerably higher pharmacological activity than isolated berberine alone, underscoring the importance of phytochemical synergy. Flavonoids, phenolic acids, and alkaloids act cooperatively to enhance anti-inflammatory and antibacterial responses, as documented across multiple scientific sources.

A third essential aspect concerns the efficiency of extraction methods. While Soxhlet extraction is frequently regarded as highly effective for obtaining elevated alkaloid concentrations, ultrasound-assisted extraction is favored for its cost-effectiveness and superior preservation of

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phenolic constituents. These insights provide valuable guidance for developing optimized pharmaceutical technologies for *Berberis*-based formulations.

Furthermore, literature findings converge on several overarching conclusions regarding biological activity: The antioxidant properties of *Berberis* alkaloids extend beyond direct radical scavenging and include modulation of intracellular signaling pathways, particularly Nrf2. Antimicrobial activity is more pronounced against Gram-positive microorganisms, although inhibitory effects on Gram-negative species have also been reported. Metabolic stabilization is closely linked to the activation of the AMPK signaling pathway.

These findings collectively offer a robust theoretical basis for the expanded application of *Berberis* preparations in modern phytotherapy.

Antimicrobial Activity- The antimicrobial potential of berberine against both Gram-positive and Gram-negative microorganisms has been detailed extensively in the literature. Mechanistic studies indicate that berberine disrupts membrane permeability, inhibits DNA-topoisomerase IV, and interferes with quorum-sensing systems—together contributing to its broad-spectrum antimicrobial action.

Anti-inflammatory Effects- Berberine's ability to suppress NF-κB activation and reduce the production of inflammatory mediators such as TNF-α and IL-6 positions it as a potent immunomodulatory agent. These effects are crucial for managing chronic inflammation and inflammatory metabolic disorders.

Metabolic Stabilization- A considerable body of evidence supports berberine's capacity to enhance glucose utilization, improve insulin sensitivity, and reduce lipogenesis through AMPK pathway activation. These mechanisms substantiate its therapeutic relevance in metabolic syndrome, Type 2 diabetes, and related disorders.

Synergistic Activity of Phytocomplexes- Multiple studies highlight that whole *Berberis* extracts often demonstrate greater biological efficacy than isolated alkaloids. Synergistic enhancements arise from: flavonoids improving alkaloid stability against oxidation; phenolic acids potentiating antimicrobial activity; organic acids facilitating membrane permeability of alkaloids.

Such synergistic interactions explain why complex extracts frequently outperform single-compound preparations such as pure berberine. Applications in Nutraceuticals and Pharmaceuticals- Recent advances show increasing interest in developing phytopreparations, nutraceutical capsules, antioxidant complexes, and hepatoprotective formulations based on *Berberis* alkaloids. Literature reports their clinically documented benefits, including: improved glycemic control in metabolic syndrome; reduction of inflammatory responses; modulation of gut microbiota composition; inhibition of cancer cell proliferation. These findings firmly establish *Berberis* alkaloids as promising candidates for wider use in phytotherapy and pharmaceutical development.

CONCLUSION

The literature-based analysis allows the following scientific conclusions regarding the chemical composition, extraction characteristics, and biological activity of *Berberis vulgaris* L. alkaloids: *Berberis* alkaloids possess a chemically diverse and structurally complex profile, with berberine,

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palmatine, and jatrorrhizine serving as the most significant constituents. Their concentrations vary markedly among different plant parts. Extraction conditions exert a decisive influence on the chemical composition: solvent type, polarity, temperature, and extraction time are primary determinants of alkaloid yield. Extensive literature confirms the strong antioxidant, antimicrobial, and metabolic modulatory activities of *Berberis* alkaloids. The superior efficacy of complex extracts compared with isolated compounds demonstrates the importance of phytochemical synergy in enhancing biological effects. The scientifically validated bioactive profile of *Berberis* establishes it as a highly promising plant source for modern phytotherapy, nutraceutical design, and pharmaceutical innovation. Overall, *Berberis vulgaris* L. represents a multifunctional medicinal plant with considerable therapeutic potential, warranting continued investigation and development in integrative medicine and natural product pharmacology.

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