

Phytochemistry and Pharmacological Insights on *Berberis napaulensis* (DC.) Spreng.: An Updated Review

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ABSTRACT

In the temperate and sub-temperate zones of the eastern Himalayas, the abundance of medicinal flora, notably *Berberis napaulensis*, assumes substantial significance. *Berberis napaulensis* is a member of the Berberidaceae family, which encompasses 500 species world wide under the genus *Berberis*, each possessing considerable significance. Notably, one such species, *B. napaulensis*, is particularly impactful in ongoing medicinal research. This review elucidates the botany, traditional uses, phytochemical, biosynthesis of phytochemicals and pharmacological attributes of *Berberis napaulensis*, illuminating its potential within traditional medicine. Photographs were captured during the extensive field surveys conducted in the Darjeeling district, and a comprehensive literature review was undertaken for the purpose of this study. This approach highlights the global importance of the plant in addressing various health concerns. The recognized phytochemical compounds in *Berberis napaulensis* demonstrate significant pharmacological effectiveness, highlighting the need for careful recognition. The integration of traditional knowledge and pharmacological understanding holds promise for addressing a range of conditions, cancer, viral diseases, and neurological disorders and many others.

Keywords: Berberine, *Berberis napaulensis*, Isoquinoline alkaloids, Jatrorrhizine, Pharmacological activities, Traditional applications.

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INTRODUCTION

Plant natural products hold significant importance in various aspects of human life and the natural world.^[1-3] The Himalayas have always been a treasure house for several medicinal plant and many species from eastern Himalaya have been reported to show immense medicinal prospects.^[4-7] One such plant taxon is *Berberis napaulensis*, a prominent member of the *Berberis* genus, contributing to the diverse flora of Nepal, which boasts a rich array of 21 species.^[8] The first description of the genus *Berberis* was provided by Linnaeus in his publication Genera Plantarum.^[9] It is native to eastern Himalaya and China and is placed under family Berberidaceae, which comprises both herbaceous and woody taxa and is represented by 13 accepted genera and about 733 species.^[10] The name 'berberys' originates from its Arabian designation for the fruit.^[11] The species *Berberis napaulensis* (DC.) Spreng., currently accepted, was initially described by Candolle in 1821, using Buchanan-Hamilton's Nepal data^[12] noted early 19th-century descriptions for *Berberis acanthifolia* and *Berberis*

napaulensis based on Hamilton and Wallich's specimens from 1802. *B. napaulensis* was assigned to the orientales group based on biogeographic and leaf type criteria.^[13] The current accepted name is *Berberis napaulensis* (DC.) Spreng., published in 1825. In Nepal and the Darjeeling-Sikkim eastern Himalaya, it is known as 'Chutro', while its English name is 'Nepal Barberry'.^[14] *Berberis napaulensis* encompasses chemical diversity, traditional uses, and pharmacological potential, bridging traditional knowledge with modern medicinal applications. The following review delves deeper into the multifaceted aspects of these plants, drawing insights from a diverse range of studies and research endeavours.

METHODOLOGY

In this review, a comprehensive information on *Berberis napaulensis* has been compiled from multiple peer-reviewed research articles accessed through electronic databases such as ScienceDirect, Scopus, Google Scholar, PubMed, Google, and ResearchGate. The keywords used during the literature search included, *Berberis napaulensis*, Isoquinoline alkaloids, berberine, jatrorrhizine, Traditional applications, Pharmacological activities. Traditionally used as an ethnomedicine for treating various ailments, *B. napaulensis* owes its therapeutic value to the presence of diverse bioactive compounds. Its promising pharmacological profile highlights significant potential for future research and



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clinical applications. Additionally, photographs depicting the plant's habit were taken during field visits in the Darjeeling region.

RESULTS

Morphology and distribution

B. napaulensis (syn. *Mahonia napaulensis* DC.) is an early winter blooming plant that blooms around October to December. It is an evergreen shrub or small tree that can reach heights upto 2-7 m, though it typically develops to be shorter, and the leaves have fewer, more elongated leaflets approximately 61cm long. The terminal leaflet is often not noticeably bigger than the rest. The racemes of fragrant flowers are approximately 20-22 cm long and carried in protracted clusters at the terminal ends (Figure 1). The colours of the petals range from pale orange to deep yellow. The outer sepals measure 3-4 x 2 mm, and the style is around 0.4 mm long. The dark blue, extremely pruinose fruit, measuring about 9 x 6 mm, ripens during April to June. *B. napaulensis* is distributed in temperate and sub-temperate regions of eastern Himalaya, western Himalaya, south-central and south-east China, Myanmar, Nepal, Thailand, Tibet, Bhutan, Vietnam, NE India at altitudes of 2000-2900 m, and Southern Western Ghats.^[10-14]

Traditional uses

Traditionally, plants containing a variety of secondary metabolites such as tannins, terpenoids, alkaloids, and polyphenols are known to exhibit potent antimicrobial activities, which are well-documented in phytochemical research.^[15,16] *M. napaulensis*, rich in isoquinoline alkaloids such as berberine (0.173%±0.03), has been highlighted in comparative pharmacognostic studies as a potential substitute for the Ayurvedic drug Daruharidra (*Berberis aristata*).^[17] This species is traditionally used in Ayurveda, Homeopathy, Unani, Chinese medicine, and Allopathy for the treatment of various ailments.^[17-19] In the Chinese medicinal system, the stem and root of *M. napaulensis* have traditionally been used to treat dysentery, likely due to the antimicrobial properties of its alkaloid compounds.^[20] A decoction made by boiling 20 g of *M. napaulensis* bark in 200 mL of water for 10-15 min is traditionally used in the treatment of ophthalmological conditions such as eye boils and irritation, possibly due to its anti-inflammatory and wound-healing properties.^[21,22] Additionally, the stem of *B. napaulensis* provides a natural dye, used traditionally by the Apatani tribe, with scientific evidence supporting its effectiveness as a textile dye due to the presence of bioactive compounds.^[23,24]

Phytochemicals in *B. napaulensis*

To further elucidate the medicinal potential of *Berberis napaulensis*, its phytochemical profile has been thoroughly investigated. *B. napaulensis* reveals distinct bright yellow colorants visible on the underside of bark as shown in Figure

1D. Berberidaceae plants, notably the genus *Berberis* are known for various isoquinoline alkaloids^[25,26] and it has been observed that alkaloid production occurs during the active growth phase and gets stored within the cortex and bark.^[27] Govindachari *et al.*, first extracted *B. napaulensis* bioactives, revealing significant isoquinoline alkaloids berberine (C₂₀H₁₈NO₄⁺) (Figure 3A) and jatrorrhizine (C₂₀H₂₀NO₄⁺) (Figure 3B) from root and stem bark of the plant.^[28] Isoquinoline alkaloids, notable for wide bioactivities, including antitumor and neuroprotection, have captured global research interest.^[29] After a long gap of research on *B. napaulensis* phytochemicals, Vankar *et al.*, identified additional bioactive compounds from stem of the plant such as coptisine (C₁₉H₁₄NO₄⁺) (Figure 3D) palmatine (C₂₁H₂₄NO₄⁺) (Figure 3C) and columbamine (C₂₀H₂₀NO₄⁺) (Figure 3E) along with berberine and jatrorrhizine.^[30] Furthermore, Mai *et al.*, isolated and characterized two bisbenzylisoquinoline compounds homoaromoline (C₃₇H₄₀N₂O₆) (Figure 3N) and isotetrandrine (C₃₈H₄₂N₂O₆) (Figure 3O) from wood of the plant.^[31] Berberine has many metabolites such as berberrubine (C₂₀H₁₈NO₄⁺) (Figure 3G), thalifendine (C₁₉H₁₆NO₄⁺) (Figure 3H), demethyleneberberine (C₁₉H₁₈NO₄⁺) (Figure 3I), and jatrorrhizine (C₂₀H₂₀NO₄⁺) is also one of them, and comparatively, berberrubine and jatrorrhizine are pharmacologically more active metabolites than berberine.^[32] Subsequently, Singh *et al.*, identified eight bioactive chemicals from roots of the plants, magnoflorine (C₂₀H₂₄NO₄⁺) (Figure 3J), isocorydine (C₂₀H₂₃NO₄⁺) (Figure 3K), glaucine (C₂₁H₂₅NO₄⁺) (Figure 3L), tetrahydropalmatine (C₂₁H₂₅NO₄⁺) (Figure 3M), tetrahydroberberine (C₂₀H₂₁NO₄⁺) (Figure 3F), jatrorrhizine (C₂₀H₂₀NO₄⁺), palmatine (C₂₁H₂₂NO₄⁺), and berberine (C₂₀H₁₈NO₄⁺) using UHPLC-ESI-MS/MS technique from the root part of *B. napaulensis*.^[33] When compared, *B. napaulensis* showed the greatest concentration of berberine i.e., 86580.00 µg/g, followed by the concentrations of palmatine 13877.50 µg/g and jatrorrhizine 47765.00 µg/g.^[33] Thusa and Mulmi (2017) identified isoquinoline compounds, quinones, glycosides, terpenoids, cardiac glycosides, and steroids. Berberine and β-sitosterol were confirmed through.^[34] Chaudhary *et al.*, found flavonoids, phenols, starch, sugars, and tannins from the roots of the plant.^[35] In 2022, Khang *et al.*, isolated the 1-C-syringylglycerol 4-O-β-D-glucopyranoside, 5,6-dihydro-2,3,9,12-tetramethoxydibenzoquinolizinium, 7-hydroxy-6-methoxyisochroman-1-one, 6,7-dimethoxyisochroman-1-one, and 4',7-dihydroxyflavanone from the stems of *Mahonia napaulensis*.^[36] Furthermore, this review provides an in-depth analysis of various isoquinoline compounds, including berberine and jatrorrhizine, focusing on their bioactivities, biosynthesis, chemical structures, and molecular mechanisms of action. Figure 2 represents the different compounds presents in *B. napaulensis* and Figure 3 represents the structural representation of different isoquinoline alkaloids.

DISCUSSION

Biosynthesis of berberine and jatrorrhizine

These alkaloids, mainly derived from the amino acids phenylalanine and L-tyrosine, generate the intermediate dopamine (3, 4-dihydrophenylalanine) via reaction with an aldehyde or ketone, and the basic pathway of biosynthesis, which runs from norcoclaurine to reticuline, is shared by all alkaloid-producing plant species and widely dispersed for isoquinoline alkaloids.^[37] Enzymological research on biosynthesis is widely conducted, with a focus on cultured plant cells. Almost all of the enzyme genes in the biosynthesis pathway for berberine have been identified and described.^[38] Dopamine undergoes a Mannich reaction to produce (S)- Norcoclaurine when it condenses with 4-hydroxy-phenylacetaldehyde^[39] (4HPAA) with the enzyme Norcoclaurine Synthase (NCS).^[40] S-adenosyl methionine (S)-reticuline is produced after further oxidation and methylation, which is an essential stage in the formation of isoquinoline alkaloids in plants.^[41] Common first stages in biosynthesis lead to the formation of (S)-reticuline and the branch point intermediate in the biosynthesis of several isoquinoline alkaloids is this crucial step.^[40] A well-known flavin-dependent enzyme called Berberine Bridge Enzyme (BBE) converts (S)-reticuline to (S)-scoulerine in one important route.^[42,43] Scoulerine 9-Omethyltransferase (SOMT) then methylates (S)-scoulerine to produce (S)-Tetrahydrocolumbamine (THCB). The enzyme produced by heterologous expression had the anticipated substrate selectivity.^[44] The methylene dioxy bridge of (S)-canadine is produced by the substrate-specific cytochrome P-450 oxidase canadine synthase.^[45] S-Tetrahydroprotoberberine Oxidase (STOX), a substrate-specific oxidase whose sequence has not yet been determined, catalyses the last stage of berberine production.^[46] The discovery of several biosynthetic enzymes has also been made possible by earliest examples of the creation of a benzyloisoquinoline alkaloid in cell culture at levels required

for commercial manufacturing is the overproduction of Berberine in *Coptis japonica*.^[47,48] According to Rueffer *et al.*, 3-O-demethylation of (S)-scoulerine coupled with 2-O and 9-O methylation may result in the formation of jatrorrhizine and other way is from the oxidation of Berberine.^[49] The diagrammatic representation of the biosynthesis of Berberine and Jatrorrhizine is presented in Figure 4.

Pharmacology of isoquinoline alkaloids

The *Berberis napaulensis* roots are reservoirs of isoquinoline alkaloids and modern medicine also confirms the pharmacological advantages of isoquinoline alkaloids as anticancer, antitumour, anti-inflammatory, wound healing, antidiabetic, antioxidant, antimicrobial, antibacterial, hepatoprotective, hypolipemic and more.^[38,51,52] The compounds, berberine and jatrorrhizine with others isoquinoline alkaloids have a potential of various anticancer activities that make these compounds truly beneficial in the field of pharmacology.^[38,50-53] Table 1, includes several bioactive compounds identified in *Berberis napaulensis*; however, detailed discussions on pharmacological activities in this review primarily focus on berberine and jatrorrhizine. The chemical structures of these compounds were retrieved from PubChem.^[54]

Antitumor and anticancer properties

Yang *et al.*, evaluated the methanolic stem extract of *M. napaulensis*, followed by BuOH fractionation, and identified the antiproliferative effects of compounds, particularly berberine and palmatine, using the MTT assay. The results showed a significant reduction in cell viability of more than 70% in human colon carcinoma CoLo 205 cells at the highest tested concentration (200 µg/mL).^[139] Earlier studies show that the Berberine treatment at concentrations of 2.5, 5.0, 10, and 20 µM for 24 hr reduced the levels of transcription factors NF-κB, c-Fos, and c-Jun in A549 cells.^[55] Additionally, Bao *et al.*, demonstrated that the Low-dose berberine (1.25-5 µM) promoted cancer cell proliferation, while

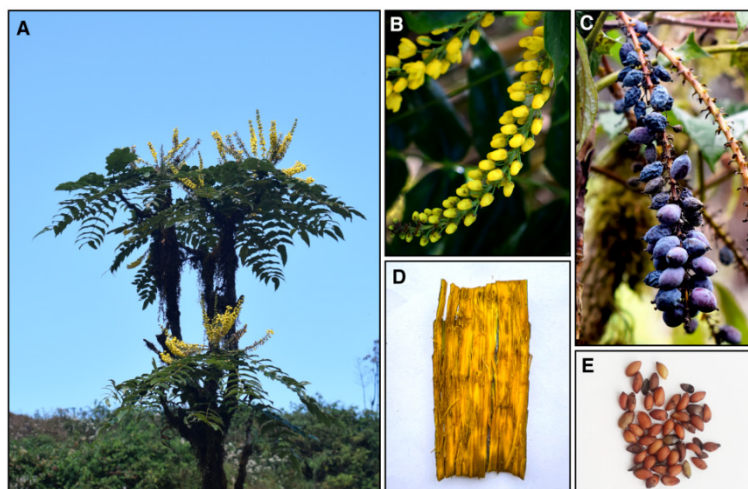


Figure 1: A. *B. napaulensis* in bloom B. portion of inflorescence C. ripened fruits D. underside of bark E. Seeds.

high doses (10-80 μ M) inhibited it. Co-treatment with low-dose berberine weakened the anticancer effects of Fluorouracil (5-FU), Camptothecin (CPT), and Paclitaxel (TAX).^[56] The anticancer activity of Methanol extract of *M. napaulensis* bark moderate against human lung cancer A549 cells (IC₅₀ value of 228.97 μ g/mL)^[57] and human cervical cancer HeLa cells (IC₅₀ value of 367.72 μ g/mL).^[58] Many researchers have concluded that berberine is effective against various cancers, including prostate, cervical, pancreatic, and bladder cancer, by regulating the proliferation mechanisms of human cancer cell lines.^[58-60] Similarly, Berberine alleviates insulin resistance in women with PCOS, enhancing fertility and pregnancy outcomes.^[61] Moreover Jatrorrhizine anticancer potential has been widely investigated. Qin *et al.*, found platinum (II) complexes with jatrorrhizine derivatives to be highly cytotoxic to HeLa cells, showing selectivity and strength via HL-7702 cells.^[76] Furthermore, Qin *et al.*, found that a jatrorrhizine-berberine platinum (II) complex induced apoptosis in bladder tumor cells and jatrorrhizine itself inhibits colorectal carcinoma proliferation.^[78]

Anti-inflammatory activities

Berberine, a natural compound with both anti-inflammatory and anti-tumor activities, holds promise for cancer treatment, particularly in the digestive system. Although its effects are moderate, structural modifications-especially at positions like C-8, C-9, C-12, and C-13 - have shown potential to enhance its efficacy, bioavailability, and metabolic stability.^[63] Future drug development should aim to optimize both anti-inflammatory and anti-cancer properties through targeted structural changes.^[63]

Bone regeneration

Berberine and Jatrorrhizine promotes osteoblast proliferation and differentiation while inhibiting osteoclast formation to

aid bone regeneration hinting at its potential for osteoporosis treatment.^[64,140]

Cardiovascular effects

Berberine has shown potential in managing heart failure and arrhythmias through its circulatory effects, primarily by blocking Potassium (K⁺) channels and activating the Na⁺/Ca²⁺ exchanger, which influence cardiac excitability and contractility.^[68] Similarly, Jatrorrhizine also demonstrates cardioprotective properties by reducing cardiomyocyte apoptosis and fibrosis via modulation of the p53/Bax/Bcl-2 apoptotic pathway and the TGF- β 1/Smad2/3 signaling cascade, as observed in myocardial infarction animal models.^[141]

Anti-diabetic

Berberine has been shown to significantly lower fasting and postprandial blood glucose levels, supporting its therapeutic potential in managing type 2 diabetes mellitus.^[71]

In addition to berberine, other isoquinoline alkaloids such as jatrorrhizine, coptisine, and palmatine also exhibit antidiabetic properties, possibly through modulation of gut microbiota and glucose metabolism pathways.^[81]

Anti-obesity and lipid regulation

Several studies have demonstrated the anti-obesity potential of berberine.^[65,66] It acts as a novel cholesterol-lowering agent by stabilizing LDLR mRNA, thereby enhancing cholesterol clearance.^[142] Recent findings also suggest that berberine alleviates lipid dysregulation in obesity by modulating central pathways, possibly through neuronal regulation.^[66] Similarly, jatrorrhizine exhibits antihyperglycemic effects by inhibiting α -glucosidase and aldose reductase.^[143] It also demonstrates lipid-lowering properties by upregulating LDLR and CYP7A1

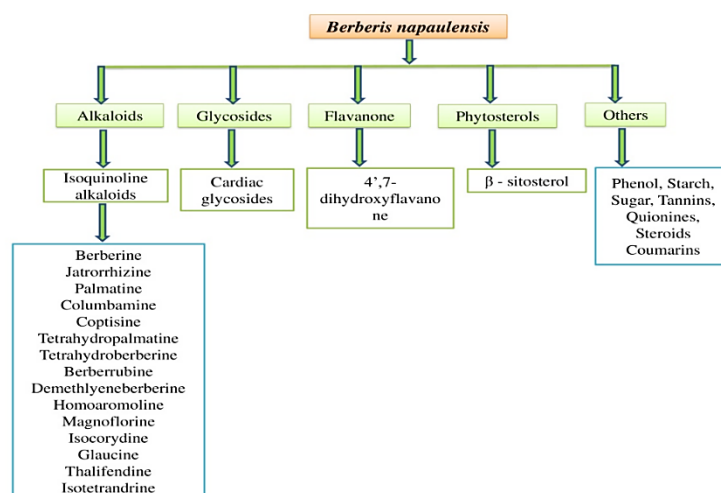
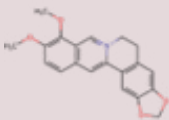
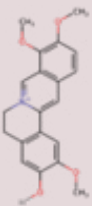
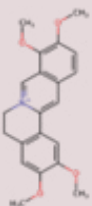
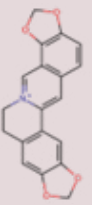
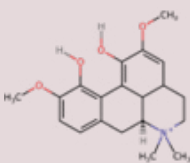
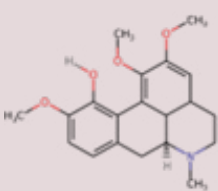
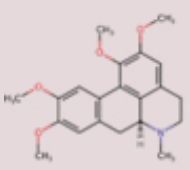
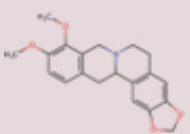
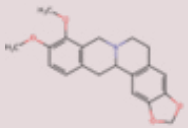
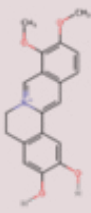
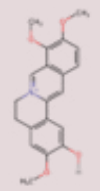
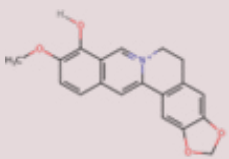


Figure 2: Compounds presents in *Berberis napaulensis*.

Table 1: Isoquinoline alkaloids of *B. napaulensis* with various pharmacological activities and bioactivities.

Phytochemical constituents	Chemical structure	Bioactivities of active constituents
(A) Berberine		Antitumor and anticancer; ^[55-61] Anti-inflammatory; ^[62,63] Bone regeneration; ^[64] Anti-obesity; ^[65-67] Cardiovascular effects; ^[68-70] Antidiabetic; ^[71] Antiviral; ^[72] Antifungal; ^[73] Neuroprotective activity; ^[74] Hypolipidemic. ^[75]
(B) Jatrorrhizine		Antitumor and anticancer; ^[76-78] Anti-inflammatory; ^[79] Antiobesity; ^[80] Antidiabetic; ^[81] Anti hypercholesterolemic; ^[82] Anti-microbial, antiviral, Antibacterial effects; ^[83] Neuroprotective; ^[84] Effects on the Central Nervous System; ^[85-87] Hepatoprotective. ^[88,89]
(C) Palmatine		Antitumor and anticancer; ^[90,91] Anti-inflammatory; ^[92] Neuroprotective; ^[93] Regulate lipid activity; ^[94] Antiviral; ^[95,96] Antibacterial. ^[97,98]
(D) Coptisine		Antitumor and anticancer; ^[99-102] Anti-inflammatory; ^[103,104] Antibacterial activity; ^[105,106] Antiviral; ^[107,108] Antifungal; ^[109,110] Antioxidant; ^[111] Cardioprotective ^[112] Neuroprotective. ^[113,114]
(E) Magnoflorine		Anti-inflammatory; ^[115] Antifungal ^[116,117] Immunomodulatory; ^[118] Anticancer; ^[119,120] Antitumor. ^[121]
(F) Isocorydine		Anticancer and antitumor. ^[122,123]
(G) Glaucine		Anti-inflammatory; ^[124] Anticancer; ^[125] Antioxidant. ^[126]
(H) Tetrahydropalmatine		Anti-inflammatory; ^[127,128] Antioxidant. ^[129]

Phytochemical constituents	Chemical structure	Bioactivities of active constituents
(I) Tetrahydroberberine		Neuroprotective. ^[130]
(J) Demethyleneberberine		Anti-inflammatory; ^[131,132] Neuroprotective; ^[133] Antioxidant. ^[134]
(K) Columbamine		Anticancer; ^[135,136] Antimicrobial. ^[137]
(L) Berberrubine		Antifungal. ^[138]

expression, promoting cholesterol utilization and excretion.^[82] These actions collectively improve lipid profiles and contribute to weight management. Moreover, jatrorrhizine therapy has been shown to reverse liver alterations in hyperlipidemic mice, suggesting its potential to treat hyperlipidemia by suppressing fatty acid synthesis and enhancing fatty acid oxidation.^[80]

Neuroprotective activity

Oren-Gedoku-To (OGT), a traditional Chinese medicinal formula, contains key ingredients such as jatrorrhizine, berberine, palmatine, and baicalein.^[84] In a study by Yu *et al.*, these components, especially jatrorrhizine were found to exhibit strong Indoleamine 2,3-Dioxygenase (IDO1) inhibitory activity, highlighting their potential in treating Alzheimer's disease. Jatrorrhizine showed IC₅₀ values of 206 μ M for recombinant human IDO1 and 17.8 μ M for HEK 293-hIDO1 cells, indicating its effectiveness.^[84] Additionally, jatrorrhizine has been identified as a potent PMAT (plasma membrane monoamine transporter) inhibitor, suggesting its role as a promising antidepressant agent by modulating monoamine neurotransmission through uptake-2 inhibition.^[86]

Anti-microbial, antiviral and anti-bacterial effects

Shrestha *et al.*, reported that the methanolic stem extract of *Mahonia napaulensis* exhibited weak antimicrobial activity, with Minimum Inhibitory Concentrations (MICs) of 100.22 mg/mL against *Staphylococcus aureus*, 50.15 mg/mL against *Escherichia coli*, and 25.08 mg/mL against *Candida albicans*.^[57] In contrast, Deng *et al.*, found that the alkaloids jatrorrhizine and palmatine showed significant antimicrobial activity against both plant and animal pathogens.^[144] Yu *et al.*, observed that jatrorrhizine alone exhibited minimal antibacterial activity at a MIC of 64 mg/L. However, when combined with Norfloxacin (NFX), it significantly enhanced the antimicrobial efficacy against Methicillin-Resistant *Staphylococcus aureus* (MRSA) strain SA1199B in mice, suggesting a synergistic *in vivo* interaction between jatrorrhizine and NFX.^[83] Similarly, berberine has demonstrated strong antibacterial potential against multi-drug-resistant *E. coli* strains.^[145] In addition to its antibacterial activity, berberine exhibits anti-viral effects by targeting various stages of the viral life cycle, including inhibition of DNA synthesis, modulation of key signaling pathways, and enhancement of host immune responses. These mechanisms position berberine as a promising candidate for the development of novel antiviral therapies, including potential applications against SARS-CoV-2.^[72] Furthermore, several studies have reported the antifungal activity of *M. napaulensis* extracts against

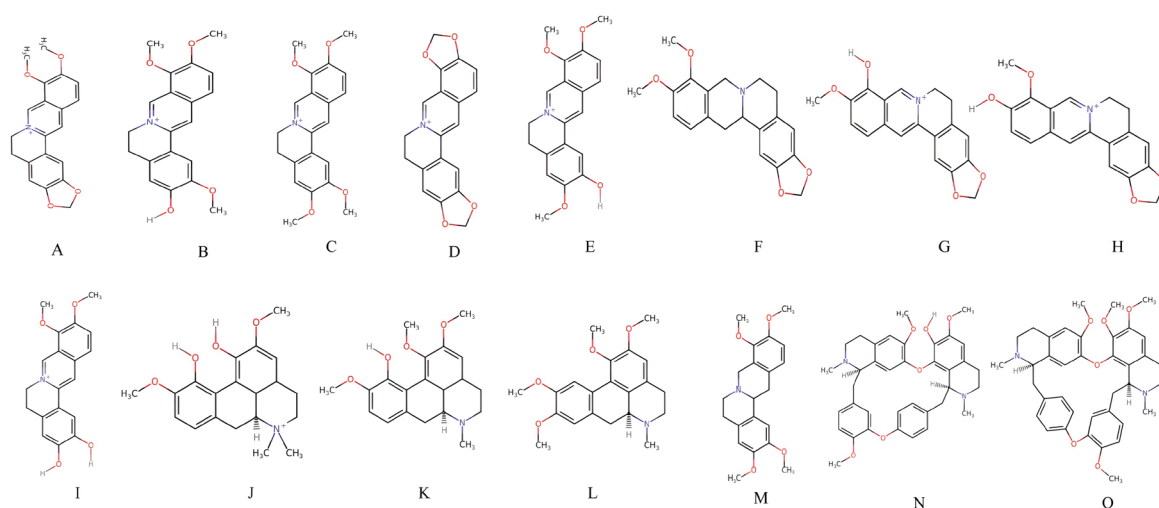


Figure 3: Structural representation of isoquinoline alkaloids in *Berberis napaulensis*. (A) Berberine, (B) Jatrorrhizine, (C) Palmatine, (D) Coptisine, (E) Columbamine, (F) Tetrahydroberberine, (G) Berberrubine, (H) Thalifendine, (I) Demethyleneberberine, (J) Magnoflorine, (K) Isocorydine, (L) Glauicine, (M) Tetrahydropalmatine, (N) Homoaromoline, (O) Isotetrandrine.

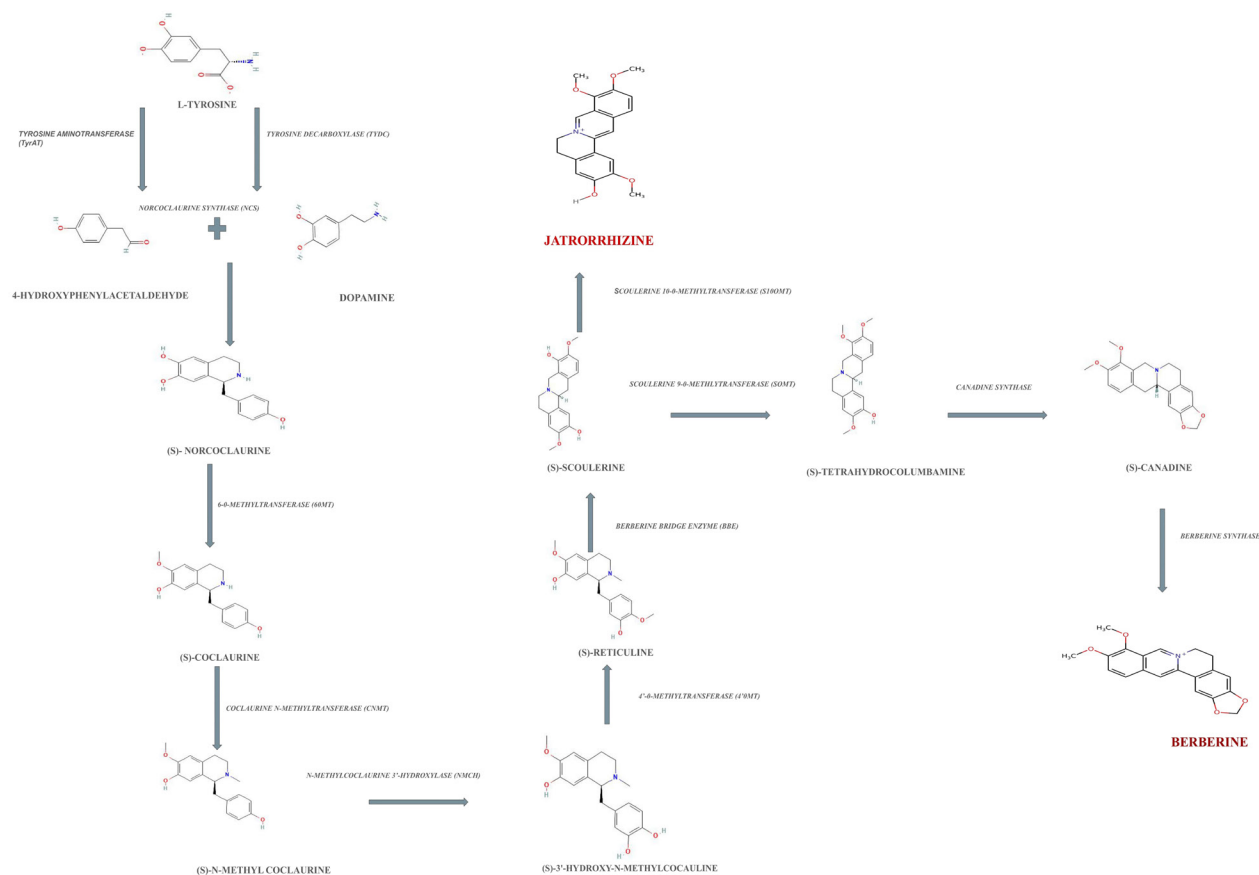


Figure 4: Biosynthetic pathway for Berberine and Jatrorrhizine.

pathogenic fungi such as *Colletotrichum capsici*, *Leptosphaerulina trifolii*, *Alternaria brassicicola*, and *Helminthosporium solani* at concentrations ranging from 20 to 100 µg/mL. A significant reduction in colony growth was also observed in *Trichoderma* species.^[20]

Hepatoprotective activity

Berberine provides hepatoprotective effects against CCl₄-induced liver damage by exerting antioxidant activity, reducing oxidative stress, and suppressing inflammation.^[88] Similarly, jatrorrhizine, used in traditional Chinese medicine formulations, shows liver-protective potential by lowering lactate dehydrogenase release and preventing oxidative injury.^[89]

Antioxidant activity

Paudel *et al.*, reported that the methanolic extract of *Mahonia napaulensis* bark exhibited DPPH radical scavenging activity with an IC₅₀ value of 230.89 µg/mL, compared to 182.73 µg/mL for ascorbic acid.^[146] Similarly, Shrestha observed moderate antioxidant activity with an IC₅₀ of 212.97 µg/mL for the bark extract.^[57] Yang *et al.*, demonstrated that the ethyl acetate fraction of the stem extract showed strong antioxidant potential, with an IC₅₀ of 48.93±0.59 µg/mL.^[139] Additionally, Racková *et al.* found that jatrorrhizine and magnoflorine exhibit significant antioxidant activity.^[147,148] Furthermore, studies suggest that the presence of catechol rings in berberine and its derivatives enhances their antioxidant capacity.^[148]

Safety and toxicity considerations

Berberine, a major active constituent of *Berberis napaulensis*, is associated with adverse effects such as cramping, diarrhoea, gas, constipation, stomach pain, nausea, and abdominal distention.^[149,150] High doses of berberine have also been linked to stomach lesions, flu-like symptoms, arterial hypotension, and dyspnea.^[151] Furthermore, due to the risk of bilirubin-induced brain damage, the use of berberine-containing plants is not recommended for jaundiced new borns, pregnant women, and nursing mothers.^[152] In contrast, jatrorrhizine demonstrates a better safety profile. A 90-day subchronic toxicity study in rats receiving jatrorrhizine at 70.05 mg/kg/day reported no changes in body or organ weights, and no abnormalities in urinalysis, hematological parameters, gross necropsy, or histological assessments.^[153]

CONCLUSION

Berberis napaulensis holds significant promise as a valuable medicinal plant due to its rich phytochemical profile, especially the presence of isoquinoline alkaloids such as berberine and jatrorrhizine. Traditionally used across various medical systems-Ayurveda, Chinese medicine, and local ethnomedicinal practices-for treating ailments like dysentery, ophthalmic issues, and skin diseases, this plant is now gaining scientific validation.

Studies highlight its wide-ranging pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, and cardiovascular protective effects. Berberine and jatrorrhizine, in particular, have demonstrated strong bioactivity in areas such as lipid and glucose regulation, neuroprotection, and cancer therapy, often through well-characterized molecular pathways. While the review focuses mainly on these two compounds, the plant contains several other bioactives with therapeutic potential, warranting deeper exploration.

Going forward, a more detailed understanding of its lesser-known constituents, mechanisms of action, and structure-activity relationships will enhance its clinical relevance. With further pharmacological, toxicological, and clinical investigations, *B. napaulensis* may emerge as a sustainable natural source for novel therapeutic agents.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

UHPLC-ESI-MS/MS: Ultra High-Performance Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry; **LDLR:** Low-Density Lipoprotein Receptor; **ROS:** Reactive Oxygen Species; **MRSA:** Methicillin-Resistant *Staphylococcus aureus*; **NFX:** Norfloxacin; **MIC:** Minimum Inhibitory Concentration; **IDO1:** Indoleamine 2, 3-Dioxygenase 1; **NF-κB:** Nuclear Factor Kappa B; **MAPK:** Mitogen-Activated Protein Kinase; **OGT:** Oren-Gedoku-To; **MIC:** Minimum Inhibitory Concentration; **IC₅₀:** Inhibitory concentration 50; **DPPH:** 2-2-Diphenyl-1-Picrylhydrazyl.

ETHICAL STATEMENTS

We, the authors of this review paper, confirm that the manuscript is our original work. It has not been published previously and is not under consideration for publication elsewhere. All sources of information, ideas, and/or words that are not our own have been properly acknowledged through appropriate citations and quotations. As this is a review article, it does not involve any studies with human participants or animals conducted by us.

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