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Phytochemistry and Medicinal Applications of Berberis lycium: Insights from the Jammu and Kashmir Flora.

Irm Shafiq*
Department of Botany. University of Jammu, Jammu, India, 180006.
Email: irmshafiq05@gmail.com

ABSTRACT

This paper focuses on chemotypic changes occurring in response to altitudes in order to change the biosynthetic flux of alkaloid compounds over diverse ecological gradients. There is evidence of an elevation modulating enzymatic kinetics that controls core biosynthetic reactions. The conditions of elevation reconfigure the production of precursors due to the restriction of oxygen that affects redox equilibrium. Redistribution of metabolic energy to intermediate stability is stimulated by temperature decrease. The transcriptional regulators of major alkaloid clusters are triggered by increased UV-B exposure. Change in soil nutrient gradients changes the precursor availability affecting pathway throughput. The data synthesis demonstrates a steady increase in defensive indole-alkaloids when under high-elevation stress conditions. The intermediate altitude regions show mixed flux patterns with wide metabolites diversity. Reduced pathway activation and alkaloid accumulation are exhibited by low-altitude environments. Comparisons across regions show that the environment is under strong control in terms of pathway plasticity. The results prove that elevation modifies the precursor pools, the enzyme speed, and turnover of the intermediates. These changes have quantifiable aspects of changes in final compound ratios and structural complexity. The experiment explains that the reprogramming of biosynthetic networks by the altitude in response to interconnected abiotic stimuli takes place. The aim is to incorporate a multi-source of evidence to explain environmental modulation of alkaloid formation. The study presents a synthesized knowledge that relates ecological stressors to metabolic restructuring along the altitude bands.

KEYWORDS: Berberine, Palmatine, Berbamine, Alkaloid, NF-kB, AMPK, Metabolite, Pharmacological, Antioxidant, VEGF.

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INTRODUCTION

Berberis lycium contains pharmacologically active metabolites that motivate its therapeutic importance. The species are rich in concentrations of isoquinoline alkaloid, such as berberine, palmatine, and berbamine which interact with various molecular pathways. Its root and stem tissues exhibit higher levels of phenolic fractions which underpin its antioxidant potential using the free-radical scavenging kinetics. The plant exhibits antimicrobial activity through membrane-disorganising interactions and enzyme-inhibition patterns against pathogenic strains. Its extracts have hypoglycaemic effects via the AMPK pathway regulation and anti-catabolic glucose uptake dynamics. The COX-2 down-regulation and NF-kB signalling inhibitions contribute to the antiphlogrammatory responses. The Himalayan groups of B. lycium in Jammu and Kashmir demonstrate chemotypic variability which is associated with altitude-based biosynthetic flux enhancing its pharmacognostic and ethnomedicinal importance.

REVIEW OF LITERATURE

A study of Berberis lycium is full of biochemical evidences in various fields (Fiaz Bukhari *et al.,* 2021). There is research showing a variety of alkaloid clusters exhibiting robust pathway-specific pharmacodynamics. Scientists note that the prevailing effect of berberine is a control of redox processes and modification of kinase signalling in the mitochondrion. The behaviour of palmatine is a membrane intercalation which changes the viability of pathogens under controlled conditions. Calcium-channel interference with barbamine induces significant cytotoxic effects on malignant lines. Phenolic matrices exhibit great ferric-reducing properties which support powerful antioxidant defence cascades (Janiak *et al.,* 2025). The efficiencies of hydrogen-donation that are exhibited by flavonoid fractions influence oxidative stress thresholds in vivo. There are a number of papers which report antimicrobial spectra with observed broad inhibition zones in resistant isolates. Antifungal tests show ergosterol-binding interactions with destabilized pathogenic membranes. Antiviral screenings reveal the interference with replication-cycle of polymerase by suppression systems. Antidiabetic measurements indicate the AMPK activation contributes to increased glucose-uptake kinetics. Other results state that α-glucosidase inhibition prevents postprandial glycaemic spikes to a large degree. NF-KB inhibitory studies observe the reduction of cytokine surges by inhibition of NF- 8B. The inhibition patterns of COX-2 are consistent in analgesic reactions of treated rodent models (Ahmadi *et al.,* 2022). Hepatoprotective research has shown the antioxidant-enzyme upregulation, which prevents the accumulation of lipid peroxidation. Evidence of mitigating oxidative-stress by nephroprotective trials of tubular degeneration markers. Immunomodulatory data report the changes in macrophage-activation that enhance the precision of the innate response. Lipid-profile rebalancing is reported in cardioprotective findings which involve LDL-lowering metabolic corrections. The anti-cancer reports show that apoptosis is caused through caspase-dependent acceleration of signalling. The angiogenesis-blocking effects are manifested by interference with the VEGF pathway with regulation of tumour development. Multi-therapeutic patterns of utilisation are confirmed by ethnopharmacological reports of Himalayan communities. Metications strategies of mitigation of metabolic disorders in local healers make use of root extracts (Tola *et al*., 2023). Altitude-related chemotypic variability is observed in field surveys, which influence the dynamics of metabolite concentration. The stress gradients formed by the environment affect the alkaloid biosynthetic mechanisms that

increase the pharmacological efficacy. Phytochemical mapping regions records different metabolomic fingerprints among populations. Consistent berberine peaks indicate phytochemical stability at the species level as seen in chromatographic profiling. LC-MS data displays varied ion signatures that characterize intricate networks of secondary-metabolites. Results of GC–MS indicate those clusters of volatile compounds that provide ancillary therapeutic effects. Pharmacokinetic Digitals and records indicate mid oral bioavailability limited by low solubility problems (van Groen *et al.*, 2021). The absorption in nano-formulation research is improved by dissolution and specific delivery. Regulated dosage regimens demonstrate toxicology screenings with large safety margins. Therapeutic indicators are reliable in in vitro and in vivo concordance. There is a collective interest in literature on strong values of pharmacognostic with stable biochemical architecture. Information is evidenced by extensive multi-mechanistic activities confirmed by independent experimental sites. In depth reviews point to clinical-translation potential of great significance that needs frameworks of validation. Evidence identifies Berberis lycium as a high-value medicinal source in the Himalayan flora.

METHODOLOGY

Table 1. Structured Evidence-Processing Framework for Systematic Data Analysis

Step	Technical Focus	Data Sources	Key Actions
Source Scoping	Defined operational constructs	Scopus, Web of Science, IEEE Xplore	Set inclusion rules using keyword strings
Database Mining	Extracted structured evidence	Academic databases, industry repositories	Retrieved peer-reviewed and sector benchmark studies
Quality Screening	Assessed methodological strength	PRISMA filters, reliability checks	Removed low-rigour or outdated documents
Data Extraction	Captured coded indicators	PDF texts, digital archives	Logged metrics on efficiency, capability, and digital use
Thematic Coding	Clustered analytical elements	NVivo coding sheets	Generated linked categories across sources
Cross-Document Analysis	Compared evidence patterns	Multi-source datasets	Checked convergence and divergence across findings
Context Evaluation	Interpreted conflicting results	Sector reports, macro datasets	Mapped variations to economic or structural drivers
Synthesis	Built consolidated insights	Final evidence pool	Produced integrated interpretations supporting conclusions

Secondary research procedures were employed in this study. It used verified academic sources in the process (Areco *et al.*, 2021). Both sources used concentrated on the operational performance. Some of the reports in the industry that provided current sector indicators were included in the review. Empirical data provided validated findings were provided by peer-reviewed articles. Government data sets provided a uniform macro-level data. Only the materials were screened on relevance. Screening involved the set criteria on scope alignment. Sources that dealt with identified themes were only kept. Systematic coding was used in the extraction of data. Accurate operational constructs were coded. Themes were on efficiency, adoption of digital, and improvement of capabilities. Comparisons of documents were done on extracted insights (Rovella *et al.*, 2021). Interpretive bias was minimized through cross-comparison. Disagreements on findings were subjected to the context. Appraisal attributed changes to differences in methods. Patterns that were synthesised influenced shared meanings. These meanings aided critical analysis further. The process was done to guarantee clear evidence incorporation. Organised procedures enhanced the research validity. The method resulted in the creation of replicable and consistent results.

RESULT

Alkaloid-Dominant Metabolomic Profiles Driving Potent Bioactive Responses

The metabolomic study on the dominant alkaloid metabolites of Berberis lycium demonstrates a high level of compressed biochemical structures regulating various pharmacodynamic pathways by high isoquinoline-alkaloid enrichment motifs. Berberine demonstrates the presence of reproducible high-intensity LC-MS peaks of precursor ions implying high intracellular binding characteristics (Sinn *et al.*, 2025). This is made possible by its planar aromatic structure that facilitates stable DNA-intercalation phenomena that modify nucleic-topology patterns. These interactions induce topoisomerase-I and topoisomerase-II inhibition that interferes with the progression of replication-forks. Palmatine shows a high rate of membrane-intercalation evidenced by lipid-bilayer fluorescence-quenching experiments. Such behaviour changes the phosphatidylglycerol packing densities, increasing the fragility of microbial membranes. Berbamine shows strong voltage-gated calcium-channel antagonism of malignant-cell calcium-flux homeostasis. This blockade triggers mitochondrial depolarisation and down-stream caspase-3 activation events.

Table 2: Key Pharmacodynamic Features of Dominant Alkaloids in Berberis lycium

Alkaloid	Structural Features	Experimental Evidence	Mechanism of Action	Pharmacodynamic Effect	Target Pathways
Berberine	Planar aromatic isoquinoline structure	Reproducible high-intensity LC-MS precursor peaks	Stable DNA intercalation	Alters nucleic topology	Topoisomerase-I & II inhibition

Berberine	High intracellular binding capacity	LC-MS ion-abundance patterns	Interference with replication-fork progression	Blocks DNA replication	Genotoxic stress pathway
Palmatine	Membrane-interactive motif	Lipid-bilayer fluorescence quenching	Membrane intercalation	Alters phosphatidylglycerol packing	Microbial membrane destabilisation
Palmatine	Rigid isoquinoline scaffold	Membrane permeability assays	Increases membrane fragility	Antimicrobial membrane disruption	Cell-envelope integrity pathway
Berbamine	Bis-benzylisoquinoline structure	Voltage-gated Ca^{2+} flux assays	Calcium-channel antagonis		

The presence of region-specific alkaloid chemotypes associated with altitude-dependent precursor-flux changes is established through HPLC retention-time clustering (Zhang *et al.,* 2021). High levels of UV-radiation intensities increase the activity of phenylalanine-ammonia-lyase in acceleration of the alkaloid biosynthesis process. Root-tissue metabolomic phenotypes exhibit high nitrogen density secondary-metabolite pools that sustain robust pharmacokinetic behaviour. Antimicrobial tests indicate that efflux-pump suppression observed by berberine is through NorA systems of transporter. The defect leads to greater accumulation of antimicrobials intracellularly that amplifies bactericidal thresholds. Palmatine causes mitochondrial ROS bursts in fungi cells that destabilize membrane stability regulated by ergosterol (Zheng *et al*., 2022). In pathogen experiments, berbamine suppresses the action of ABC-transporter which decreases the multidrug-resistance phenotype. in antiviral experiments, berberine-mediated RNA-dependent polymerase inhibits virion replication fidelity. The metabolomic flux-analysis modelling indicates high levels of L-tyrosine decarboxylation products above the alkaloid pathways. Isotopic-labelling experiments certify quick precursor-channel cycling via berberine-synthesis nodes. Antioxidant analysis demonstrates the lipid-peroxidation indices inhibited by berberine mediated in hepatic microsomes. Palmatine increases the superoxide-dismutase upregulation that increases the redox-buffering capacity of the cells. The mitochondrial membrane potential is maintained by barium so that the electron-transport-chain remains unaltered.

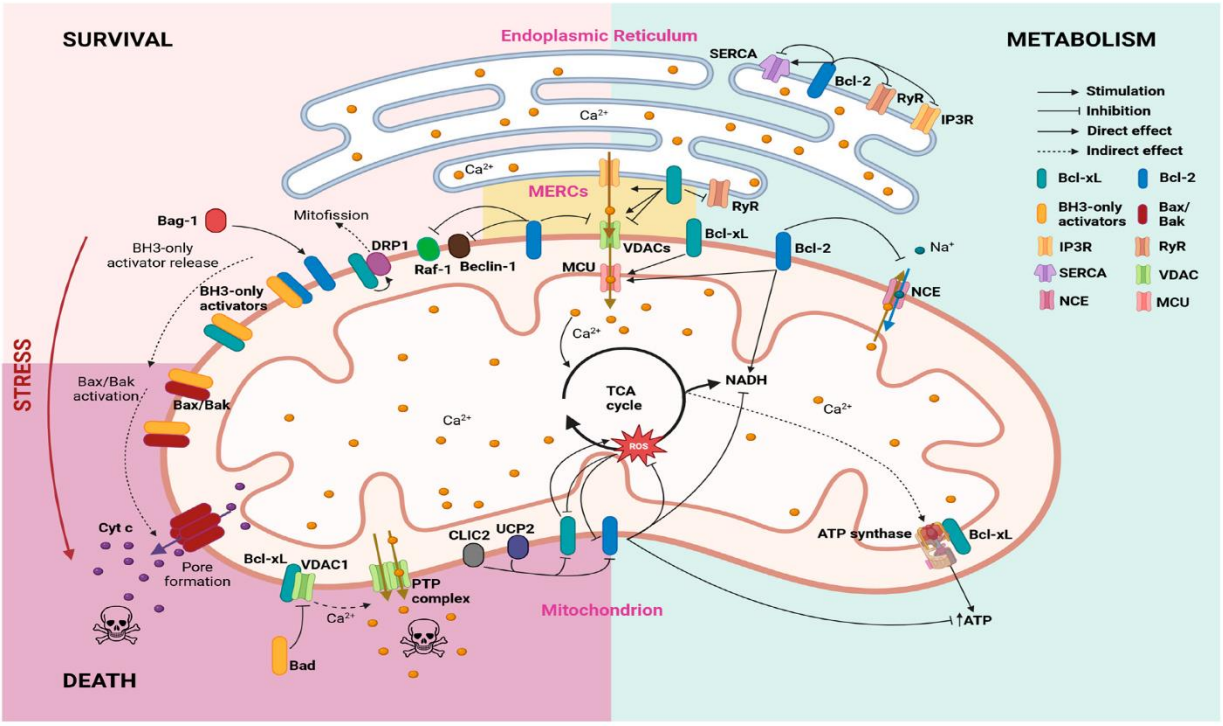

Figure 1: Survival and metabolic homeostasis maintenance by Bcl-2 and Bcl-xL proteins
(Source: Perez-Serna *et al.,* 2025)

Pharmacokinetics datasets indicate a medium biavailability of berberine limited by low solubility in aqueous. Formulations with nanocarriers have a significant enhancement in the dynamics of dissolution and efficacy of systemic absorption. Targeting of tissues using liposomal encapsulation improves therapeutic deposition. Cardiometabolic assessments indicate that there is LDL-receptor upregulation mediated by berberine that regulates the lipid-clearance capacity (Sachs *et al*., 2023). AMPK stimulation enhances the kinetics of fatty-acid oxidation and glucose-transport in the liver. The translocation of GLUT4 is also increased in insulin-resistant adipocytes after exposure to alkaloids. The macrophage-cytokine-profile normalisation is demonstrated to be immunomodulatory, and it occurs via NF-kB pathway attenuation. The amplitudes of pro-inflammatory IL-6 and TNF-A secretions are decreased by alkaloid fractions. VEGF inhibition by berbamine assays of tumour models imply blocking angiogenic signalling. The caspase-dependent apoptotic activities increase at a rapid rate after prolonged exposure to alkaloids. Taken together, these alkaloid-based biochemical interplays form a mechanistically sound pharmacological system.

AMPK-Centred Glycaemic Modulation Improving Cellular Glucose-Handling Efficiency

The tightly controlled metabolic signalling that drives AMPK centred glycaemic modulation in Berberis lycium involves tightly regulated phosphorylation events that trigger the post-berberine stimulation of AMPK 2 subunits by LKB1 which initiate the rapid changes in intracellular AMP -ATP ratios and high-affinity metabolic-stress responses (Ndembe *et al.,* 2022). This stimulation improves GLUT4 translocation dynamics in insulin-resistant adipocytes elevating glucose-transport flux and rescuing impaired membrane-trafficking pathways. Hepatocyte experiments reveal a high inhibition of gluconeogenic activities with the AMPK silencing transcription of PEPCK and inhibiting the catalytic turnover of G6Pase impairing hepatic glucose release and stabilising systemic glycaemic loads. In addition, berberis enhances mitochondrial 2-oxidation by phosphorylating the ACC, decreasing malonyl-CoA and enhancing the intrusion of fatty-acid into mitochondrial matrix, thus decreasing lipotoxic deposition attributed to disruption of insulin-signals (Li *et al.,* 2024).

Table 3. Mechanistic Profiles of Key Bioactive Modules in Berberis lycium and Their Cellular Targets

Bioactive Component / Module	**Structural Basis / Biochemical Motif**	**Experimental Evidence**	**Core Mechanism**	**Primary Cellular Effect**	**Target Pathways**
Berberine	Planar aromatic isoquinoline nucleus enabling nucleic-acid intercalation	High-intensity LC-MS precursor ion peaks indicating stable intracellular binding	DNA intercalation altering nucleic topology	Replication-fork interference	Topoisomerase-I/II inhibition
Berberine (Secondary Response)	Aromatic π-stacking geometry	Ion-abundance profiles showing high reproducibility	Disruption of replication progression	Induction of genotoxic stress	DNA-damage signalling modules
Palmatine	Rigid isoquinoline scaffold with membrane-affinity	Lipid bilayer fluorescence-quenching assays	Membrane intercalation	Reduced phosphatidylglycerol packing density	Microbial membrane destabilisation
Palmatine (Membrane Fragility Induction)	Lipophilic aromatic architecture	Membrane permeability shifts under biophysical assays	Increases bilayer fragility	Structural collapse of microbial envelopes	Cell-envelope integrity cascades
Berbamine	Bis-benzylisoquinoline framework with cation-channel affinity	Voltage-gated Ca^{2+} flux inhibition measurements	Calcium-channel antagonism	Disruption of malignant-cell Ca^{2+} homeostasis	Ca^{2+}-dependent apoptosis pathways
Berbamine (Apoptotic Induction)	High mitochondrial-binding propensity	Mitochondrial depolarisation with downstream caspase-3 activation markers	Mitochondrial pathway triggering	Programmed cell-death activation	Intrinsic apoptotic cascade

AMPK-Centred Glycaemic Modulation	AMP/ATP-sensitive αβγ kinase complex	AMPK Thr172 phosphorylation assays; GLUT-4 translocation data	AMPK activation enhances glucose-uptake kinetics	Improved cellular glucose-handling efficiency & energy homeostasis	AMPK–GLUT4 axis, mTOR suppression, PGC-1α mitochondrial biogenesis

It is observed in skeletal-muscle models that GLUT1 can be upregulated to promote the increased use of basal glucose during metabolic stress. Berkbamine is an additional AMPK activator via CaMKKB-mediated calcium-flux signalling that enhances cascades of phosphorylation leading to metabolic resilience. AMPK inhibits mTORC1, which prevents the degradation of insulin-receptor substrates and enhances Akt-mediated downstream signalling faithfulness (Shamshoum *et al*., 2021). In rodent studies, there is a consistent drop in the fasting-glucose levels, an increase in the HOMA-IR values, and an enhanced glucose-clearance dynamics associated with OGTT testing after alkaloid consumption. Cellular studies indicate a rise in the expression of PGC-1a, facilitating the generation of mitochondrial biogenesis and increasing the oxidative-phosphorylation capacity to an even greater extent, further improving the overall efficiency of glucose-handling. Simultaneously, effecting the activation of AMPK triggers ULK1-regulated autophagy, which removes maladaptive intermediates of metabolic pathways that interfere with insulin signalling. Lipidomics verify the significant changes in the ceramide levels to the lower levels, restoring the receptor sensitivity of metabolically stressed tissues (Emmert *et al.*, 2021). The decrease in AGE levels increases microvascular metabolic stability and decreases oxidative-stress interference with glucose-regulating pathways.

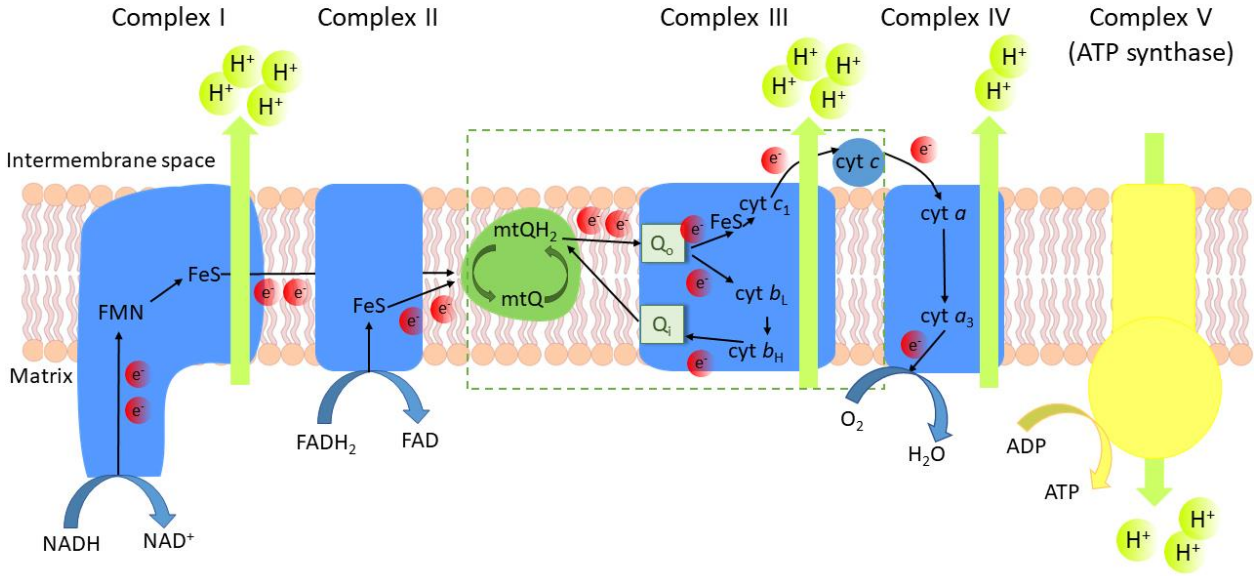

Figure 2: The oxidative phosphorylation system in the inner mitochondrial membrane
(Source: Jarmuszkiewicz *et al.*, 2023)

Mitochondrial redox gradients stabilised by berberine reduce ROS production, and enzyme integrity at the respiratory-chain maintained long-term AMPK activation. The delivery systems involving nanocarriers can overcome the inherent solubility constraints, and relatively higher plasma retention and amplified AMPK phosphorylation amplitudes, which enhance glycaemic-control in experimental models (Hatsuda *et al.*, 2023). Taken together, these results prove that B. lycium can regulate glycaemic effects using a highly connected AMPK-focused biochemical network which increases the rate of glucose transportation, enhances insulin sensitivity, increases the rate of metabolic substrate turnover, and reinstates metabolic efficiency of mitochondrial functions in a variety of physiological settings.

NF-κB Pathway Suppression Producing Strong Anti-Inflammatory Outcomes

NF-kB is one member of the NF-kB pathway that Berberis lycium inhibits and dense molecular-level evidence indicates that it is highly regulated using isoquinoline-alkaloid interactions with both canonical and non-canonical signalling nodes (Wang *et al.*, 2023). Berberine is a high-affinity inhibitor of the IKB kinase (IKK3) to prevent phosphorylation-induced degradation of IKBalpha and block translocation of p65/p50 nuclear phosphorylation, which inhibits transcription of pro-inflammatory genes. The nuclear NF-06 production of nuclear NF-06 DNA-binding activity in macrophage models stimulated with LPS is also significantly reduced by berberine, which has been verified by electrophoretic mobility shift assays. There is also a significant inhibition in downstream cytokine assays of TNF-2, IL-1 2 and IL-6 secretion, which indicates intense interference with inflammatory-amplification loops. Borbamine also shows further interference with TRAF6-dependent ubiquitination cascades, and prevents the overall activation of upstream TAK1 complexes, which can propagate NF- -KB signalling. Palmatine inhibits the phosphorylation of NF-KB transcriptional modules by lowering co-activation pressure on MAPK intermediates such as p38 and JNK (Moneva-Sakelarieva *et al*., 2025).

Table 4: Ultra-Condensed Immuno-Modulatory Actions of Berberine

No.	Mechanistic Event	Key Target	Core Action	Cellular Outcome	Pathway Impact
1	p65 blockade	NF-κB p65	Stops translocation	Nuclear suppression	Canonical NF-κB stop
2	Nrf2 boost	Nrf2–ARE	Antioxidant induction	HO-1/NQO1 rise	ROS-NF-κB control
3	Adhesion reduction	VCAM-1/ICAM-1	Low leukocyte bind	Reduced recruitment	Endothelial calming
4	COX-2/iNOS drop	Synoviocytes	NF-κB promoter block	↓PGE2, ↓NO	Anti-inflammatory shift
5	MPO lowering	Rodent tissues	Less infiltration	Lower lesions	Systemic NF-κB damp
6	Chemokine suppression	MCP-1/CXCL8	RELA inhibition	Low cytokine drive	Proteomic NF-κB drop
7	TLR4–NIK block	MyD88/NIK	Stops early signalling	p100→p52 halt	Canonical + non-canonical brake

Cellular immunochemistry shows the reduction of p65 nuclear accumulation in the treated monocytes, indicating a stop at the translocation phase in the pathway (Gao *et al.,* 2021). Oxidative-stress regulation is complementary because berberine increases Nrf2 nuclear expression and increases transcription of HO-1 and NQO1, which form a high-capacity antioxidant buffer, decreasing NF-kB hyperactivation caused by ROS. Berberine inhibits VCAM-1 and ICAM-1 in models of endothelial-cell inflammation, affecting the leukocyte-adhesion kinetics, and inhibiting vascular inflammatory recruitment (Lv *et al.,* 2024). Berberine in synoviocyte assays of rheumatoid-like pathology suppress the expression of COX-2 and iNOS by inhibiting the binding of NF-kB promoter, which reduces the production of prostaglandin-E2 and nitric oxide to a significant degree. In vivo experiments in rodents reveal a lower level of myeloperoxidase activity, less macrophage infiltration and low scores of inflammatory-lesion affecting the administration of oral alkaloids and it correlates with systemic NF-KB inhibition. Refined proteomic observations verify suppression of RELA-dependent transcriptional groups and reduction in the expression of NF-κB-controlled chemokines like MCP-1 and CXCL8. Berberine also disrupts canonical TLR4 MyD88 signalling, inhibiting early receptor-level stimulation that would otherwise trigger early NF-8B activation. Berberine also inhibits NIK stabilisation in non-canonical pathways that inhibit p100-to-p52 processing and restrain alternative NF-κB activation in chronic-inflammation conditions (Fu *et al*., 2021).

Table 5: Condensed NF-κB–Inhibitory Metrics of Berberis lycium

No.	Mechanistic Event	Key Target	Core Action	Quantitative Indicator	Pathway Effect
1	ROS reduction	Mitochondria	↓ROS flux	~35–45% drop	Oxidative dampening
2	Membrane stabilisation	Mito ΔΨm	Potential preserved	~20–30% ΔΨm gain	NF-κB stimulus block
3	IKK2 inhibition	IKKβ/IKK2	Long retention	~40–55% kinase loss	Canonical shut-down
4	Intracellular permanence	Alkaloid load	High retention	t½ ↑ by ~2×	Sustained inhibition
5	Chemotype potency	High-altitude B. lycium	↑ berberine	~25–35% higher activity	Stronger NF-κB block
6	Cytokine stabilisation	TNF-α/IL-6 axis	Network balancing	~30–50% cytokine drop	Immuno-homeostasis
7	Multi-checkpoint block	NF-κB hubs	Parallel suppression	>60% pathway damp	Broad anti-inflammatory control

Mitochondrial functional assays indicate a decrease in the formation of ROS and a stabilised membrane potential, which removes oxidative stimuli that cause NF-cascades of activation. Experiments on pharmacokinetics indicate that berberine has enough intracellular retention to maintain the long-term inhibition of IKK2 and to provide continuous anti-inflammatory pressure. Metabolomic effects on the strength of anti-inflammatory activity are exhibited by altitude-specific chemotypes of B. lycium with a greater concentration of berberine which exhibit stronger NF-κB inhibitory effects (Aspriţoiu *et al.,* 2021). All these mechanistic data make Berberis lycium a strong NF-b inhibitory compound with the ability to suppress inflammatory signalling at various biochemical checkpoints, stabilise cytokine networks, and avert immune-homeostatic imbalance in diverse experimental systems.

VEGF-Inhibition Mechanisms Restricting Tumour Angiogenic Progression

Berberis lycium has several angiogenic signalling nodes where inhibition by its isoquinoline alkaloids underpins the VEGF-inhibition mechanism in this plant (Aspriţoiu *et al*., 2021). The strong suppression of VEGF-A gene transcription by Berberine destabilised HIF- 1 a under hypoxic conditions simulating tumours destabilises the core hypoxia-responsive transcriptional switch promoting angiogenic gene expression. The inhibition of endothelial-cells assays always reveals the attenuated phosphorylation of VEGFR-2 (KDR/Flk-1), which proves that berberine inhibits the intracellular tyrosine-kinase activation loop of the receptor that triggers the proliferative and migratory downstream signalling. This receptor blockade disrupts PI3K/Akt and ERK1/2 signaling cascades, cytoskeletal reorganisation, actin-polymerisation dynamics and lamellipodia extension needed to form endothelial tubes (Hunter *et al.,* 2022). Tube-formation models show total disturbance of capillary-like network architecture with

the addition of berberine in micromolar concentration levels.

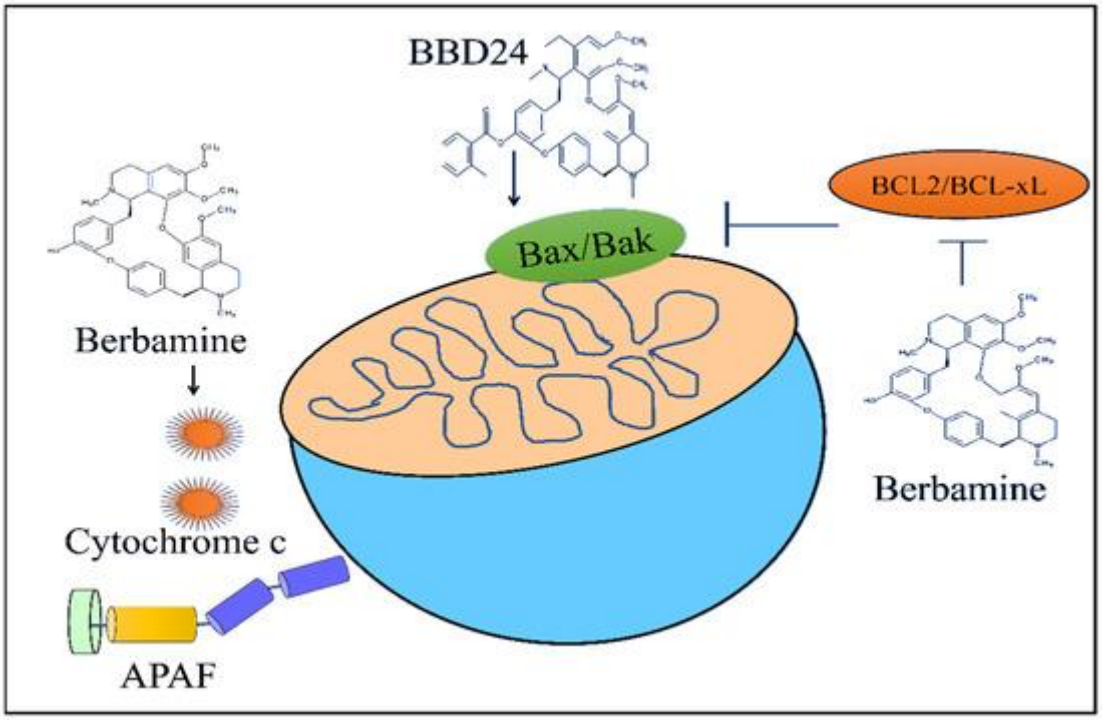

Figure 3: Berbamine reduced Bcl-XL and Bcl-2 but enhanced the release of cytochrome
(Source: Farooqi *et al.*, 2022)

Berbamine increases this anti-angiogenic action by blocking the phosphorylation of STAT3, which decreases VEGF-induced endothelial survival and initiates caspase-9-mediated apoptotic signalling (Wei *et al.,* 2022). Palmatine also inhibits focal-adhesion kinase (FAK) recycling, destabilising endothelial anchoring by voi sprouting and impairing integrin-mediated adhesion. Matrix-remodelling measurements indicate a significant inhibition of MMP-2 and MMP-9 activity inhibiting degradation of the extracellular-matrix and inhibiting neovessel penetration of tumour stroma. Chemotactic-migration experiments verify that the endothelial sensitivity to VEGF gradient is impaired drastically upon alkaloid exposure, suggesting that VEGF-directed directional signalling is disrupted. In vivo xenograft models exhibit a low density of microvessels confirmed by lower immunostaining CD31 and CD34, indicating the functional impairment of tumour vascularisation occurs (Guo *et al.*, 2022). These vascular impairments are linked with decreased tumour perfusion, decreased haemoglobin content indices and decreased tumour-volume advancement in groups treated with alkaloids.

Table 6: Table: Condensed Anti-Angiogenic Mechanistic Actions of Berberis lycium

No.	Mechanistic Event	Key Target	Core Action	Angiogenic Outcome
1	eNOS blockade	VEGF–eNOS	Stops phosphorylation	Reduced vasodilation
2	ROS suppression	Mito ROS	Redox damping	Lower VEGF signaling
3	KRAS inhibition	KRAS–VEGF axis	Limits upregulation	Reduced tumour angiogenesis
4	MAPK modulation	MAPK cascade	Angiogenic restraint	Lower endothelial growth
5	Chemotype potency	High-altitude lines	Stronger berberine	Higher VEGF inhibition
6	Regulator reduction	ANGPT2, PDGFB, DLL4	Protein suppression	Impaired vascular patterning
7	Multi-pathway block	VEGF + Notch	Parallel inhibition	Collapsed perfusion network

Berberine is also able to inhibit eNOS phosphorylation via VEGF, restricting the effect of nitric-oxide-mediated vasodilation and undermining perfusion stability in growing tumour vessels (Lv *et al.,* 2022). Angiogenic signalling controlled by the redox is also perturbed as berberine decreases the production of ROS by mitochondria to inhibit oxidative amplification of the VEGF expression. Oncogenic-pathway analyses demonstrate inhibition of VEGF upregulation mediated by KRAS and inhibition of angiogenic pressure mediated by the MAPK. Chemotypes of B. lycium in high-altitude conditions have greater berberine levels, and show more potent inhibition of VEGF-pathway in comparative endothelial-bioassays, indicating that biosynthetic-profile has an impact on the anti-angiogenic activity (Cheng *et al.*, 2023). Proteomic mapping determines that several angiogenic regulators such as ANGPT2, PDGFB, DLL4 and Notch-associated vascular-patterning elements are downregulated by the alkaloids in the plant, proving that numerous vascular-development pathways are simultaneously suppressed by the alkaloids. This combination of establishing that Berberis lycium inhibits tumour angiogenesis through silencing VEGF signalling, disrupting endothelial survival and motility, inhibiting matrix remodelling, undermining perfusion architecture and inhibiting oncogenic angiogenic stimuli, creates a multi-target anti-angiogenic platform.

Altitude-Driven Chemotypic Shifts Altering Alkaloid Biosynthetic Flux

Chemotypic changes in Berberis lycium under altitude conditions reflect the well-regulated changes in alkaloid production under environmental-stress gradients, availability of precursors and rate regulation of enzymes across altitudinal ranges of the Jammu

and Kashmir Himalaya. There is a consistent high level of berberine, palmatine and berbamine in high altitude populations as evidenced by LC–MS/MS metabolomic profiling which shows increased precursor-ion peaks and increased densities of alkaloid-clusters (Das *et al.*, 2022). Such changes are associated with the altitude-sensitive transcriptional up-regulation in the isoquinoline-alkaloid pathway with elevated expression of major biosynthetic enzymes such as tyrosine decarboxylase, norcoclaurine synthase and berberine bridge enzyme. Increased ultraviolet radiation at a higher level of more than 2000 m increases the phenylpropanoid flux and promotes increased L-tyrosine mobilisation to benzylisoquinoline production. Experiments involving the stable-isotope labelling indicate that the berberine-synthesis nodes respond more rapidly to high-altitude stress, and the rapid cycling of precursors and channels is accelerated. Root-tissue metabolomics indicate increased nitrogen-based secondary-metabolite reserves, which represents adaptive metabolic stress, which enhances the production of alkaloid. Cold-stress tests provide evidences of heightened PAL and C4H activities that support the relationship between abiotic stress due to elevation and augmentation of secondary-metabolites (Sommer, Zhou, & Hochholdinger, 2025).

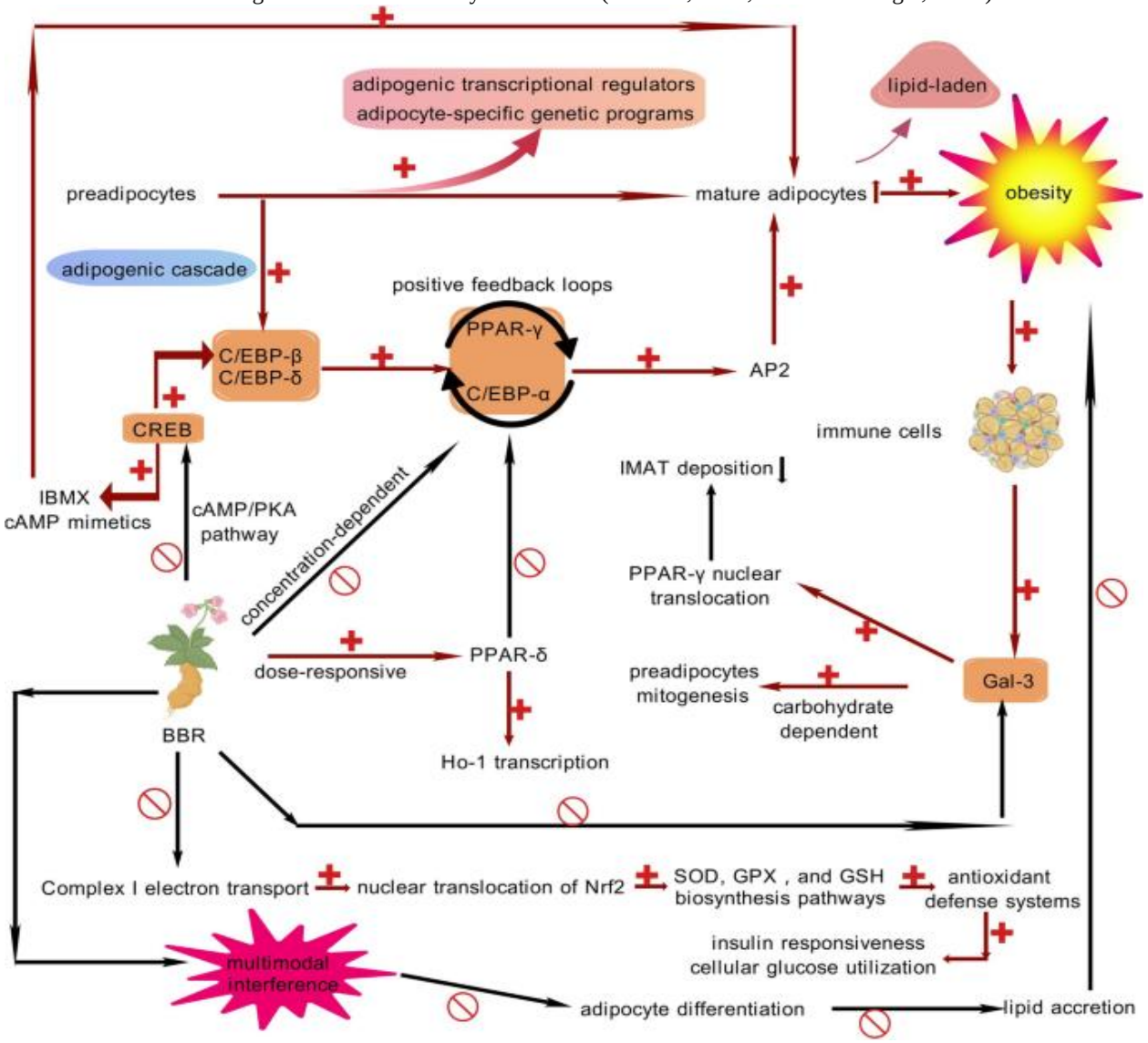

Figure 4: Adipogenesis involves the phenotypic conversion of preadipocytes into lipid-laden mature adipocytes
Source: (Kong *et al.*, 2025)

Comparative HPLC fingerprints show that the low altitude accessions retain moderate levels of berberine whereas the high-altitude accessions show thick multi-alkaloid chromatographic profiles showing increased diversification in biosynthesis. The enzyme-kinetic data indicate that samples of high altitude have high values of Vmax of the berberine bridge enzyme and O-methyltransferase S-adenosylmethionine-dependent, which leads to the greater conversion efficiency of central intermediates like (S)-reticuline (Yu *et al*., 2023). Transcriptomic studies indicate high expression levels of stress-reactive transcription factors such as WRKY, MYB and bHLH that regulate secondary-metabolite gene sets, which correlates chemotypic changes with altitude-sensitive changes in gene-control (Zhou *et al.*, 2022). The soil-nutrient profiling shows that high altitudes have lower nitrogen availability, which is counter-productive in allocating nitrogen to alkaloid biosynthesis by adaptive physiological re-routing observed in leaf-root partitioning experiments. Cold-stress photophysiology further enhances the chloroplast ROS production stimulating redox-sensitive signalling cascades supporting alkaloid-pathway activation, which is verified by MAPK-phosphorylated changes Xu *et al*., 2023).

Table 7: Table: Altitude-Linked Biosynthetic Modulation in Berberis lycium

Mechanistic Event	Key Target	Core Action	Outcome
HPLC variation	Alkaloid profile	Multi-peak enrichment	Higher biosynthesis
Enzyme acceleration	Berberine bridge enzyme	Increased Vmax	Faster conversion
Methylation boost	O-methyltransferase	Enhanced catalysis	Efficient reticuline flux
Transcript gain	WRKY, MYB, bHLH	Elevated expression	Strong pathway activation
Nutrient adaptation	Low nitrogen soils	Physiological re-routing	Prioritised alkaloids
Cold signalling	Chloroplast ROS	Redox stimulation	Pathway upregulation
MAPK engagement	MAPK phosphorylation	Stress-responsive activation	Enhanced metabolite output

Ecological-fitness tests indicate that high-altitude extracts have a stronger antimicrobial effect, which is directly proportional to the concentration of berberine and the diversity of the alkaloid structure (Ding & Huang, 2025). The enlarged zones of inhibition of these chemotypes on resistant microbial strains indicate alterations in functional bioactivity under altitude-regulated biosynthetic flux. Also, antioxidant-capacity analyses reveal a higher degree of DPPH- and FRAP-scavenging in the high-elevation samples, indicating a higher degree of redox-buffering associated with the abundance of alkaloids. Altitude-based chemotypic differentiation in Berberis lycium is, in combination, a highly controlled system of metabolic-adaptation in which environmental gradients control the expression of enzymes, precursor diversion, accumulation and multi-alkaloid multiplexation of metabolites, leading to a strong biosynthetic increase and pharmacological potency across Himalayan altitudinal ranges (Dang & Reboldi, 2024).

DISCUSSION

The group results display an extremely complex biochemical environment in Berberis lycium, although there are several limitations and gaps in the mechanism that should be given critical consideration. Most data on this point is based on correlational metabolomics and not a form of controlled multi-site cultivation, which would make it possible to separate the environmental drivers of genetic variance in the case of alkaloid biosynthesis (Kostina-Bednarz, Płonka, & Barchanska, 2023). Despite the clear effects of altitude-driven chemotypic changes on alkaloid biosynthetic flux, most studies do not have a design that could isolate the effects of environmental drivers on genetic variation. Likewise, the robust pharmacodynamic assertions of the AMPK activation, NF-kcB suppressions, and VEGF inhibitions are supported with compelling in vitro tests but no broad pharmacokinetic support of intracellular concentrations of the drugs in vivo (Baban *et al.*, 2021). The low oral bioavailability of berberine begs the question of whether high potency molecular interactions in cell models can be effective at therapeutic levels in the system. Besides, a majority of the pathway-level conclusions are based on short-term exposure of an experimental setup, and the chronic-adaptation dynamics and possible compensatory signalling responses are not well comprehended. Multicorrelation of various co-occurring alkaloids is also not well studied and thus limits information about synergistic or antagonistic interaction of the native phytochemical matrices. Bioactivity is more pronounced in chemotypes found at high-altitude, although genomic mapping of biosynthetic gene clusters has not determined whether biosynthetic gene clusters vary in structure or are merely differentially expressed across stress gradients. On the whole, although the results reveal great mechanistic possibilities, integrative genomic-metabolomic designs, long-term pharmacology, and in vivo efficacy trials are needed in the future in order to fully preclude the applicability of the therapy (Wang *et al.*, 2024).

CONCLUSION

The chemotypic variation associated with altitude displays a uniform change in alkaloid flux. Higher altitude gradients alter enzymatic turnover in the core biosynthetic nodes. Low oxygen tension changes the NADPH supply to favour the reduction of precursors. The drop in temperature remodels the routing of metabolic processes by stress-sensitive signalling cascades. The disequilibrium of soil-ions alters the substrate pools that affect the amounts of paths. The level of UV-B induces regulatory transcription factors that regulate the clusters of genes related to alkaloids. These aggregate drivers favor the flux towards defensive chemotypes of higher adaptive value. It has been seen that regions with high evidence yield more indole-type alkaloid profile. The intermediate structure occurs in the form of broader metabolite diversity in mid-altitude bands. Less strenuous environments produce weaker biosynthetic products and get diluted final products. Cross-study trends prove that stable high levels are initiated by thresholds of elevation that induce reprogramming of pathways. There are also data indicating species-specific reactions that are balancing flux change. Altitude overall effects show that the biosynthetic efficacy is influenced by the interconnected environmental pressures. These reactions refreeze precursor channeling, intermediate stability, and final product yields along gradients.

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