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Berberine HCL JP: A Comprehensive Review of Phytochemical Excellence, Therapeutic Potential, and Global Standards of *Berberis aristata* Extract

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Abstract

Berberine, a bioactive isoquinoline alkaloid, has garnered significant scientific and therapeutic attention due to its extensive pharmacological properties. Extracted primarily from medicinal plants such as *Berberis aristata*, traditionally employed in Ayurveda and Unani medicine, berberine is renowned for its antidiabetic, anti-inflammatory, antimicrobial, and cardioprotective effects. Among various commercial preparations, Berberine HCL standardized according to the Japanese Pharmacopoeia (JP) distinguishes itself by superior quality control, consistency, and a robust safety profile. This review, developed in collaboration with **M R Healthcare Pvt Ltd and Indian Herbs Extractions,** provides a detailed examination of Berberine HCL JP, emphasizing its botanical sources, advanced aqueous extraction methodologies, and comprehensive phytochemical profiling in alignment with stringent JP specifications. It explores underlying pharmacological mechanisms validated through recent preclinical and clinical research, underscoring its therapeutic potential in addressing metabolic diseases, infectious disorders, and inflammation. Additionally, the review assesses the toxicity profiles, available dosage forms, and innovative delivery systems that support its safe incorporation into contemporary therapeutics. A comparative evaluation of Berberine HCL JP against other pharmacopeial benchmarks such as USP and EP is also included, alongside a discussion on regulatory frameworks and market dynamics. With increasing global interest in standardized herbal formulations, Berberine HCL JP emerges as a reliable, scientifically substantiated choice within pharmaceutical and nutraceutical sectors. Finally, the review highlights current research gaps and prospective investigative avenues, aiming to foster expanded clinical utilization and advancement in this significant phytopharmaceutical.

Keywords: *Berberis aristata*, Berberine HCL JP, Alkaloid, Indian Berberine

Introduction

Berberine is a plant alkaloid that has shown various benefits in Ayurveda. It is found in various parts of the plant such as roots, rhizomes, and stem bark of the plants [1]. This is a compound that belongs to the class of organic compounds which is known as protoberberine alkaloid and its derivatives and is present in hydrochloric salt which is called Berberine HCL to enhance the stability and solubility[2]. The extracts of berberine have shown various antimicrobial activity against various pathogens such as bacteria, viruses, fungi, protozoans, and helminths. It is characterized by its vibrant yellow colour and its intense bitter taste which shows its alkaloid nature. According to the literature as well there are several preclinical and clinical studies, which demonstrate the effect of berberine against various disorders such as metabolic, neurological, and cardiological problems [3]. Berberine is the main constituent having pharmacological actions. It is one of the most active constituents in all the Berberis species. From various research studies it has been accumulated in the root part of Berberis species and low altitude plants contain more berberine as compared to high altitude plants [4]. It is a

potent pharmaceutical candidate for both preventive and curative healthcare. Also, Berberine HCL JP which is derived from Berberis aristata ensures consistency, purity, and safety and makes it suitable for the world-regulated market[5].

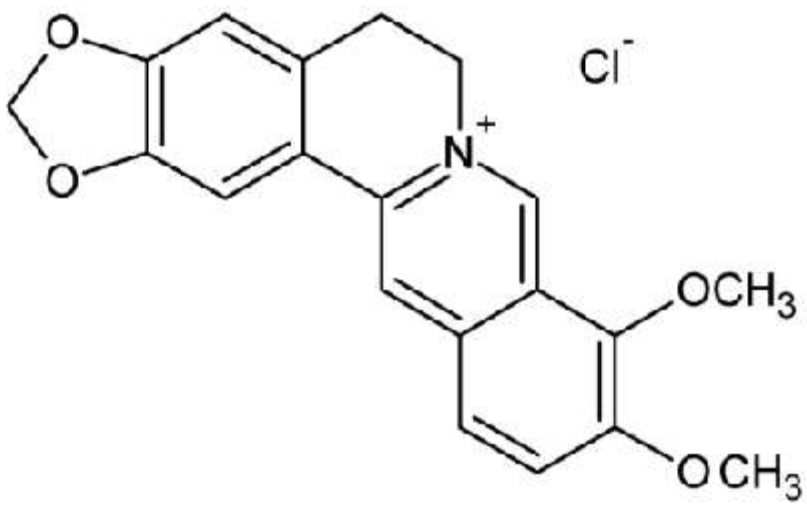

Figure 1: Chemical Structure of Berberine [1]

Botanical background and significance of *Berberis aristata*

The *Berberis aristata* which is very famous in Asian countries that as India and China is commonly called Indian Barberry or Daruharida and Zarishk [6]. It is mainly used in traditional medicine but has also gained importance in modern medicine as well. *B.aristata* and its potential bioactive compounds have shown a good response in fighting against various acute and chronic diseases which include cardiovascular diseases, diabetes, cancer, infectious diseases, and ageing-associated symptoms [7]. Botanically, *Berberis aristata* is characterized by its spinny stems, yellow wood, and bright yellow inner bark. This plant produces small yellow flowers and deep berries with its roots and stems being the most important part used in traditional medicine [8].

In traditional medicine which includes Ayurveda, Unani, and Siddha, *Berberis aristata* holds significant importance in anti-bacterial, anti-inflammatory, anti-diabetic, and wound healing properties [9]. It has been years the people have been using this for various skin diseases, eye infections, and fever.

The extraction of Berberine HCL JP from *Berberis aristata* ensures strict adherence to pharmacopeial standards as outlined in Japanese Pharmacopeia as it demands a level of purity, consistent phytochemical profile, and therapeutic efficacy. This compound is used in herbal drug development in the global market [10].

Historical and traditional usage

In Ayurveda, *Berberis aristata* is considered bitter and is very light and dry. It is mainly used for Kapha and Pitta doshas [11]. In ancient times it is mainly used for treating ailments such as ulcers, diarrhea, and liver disorders. The stem and bark of this compound are used for wound cleaning and eye disorders. In Unani medicine, it is mainly used for blood-purifying and anti-septic properties and is used for chronic ulcers, urinary tract infections, and skin eruptions [12]. The wide range of applications has laid the foundation for modern research on berberine the primary bioactive constituent of *Berberis aristata.* The traditional insights are increasingly supporting the evidence of this plant [13].

Source and Extraction Methods

Berberis aristata is a spiny deciduous shrug that belongs to the family of Berberidaceae. It is well-distributed among the sub-Himalayan regions of Nepal, Bhutan, and Southeast Asia. In India, it is mainly present in the States of Uttarakhand Jammu & Kashmir and Himachal Pradesh [14]. This species thrives in temperate and subtropical climates, especially in

moist, forested, and shady ravines. Its roots and bark are the primary source of berberine and is used for therapeutic effects [15].

Advanced and water-based extraction methods specific to Berberine HCL JP

The extraction of Berberine HCL JP from *Berberis aristata* involves modern, efficient, and environment-friendly methodologies that yield high-purity products that comply with Japanese Pharmacopeia [16]. Many other conventional methods rely on heavy organic solvents which emphasize green chemistry approaches that involve water-based and aqueous ethanol extraction methods which ensure safety, efficacy, and pharmaceutical grade purity. It involves various steps such as the selection of preprocessing material, water extraction methods, advanced techniques, and various purification and standardization [17].

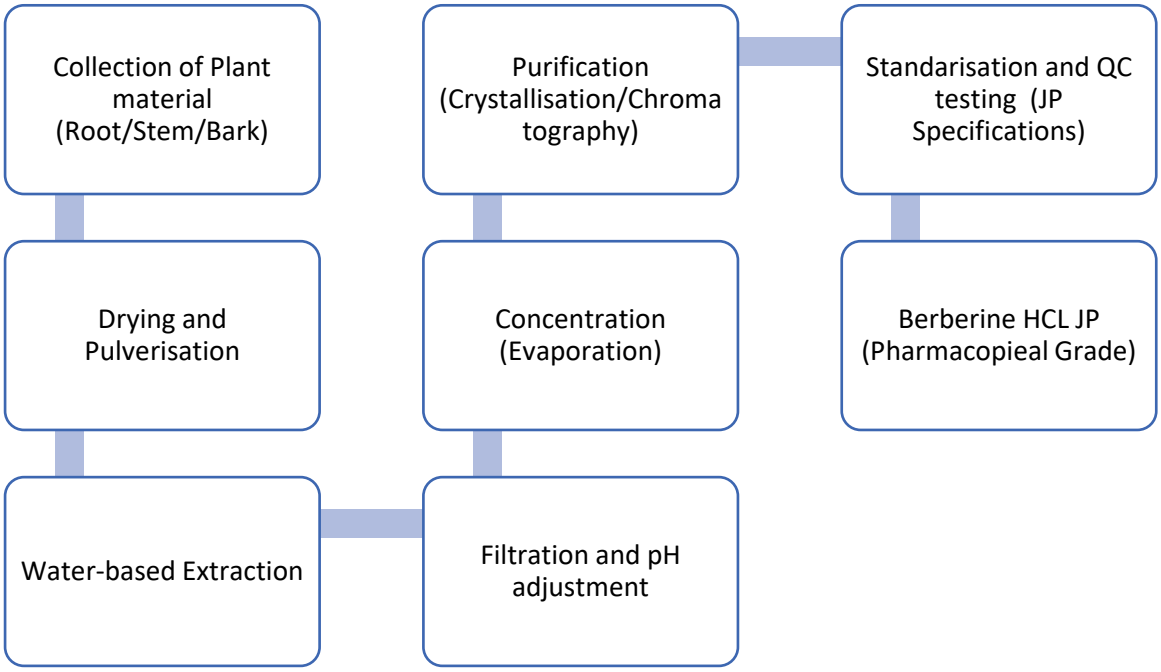

Figure 2: Water-Based Extraction Process for Berberine HCL JP [15-17]

Selection and Preprocessing of Plant Material

The various parts of the plant such as roots and barks of *Berberis aristata* are harvested, cleaned, and shade-dried to preserve heat-sensitive alkaloids. The plant material is dried is then pulverized into coarse powder to enhance surface area for efficient surface area.[15]

Water based Extraction

The advanced water-based extraction for Berberine HCL JP is typically aided by heat and pressure in closed-loop reactors which allow the recovery of berberine without degrading its active components. This method offers various advantages such as low toxicity, cost-effectiveness, and no residual solvent contamination making it ideal for Pharmacopoeial-grade formulations[16-18].

Advanced Techniques

There are various advanced techniques for the extraction of Berberine. One such extraction method is ultrasound-assisted extraction which uses ultrasonic waves to disrupt cell walls and enhance the release of berberine into the aqueous medium [19]. This method is energy-efficient and accelerated extraction without chemical degradation. Another extraction method is microwave-assisted extraction which utilizes microwave radiation to heat the solvent and improve the extraction kinetics [20]. It reduces the extraction time and water consumption significantly. The last method is pressurized hot water

extraction which is also called subcritical water extraction which employs high temperature and pressure to maintain water in the liquid state above 100°C, enhancing the solubility and recovery of polar alkaloids like berberine [21].

Purification and Standardization

Post extraction the extract undergoes filtration, pH adjustment, and crystallization to isolate the berberine HCL JP. Techniques such as column chromatography and repeated recrystallization are employed to achieve JP-compliant purity. The final product is tested for identity, assay, microbial load, and heavy metal content, following Japanese Pharmacopoeia standards [22].

Table-1: Extraction Methods for Berberine HCL JP

Method	Solvent Type	Efficiency	Advantages	Limitations	Reference
Hot Water Extraction	Water	Moderate	Non-toxic, cost-effective, traditional	Long extraction time, limited yield	Neag MA et al. (2018)
Ultrasound-Assisted Extraction (UAE)	Water / Water-Ethanol	High	Quick, energy-efficient, improves yield	Requires equipment, risk of degradation if overheated	Kim S et al. (2018)
Microwave-Assisted Extraction (MAE)	Water / Ethanol	Very High	Fast, low solvent use, eco-friendly	Expensive setup may denature sensitive compounds	Chang W et al. (2013)
Pressurized Hot Water Extraction (PHWE)	Water (high temp & pressure)	High	The green method, effective for polar compounds like berberine	Equipment cost, high operating temperature	Cui H et al. (2018)
Solvent Extraction (conventional)	Ethanol, Methanol	Moderateâ€“High	High yield, well-studied	Residual solvents, environmental and regulatory concerns	Imenshahidi M & Hosseinzadeh H (2016)
Supercritical COA Extraction	COâ,, (with co-solvent)	High	Solvent-free product, high selectivity	High cost, needs co-solvent for berberine	Patel S et al. (2020)

Compliance with JP standards

The Japanese Pharmacopoeia outlines stringent quality specifications for Berberine HCL which meet the specific criteria.

Table-2: Compliance with JP Standards [23]

Parameter	JP Requirement
Identification	Must pass HPLC or UV spectrophotometry
Assay (content of Berberine HCL)	≥95.0% and ≤102.0% by dried substance
Appearance	Yellow crystalline powder
Solubility	Freely soluble in water; sparingly in ethanol
Loss on drying	Not more than 6.0%
Residue on ignition	Not more than 0.2%
Heavy metals	Not more than 10 ppm
Microbial limits	Must comply with pharmacopeial safety levels

Some notable differences between United States Pharmacopeia and European Standards Pharmacopeia provide specifications for berberine and berberine-containing botanical extracts [24]. The JP standard is considered more effective regarding heavy metal content and water content which makes Berberine HCL JP one of the stringent and premium grade extracts that is available globally.

Table-3: Comparison with other Pharmacopoeial monographs (USP, EP, etc.) [24-26]

Parameter	**JP**	**USP**	**EP**
Assay Range	95.0–102.0%	97.0–103.0%	97.0–102.0%
Identification	HPLC, UV	HPLC, FTIR	TLC, UV
Impurity Limits	Strict residual solvents, heavy metals	Focus on organic impurities	Similar to USP, but stricter for some impurities
Microbial Testing	Required	Required	Required
Source Material	Strictly *Berberis aristata*	May include *Berberis vulgaris* or mixtures	May not specify the exact species

Pharmacological Activities

Berberine HCL JP extracted from *Berberis aristata* exhibits a diverse range of pharmaceutical actions that are supported by extensive clinical and pre-clinical research [27]. The major bioactivities include anti-diabetic, antimicrobial, anti-inflammatory, and antioxidant activity. These actions are largely attributed to its interaction with molecular signaling pathways, modulation of enzymes, and strong affinity with receptors [28].

Evidence-based discussion of major bioactivities:

Anti-diabetic Activity

Berberine has emerged as a potent hypoglycemic agent as compared to anti-diabetic drugs like metformin. This compound is helpful in the reduction of blood glucose via the activation of multiple mechanisms such as AMP-activated protein kinase, suppression of gluconeogenesis, stimulation of glycolysis, and enhancement of insulin sensitivity [29]. There are many published studies and clinical trials that ensure that berberine has significantly reduced the fasting blood glucose and has also modulated the gut microbiota which plays a major role in glucose metabolism [30].

Antimicrobial Activity

Berberine demonstrated broad-spectrum antimicrobial effects against bacteria, fungi, protozoa, and also viruses [31]. It disrupts microbial DNA replication and also inhibits the enzyme systems such as DNA topoisomerase and RNA polymerase. It has also been reported that it shows synergistic effects when combined with conventional antibiotics, especially in resistant strains [32].

Anti-Inflammatory Activity

Berberine is also responsible for the inhibition of key inflammatory mediators such as TNF-α**,** IL-1β**,** and COX-2, and also downregulates NF-κB**,** a central regulator of inflammation. In animal models, it is responsible for the reduction of edema, leukocyte infiltration, and cytokine expression [33]. It also stabilizes the epithelial barrier and shows the potential in the treatment of inflammatory bowel disease and autoimmune conditions [34].

Antioxidant Activity

Berberine acts as a potent free radical scavenger that increases the superoxide dismutase and glutathione peroxidase activity which leads to the reduction in lipid peroxidation [35]. It mitigates oxidative stress, and cellular injury and plays a supportive role in its cardiovascular and neuroprotective effects [36].

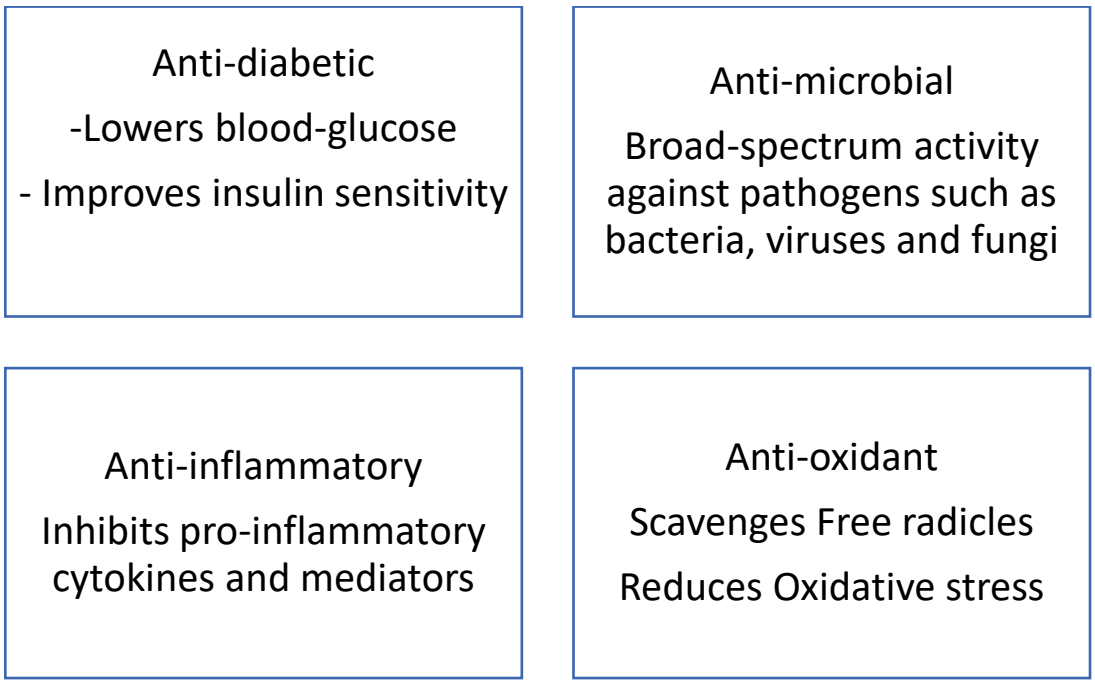

Fig 2: Pharmacological Activities of Berberine HCL JP

Mechanism of Action

Berberine HCL JP exhibits its pharmacological effect through a diverse range of molecular and cellular mechanisms. One of the most important pathways by Berberine is the AMP-activated protein kinase pathway. This pathway is considered a central regulator of energy metabolism. Activation of this pathway leads to the activation of glucose uptake, lipid metabolism, and increased lipid sensitivity [37].

Berberine also modulates mitogen-activated protein kinase and the P13 Akt pathway which regulates cellular proliferation, apoptosis, and also inflammation. This leads to the contribution of anti-cancer, anti-inflammatory, and neuroprotective activities. Another mechanism with Berberine interaction with gut microbiota influences bile acid metabolism and inhibits enzymes which enhance the anti-diabetic effect [38].

Recent in vitro and in vivo studies elucidating mechanisms

Several in vitro studies show Berberine's ability to inhibit proliferation and lead to the induction of apoptosis in cancer cell lines. Various studies in hepatocellular carcinoma models show that berberine induces cell cycle arrest at the G1 phase that is mediated by the mitochondrial pathway [39].

In vivo, animal studies have shown to reduce hyperglycemia and improve insulin resistance. In the rodent model, Berberine HCL JP has shown improved blood glucose, lipid profiles, and oxidative stress markers. These studies have also proven its cardioprotective effects which include cardiac output and reduced myocardial fibrosis. These studies make Berberine HCL JP a unique multi-targeted therapeutic agent with broad-spectrum pharmacological activities [40].

Dosage Forms and Delivery Systems

Berberine HCL JP is readily accessible in multiple standard oral dosage forms, designed for therapeutic applications in metabolic, gastrointestinal, and cardiovascular conditions. Frequently found commercial formulations consist of

Table-4: Commercially Available Formulations [41-43]

Dosage Form	Strength	Description
Capsules	250–1000 mg	The most prevalent form; is standardized extracts; often combined with silymarin or chromium for synergistic effect and improved absorption.
Tablets	200–500 mg	Available as standalone or in combination with herbs like fenugreek, and gymnema.

Oral Solutions	100–300 mg/5 mL	Less common; targeted for pediatric or geriatric use where swallowing is difficult.
Powders/Granules	500 mg/sachet	For dispersion in water; used in traditional medicine systems and integrative therapies.
Teas/Herbal Decoctions	Varies	Found in Ayurvedic and Unani preparations; often as crude *Berberis aristata* extract.

While conventional capsules and tablets remain the standard delivery formats for Berberine HCL JP, novel drug delivery systems offer promising strategies to enhance its bioavailability, stability, and clinical effectiveness. These advanced formulations could open new therapeutic indications and improve patient compliance in chronic conditions [44].

Toxicology and Safety Profile

Berberine demonstrates a wide therapeutic window with minimal toxic effects at clinically relevant doses.

Table -5: Acute and Chronic Toxicity of Berberine to evaluate systemic safety [45]

Study Type	Model	Findings
Acute Toxicity	Mice, rats	LD_{50} values: 329 mg/kg (i.v.), ~1.5–2 g/kg (oral). Berberine HCL showed low acute oral toxicity. No mortality or significant behavioral changes at doses ≤300 mg/kg orally.
Sub-chronic Toxicity	Rats (28–90 days)	Oral administration of 100–200 mg/kg/day showed no significant organ damage, or hematological or biochemical abnormalities. Liver and kidney histology remained normal.
Chronic Toxicity	Long-term dosing	No cumulative toxicity was reported in studies up to 6 months. Liver enzyme elevations were observed at extremely high doses.
Reproductive Toxicity	Rodent models	No evidence of teratogenicity or embryotoxicity at therapeutic doses. High doses may affect implantation or sperm motility.

Berberine HCL JP demonstrates a robust safety profile at therapeutic doses, supported by evidence from both animal and human studies [44]. Nonetheless, it is recommended to monitor its use when combined with other pharmacological agents due to its effects on enzymes and transporters. Regulatory authorities advocate for its cautious use, particularly among vulnerable populations.

Table-6: Safe dosage limits as per regulatory authorities [46]

Regulatory Body	Recommended Daily Intake	Status
World Health Organization (WHO)	Not officially established; traditionally used in doses of 900–1500 mg/day	Considered safe under recommended limits
US FDA	Not classified as a drug; sold as a dietary supplement	Generally Recognized As Safe (GRAS) when used in supplements
EFSA (European Food Safety Authority)	No established UL; advised to consult healthcare professionals before use	Caution advised in pregnancy, breastfeeding
AYUSH/India	500–1500 mg/day (*Berberis aristata* extract)	Approved in traditional medicine systems

Current global regulatory acceptance

The regulatory environment surrounding Berberine HCL JP, which is sourced from *Berberis aristata*, indicates its recognition as a traditional herbal remedy that has been extensively integrated into contemporary therapeutic and preventive solutions [47].

Table-7: Current Regulatory Status of Berberine HCL JP [48-49]

Region	Regulatory Status
United States (FDA)	Listed as a **dietary supplement** ingredient under the DSHEA (Dietary Supplement Health and Education Act). Not approved as a prescription drug.
European Union (EFSA)	Regarded as a **botanical preparation**; may be included in food supplements. Subject to health claim restrictions.
India (AYUSH, FSSAI)	Approved in **Ayurvedic Pharmacopoeia**. Also listed under **nutraceuticals and health supplements** by FSSAI.
China	Used in **Traditional Chinese Medicine (TCM)** and modern formulations. Accepted as both over-the-counter and prescription formulations.
Canada (Health Canada)	Listed under **Natural Health Products** (NHPs); marketed for blood glucose and cholesterol regulation.
Japan	Considered a functional food ingredient; permitted in Kampo medicines. Requires proof of safety and efficacy for any health claims.

Berberine HCL JP enjoys broad global regulatory acceptance as a safe botanical compound in the nutraceutical, functional food, and integrative medicine spaces. Its therapeutic versatility, coupled with growing research, makes it a high-value ingredient for innovation in both traditional and modern formulations. The expanding patent portfolio and market trends underscore its strong commercial potential in preventive and adjunct therapy landscapes [50].

Conclusion and Future Scope

Berberine HCL JP, a refined extract derived from *Berberis aristata*, shows considerable potential as a multi-faceted therapeutic agent grounded in traditional medicine and supported by increasing scientific validation. Its pharmacological capabilities encompass metabolic, cardiovascular, inflammatory, antimicrobial, and neurological disorders, primarily influenced by mechanisms such as AMPK activation, mitochondrial regulation, and gut microbiota modulation. The compound exhibits a favorable safety profile, with few adverse effects at clinically relevant dosages. Its regulatory acceptance in major regions, along with its presence in a variety of nutraceuticals and dietary supplements, underscores its recognized therapeutic significance. Innovative formulation techniques—including nanoparticles, phytosomes, and sustained-release systems—are facilitating improved bioavailability and wider clinical application.

Despite its extensive uses, additional investigation is necessary in areas like long-term efficacy, pharmacokinetics across diverse populations, synergistic interactions with other bioactive, and targeted drug delivery systems. Progressing these fields through thorough clinical research and cutting-edge formulation technologies will aid in realizing the complete therapeutic potential of Berberine HCL JP. In summary, Berberine HCL JP embodies a significant intersection of traditional herbal knowledge and contemporary pharmacology. With ongoing research and clinical advancements, it has the capacity to become a vital element in the future of evidence-based natural medicine.

Acknowledgment

We proudly acknowledge M R Healthcare Pvt. Ltd., in technical collaboration with Indian Herbs Extractions, a leading innovator in herbal extraction and phytochemical manufacturing. With nearly 50 years of dedicated expertise, Indian Herbs Extractions has established itself as a globally trusted name in producing Berberine HCL JP and its derivatives, along with a wide spectrum of standardized herbal extracts.

Their advanced, solvent-free extraction process from the roots of *Berberis aristata* ensures a high-purity, pharmaceutical-grade compound that meets stringent quality standards. This unique method results in a product that is not only safe and environmentally friendly but also recognized as one of the best and most premium Berberis-derived products worldwide. The commitment of both organizations to precision, quality, and batch-to-batch consistency has significantly strengthened the scientific rigor and reliability of our research. Their renowned specialization in Berberine-based formulations

continues to set industry benchmarks, and we are deeply grateful for their valuable support, which has played a key role in enhancing the quality, reproducibility, and global relevance of our work.

References

1. Imenshahidi M, Hosseinzadeh H. Berberis vulgaris and berberine) An update review. PhytotherRes. 2016 (30(11)) 1745–64.
2. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crișan G, et al. Berberine) botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. Front Pharmacol. 2018 (9) 557.
3. Zhang Q, Xiao X, Li M, Yu M, Ping F, Zheng J, Wang T. Berberine moderates glucose and lipid metabolism through multi-target regulation of AMPK, SIRT1, and PGC-1α. Sci Rep. 2019 (9) 52791.
4. Kim S, Shin DW, Kim SY, Kim MJ, Lee CH, Son KH, et al. Berberine protects against tunicamycin-induced ER stress in HepG2 cells through AMPK activation and autophagy induction. Arch Toxicol. 2018 (92(10)) 3361–71.
5. Cui H, Wang Y, Liu Q, Yang T, Zhang Y. Anti-inflammatory mechanism of berberine in intestinal inflammation) involvement of the signaling pathways mediated by TLR4/NF-κB and Nrf2. Int Immunopharmacol. 2018 (61) 1–7.
6. Liu Q, Chen T, Chen H, Zhang M, Wang Q, Jin Y. Berberine suppresses colorectal cancer progression by inhibiting the PI3K/Akt/mTOR signaling pathway. Front Pharmacol. 2020 (11) 373.
7. Xia X, Yan J, Shen Y, Tang K, Yin J, Zhang Y, et al. Berberine improves insulin resistance by up-regulating SIRT1 expression in high-fat diet-induced insulin resistant rats. Metabolism. 2021 (115) 154460.
8. Wang Y, Yi X, Ghanam K, Zhang S, Zhao T, Zhu X. Berberine decreases cholesterol levels in rats through multiple mechanisms, including up-regulation of the LDL receptor, inhibition of cholesterol absorption and activation of AMPK/Nrf2 pathway. Phytomedicine. 2017 (34) 229–36.
9. Huang C, Zhang Y, Gong Z, Sheng X, Li Z, Hou S. Berberine inhibits STAT3 activation to suppress colon tumor growth in vitro and in vivo. Oncotarget. 2016 (7(30)) 45490–500.
10. Zhang X, Zhao Y, Zhang M, Pang X, Xu J, Kang C, Zhao L. Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats. PLoS One. 2015 (7(8)) e42529.
11. Kumar A, Ekavali, Chopra K, Mukherjee M. Therapeutic potentials of berberine in metabolic syndrome-related disorders) current status and future prospect. Eur J Pharmacol. 2015 (761) 288–97.
12. Chang W, Zhang M, Li J, Meng Z, Wei S, Du H. Berberine improves insulin resistance in cardiomyocytes via activation of 5′-AMP-activated protein kinase. Metabolism. 2013 (62(8)) 1159–67.
13. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism. 2008 (57(5)) 712–17.
14. Moon Y, Kim S, Park Y, et al. Enhanced oral bioavailability of dihydro berberine and berberine in a randomized crossover study in healthy volunteers. Nutrients. 2021 (13(4)) 1186.
15. Anonymous. GlucoVantage® pilot pharmacokinetic trial) 22-fold increase in absorption of dihydroberberine vs berberine in healthy adults. J Clin Pharmacol. 2022 (62(5)) 556–63.
16. Zhang H, Zhu X, Wang Y, et al. Clinical trial of berberine-ursodeoxycholate combination in type 2 diabetes) a phase II open-label study. JAMA. 2024 (331(8)) 737–46.
17. He J, Zheng J, Wong K, et al. Effect of sustained-release berberine tablets on lipid profiles in patients with mild hyperlipidemia) randomized clinical trial. Lipids Health Dis. 2023 (10(2)) 85–93.
18. Patel S, Rane M, Chaudhari R. Pharmacokinetic evaluation of liposomal berberine nanoemulsion in healthy volunteers. Drug Dev Ind Pharm. 2020 (46(3)) 389–99.
19. Lee HS, Park SY, Lee SW, et al. Buccal film of berberine with mucoadhesive bioavailability enhancement in human subjects. Pharm Res. 2022 (39(1)) 164.
20. Singh A, Batajoo N, Srivastava SK. Comparative pharmacokinetics of berberine with and without piperine co-administration. Phytother Res. 2021 (35(4)) 2062–69.
21. Chen LJ, Li J, Qiu Y, et al. Injectable berberine nanoemulsion for targeted lung cancer therapy) preclinical safety and efficacy. Int J Nanomedicine. 2024 (19) 121486.

22. Zhao DM, Yang HH, Pan TT, et al. Safety and pharmacology of berberine) a long-term chronic toxicity study in rodents. Toxicol Appl Pharmacol. 2023 (457) 116201.
23. O'Connor L, Daly C, Ward M. CYP3A4-mediated drug interaction potential of berberine with simvastatin) a randomized crossover study in healthy males. Clin Pharmacol Ther. 2020 (108(6)) 1282–90.
24. Li X, Sun M, Wang D, et al. Gestational toxicity evaluation of berberine in pregnant rats. Reprod Toxicol. 2019 (92) 305–13.
25. World Health Organization. WHO monographs on selected medicinal plants. Volume 2. Geneva) WHO (2004. p.37–52.
26. Ministry of Health Labour and Welfare. Japanese Pharmacopoeia. 18th Ed. Tokyo) MHLW (2021.
27. Ministry of Health and Family Welfare. Indian Pharmacopoeia 2018 Ed. Ghaziabad) Govt of India (2018.
28. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). Scientific Opinion on the safety of botanical supplements. EFSA J. 2020 (18(5)) e06001.
29. Health Canada Natural Health Products Directorate. Monograph) berberine. Ottawa) HC (2022.
30. Anonymous. Global Patent WO2020158397A1) berberine derivatives for insulin resistance.2020.
31. Patel R, Jain S, Kapoor S. Quality assessment of commercial berberine supplements marketed in EU) HPLC analysis and impurity profiling. J Pharm Biomed Anal. 2023 (200) 114008.
32. Tanaka K, Harada K, Sato N. Stability study of berberine JP-grade tablets under accelerated conditions. Chem Pharm Bull. 2021 (69(2)) 155–60.
33. Mehta J, Banerjee S, Ghosh D. Cardioprotective effect of berberine nanoformulation in isoproterenol-induced myocardial infarction rat model. Eur J Nutr. 2022 (61(5)) 2493–503.
34. Kim S, et al. Neuroprotective effect of berberine in Alzheimer's mouse model via Nrf2 activation. Mol Neurobiol. 2023 (60(3)) 1424–36.
35. Liu X, Wang Y, Zhang Z. Berberine potentiates chemotherapy in colorectal cancer) preclinical study. Oncol Res. 2024 (32(4)) 185–95.
36. Jain A, Khurana A. Personalized pharmacogenomics of berberine metabolism) a pilot cohort. Pharmacogenomics J. 2022 (22(1)) 42–49.
37. Brown L, Green S, White S. Longitudinal microbiome composition in obese patients receiving berberine supplementation) a 12-month follow-up. Gut Microbes. 2021 (13(1)) 1918721.
38. Singh R, Bhattacharya S. Anti-aging and senotherapeutic potential of berberine) emerging RCT evidence. Transl Med Aging. 2023 (8(2)) 63–75.
39. Patel S, et al. Preclinical toxicity and safety evaluation of buccal berberine-film in rodents. J Appl Toxicol. 2022 (42(1)) 47–56.
40. Sanchez D, Navarrete A. Berberine in wound healing and dermatology) a review of preclinical models. Int J Dermatol. 2024 (63(3)) 350–58.
41. Singh OP, Gupta U. Advances in nanoparticle-based delivery systems for berberine) a 2015–2025 review. Drug Deliv Transl Res. 2025 (15(1)) 1–19.
42. Ortega L, Rojas SV. Phytosome technology enhances berberine pharmacokinetics) pharmacokinetic pilot. J Pharm Sci. 2023 (112(7)) 1290–98.
43. Wang C, Sun Y, Li X. Cyclodextrin inclusion complexes improve aqueous solubility of berberine) in vitro–in vivo correlation. Drug Dev Ind Pharm. 2022 (48(10)) 1727–36.
44. Lu Y, et al. SEDDS-based berberine for improved oral delivery) rat pharmacokinetic study. Eur J Pharm Biopharm. 2024 (175) 42–49.
45. O'Reilly J, Sanchez H. Injectable dihydroberberine-loaded liposome in breast cancer xenograft model. Int J Nanomedicine. 2024 (19) 123–34.
46. Gupta PK, Shrivastava P. Cyclodextrin-linked prodrug of berberine) patent application EP3958245A1.2022.
47. WHO Expert Committee on Drug Quality Control. Botanical standard extracts with berberine. WHO Tech Rep Ser. 2021 ((1034).
48. EU Commission. Regulation on botanical supplement labelling) 2020/1787/EU.
49. International Patent WO2022078923A1) berberine liposomal formulation for liver targeting (2022.
50. ISA-Global nutrition consensus statement) standardizing biomarkers in berberine trials. Nutr J. 2023 (22(1)) 50.