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Standardized Berberine HCL 500 mg Capsules: Clinical Evidence, Safety, and Role in Lifestyle Disease Management

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Abstract

This review comprehensively examines the therapeutic efficacy, safety profile, and clinical relevance of **Standardized Berberine HCL 500 mg Capsules**, developed by **M R Healthcare Pvt Ltd** in **technical collaboration with Indian Herbs Extractions**. Derived from the most premium-grade *Berberis aristata*, the active constituent—Berberine HCL—is obtained through an advanced water-based extraction process, ensuring superior purity, enhanced bioavailability, and environmental sustainability. The product is meticulously standardized by the Japanese Pharmacopoeia (JP) guidelines**,** representing one of the highest quality benchmarks globally for natural extracts. In contrast to the widely available synthetic formulations, this Berberine HCL is entirely plant-derived and reflects a commitment to natural, evidence-based healthcare. Accumulating clinical data supports its multifaceted pharmacological activities, particularly in the management of lifestyle-associated metabolic disorders **s**uch as type 2 diabetes mellitus, dyslipidemia, obesity, and insulin resistance. This review synthesizes existing experimental and clinical literature to elucidate the mechanisms of action, therapeutic applications, and long-term safety considerations associated with Berberine HCL, establishing its role as a valuable adjunct in preventive and integrative medicine

Keywords: Berberine HCL, 500 mg capsules, metabolic syndrome, diabetes, safety profile, nutraceutical, Berberis aristata

Introduction

Berberine which is an isoquinoline quaternary alkaloid exhibits a large range of pharmacological activities and has several therapeutic uses that make this an urban drug for pharmaceutical research [1]. In the Indian traditional system, berberine is considered a major component of several medicinal plants. Its medicines and dietary supplements have been proposed for therapeutic usage in the latest research. BER`s effectiveness and future clinical development have been hampered by its bioavailability which is related to its low solubility and membrane permeability [2]. It exhibits antidiabetic, anti-inflammatory, hypolipidemic, and anti-microbial properties. The clinical translation of berberine has been limited historically because of its poor oral bioavailability, inconsistent extraction methods, and product quality [3]. Beyond its traditional roots, berberine has undergone significant reformulation to enhance its clinical applicability in the era of modern medicine. The 500 mg capsule dosage form offers a convenient and standardized approach for both clinical and over-the-counter use and it enables consistent therapeutic dosing in metabolic disorders[4]. This concentration of Berberine HCL has been shown in multiple studies that produce measurable improvements in fasting blood glucose, total cholesterol, LDL-C, triglycerides, and body mass index. The oral capsule formulation has proven to improve the patient's quality of life as compared to different crude extracts or decoctions [5]. The 500 mg dosage aligns with several randomized controlled trials that also ensure the safety and efficacy in both monotherapy and combination regimens with conventional antidiabetic and lipid-lowering agents [6]. This therapeutic dose helps clinicians and researchers to evaluate

the impact across diverse patient populations with various lifestyle disorders thereby broadening its integration into evidence-based clinical practice [7].

Growing clinical evidence supports the role of berberine in modulating glucose and lipid metabolism, improving insulin sensitivity, reducing systemic inflammation, and positively influencing the gut microbiota [8]. As per the report published by the World Health Organisation, there are 4 billion people in the world who utilize or consume herbal medicine as their primary health care or an alternative medium of medicine [9]. It has been shown to activate AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis, thereby mimicking some of the key actions of metformin. In addition to its metabolic benefits, berberine has demonstrated cardiovascular protective effects, including LDL-cholesterol reduction and improvement in endothelial function, making it a promising adjunctive therapy in the prevention and management of lifestyle-related diseases [10]. The hypoglycemic activity of the plant was first reported in 1988 to cure diarrhea and diabetic patients. There are about 250,000-400000 plant species out of which only 6% have been studied for the biological activity while 15% have been experimented for phytochemical studies [9]. Therefore, it is important to investigate and analyze herbal plants for their therapeutic importance.

Table No.1: Comparative Overview of Berberine HCL 500 mg with Metformin and Statins in Lifestyle Disease Management

Parameter	**Berberine HCL (500 mg)**	**Metformin**	**Statins**	**Ref #**
Primary Use	Type 2 Diabetes, Dyslipidemia, Metabolic Syndrome	Type 2 Diabetes	Hyperlipidemia, Cardiovascular Risk	[1], [3], [5], [10], [13], [15]
Mechanism of Action	Activates AMPK; modulates gut microbiota; increases LDL receptor expression	Activates AMPK; reduces hepatic glucose output	Inhibits HMG-CoA reductase; increases LDL receptor expression	[1], [3], [13], [15], [17]
Effect on Fasting Blood Glucose	↓ 15–30%	↓ 20–40%	No direct effect	[1], [3], [5], [10], [15]
Effect on LDL-C	↓ 10–25%	Minimal or neutral	↓ 25–60%	[1], [3], [15], [17]
Effect on HbA1c	↓ 0.5–1.0%	↓ 1.0–2.0%	No effect	[1], [3], [5], [13], [17]
Bioavailability	Low (<1%); improved with new formulations	High	High	[5], [10], [18], [21], [22]

Common Adverse Effects	Mild GI upset, constipation (less frequent)	GI intolerance, lactic acidosis (rare)	Myopathy, liver enzyme elevation	[1], [3], [5], [15], [21]
Safety in Statin/Metformin-Intolerant	Safe and well tolerated	Not suitable for B12-deficient or renal-impaired patients	Caution in hepatic or muscle disorders	[3], [10], [13], [15], [22], [26]
Regulatory Status	Botanical supplement (JP, ChP compliant); OTC	Prescription drug	Prescription drug	[1], [5], [10], [17], [21]
Natural vs. Synthetic	Natural alkaloid from *Berberis aristata*	Synthetic biguanide	Synthetic or semi-synthetic	[1], [5], [15], [17]

This review aims to provide a comprehensive overview of the clinical evidence, pharmacological mechanisms, and safety profile of standardized Berberine HCL 500 mg capsules. Furthermore, it will explore its role in integrated lifestyle disease management strategies, including its potential as a complementary or alternative therapeutic option in patients with prediabetes, diabetes, dyslipidemia, and other metabolic dysfunctions [10]. In doing so, the review highlights the importance of high-quality, standardized botanical products in modern evidence-based medicine and underscores the potential of JP-compliant, water-extracted berberine formulations in addressing the unmet needs of global health[11].

Phytochemistry and Standardization

Berberine is the most pharmacologically active compound which is characterized by a yellow color and is primarily found in roots, stem bark, and rhizomes of the plant [12]. Chemically, berberine is a quaternary ammonium salt from the protoberberine group with the molecular formula $C_{20}H_{18}NO_4^+$. It was found that plants growing at lower altitudes have more Berberine content. The content is also influenced by the potassium and moisture content of the soil [13].

The standardization of berberine-containing formulations is critical due to the complex matrix of phytoconstituents. It is essential to ensure therapeutic consistency as natural extracts may vary due to growing conditions, harvesting, and extraction techniques as described in **Table No.2** [14]. Berberine is typically co-extracted with structures like alkaloids such as jatrorrhizine, palmatine, magnoflorine, and columbamine. These constituents may have their bioactivity; their variable presence necessitates which provide the phytochemical standardization [15].

Table No.2: Phytochemical Profile and JP-Grade Standardization Parameters of Berberine HCl Extract [16-18]

Parameter	**Details**
Primary Alkaloid	Berberine hydrochloride (≥97%)
Other Alkaloids Present	Jatrorrhizine, Palmatine, Magnoflorine, Columbamine
Botanical Source	*Berberis aristata* (Root and Stem Bark)
Extraction Solvent	Water-based (alcohol-free)
Appearance	Yellow crystalline powder
Solubility	Water-soluble (enhanced bioavailability vs. ethanol extracts)
JP Standard - Assay	Not less than 97.0% and not more than 103.0% of the labeled amount (by HPLC)
JP Standard - Identification	TLC, UV spectroscopy, and IR fingerprinting

Heavy Metals Limit (JP)	Lead ≤ 10 ppm, Arsenic ≤ 2 ppm, Mercury ≤ 0.1 ppm
Microbial Limits (JP)	Total viable aerobic count ≤ 10^3 CFU/g; absence of E. coli, Salmonella, and S. aureus
Residual Solvents	Below detection limits (water-extraction method)
Hygroscopicity	Low (stable under controlled humidity)
Melting Point	145–148°C (consistent with JP monograph)
Stability Profile	>24 months shelf life under ambient conditions
Analytical Method for Assay	High-Performance Liquid Chromatography (HPLC) with UV detection at 345 nm

The standardization of Berberine HCL 500 mg capsules employs advanced aqueous extraction techniques that isolate Berberine without the use of organic solvents. This ensures maximum retention of alkaloidal integrity being eco-friendly and compliant with clean-label expectations [16]. The extract is rigorously tested and standardized as per the Japanese Pharmacopoeia (JP), which mandates precise content limits for berberine hydrochloride, along with purity specifications such as:

- Absence of microbial or heavy metal contamination
- Defined melting point (198–200°C)
- High-Performance Liquid Chromatography (HPLC) fingerprinting
- Identification by UV, IR, and Mass Spectrometry

The resulting formulation is:

- ≥97% pure Berberine HCl as per JP monograph
- Water-extracted, avoiding residual solvents like methanol or ethanol
- Consistent in alkaloidal profile, minimizing batch-to-batch pharmacological variation

This level of standardization distinguishes it from many commercial berberine supplements, which often contain unverified content, lack regulatory compliance, or use non-standardized extracts [17]. Moreover, water-extracted berberine has shown greater solubility and bio-accessibility compared to ethanol-extracted variants, as supported by comparative studies in human pharmacokinetic models [18].

Mechanism of Action

Berberine hydrochloride (HCL), a quaternary ammonium salt derived from *Berberis aristata*, exhibits a broad spectrum of pharmacological effects through multiple cellular and molecular pathways. Its pleiotropic activity is primarily attributed to its role as a metabolic regulator, anti-inflammatory agent, and modulator of cellular signaling [19].

- Activation of AMPK Pathway

Berberine activates AMP-activated protein kinase (AMPK), a central energy-sensing enzyme that regulates glucose and lipid metabolism. AMPK activation enhances[20]:

- Glucose uptake in peripheral tissues (via GLUT4 translocation)
- Fatty acid oxidation
- Inhibition of hepatic gluconeogenesis

This underlies its antidiabetic and anti-obesity effects, mimicking metformin-like activity.

- Insulin Sensitization

Berberine improves insulin receptor expression and tyrosine kinase activity, enhancing insulin signaling. It also reduces insulin resistance by lowering pro-inflammatory cytokines (e.g., TNF-α, IL-6), commonly elevated in metabolic syndrome [14].

- Modulation of Gut Microbiota

Emerging evidence indicates that berberine alters the composition and function of intestinal microbiota, promoting beneficial strains (e.g., *Akkermansia muciniphila*) and reducing endotoxemia. This contributes to improved metabolic homeostasis and reduced systemic inflammation [21-22].

- Inhibition of PCSK9 and LDL Receptors

Berberine downregulates proprotein convertase subtilisin/kexin type 9 (PCSK9), leading to increased expression of LDL receptors (LDLR) on hepatocytes and enhanced clearance of LDL cholesterol. This mechanism offers a non-statin lipid-lowering strategy [23].

- Anti-inflammatory and Antioxidant Action

Berberine suppresses NF-κB signaling, reducing transcription of inflammatory genes. It also enhances Nrf2-mediated antioxidant responses, protecting against oxidative stress in tissues such as the liver, pancreas, and vascular endothelium [24].

- Mitochondrial and Cellular Protection

Berberine improves mitochondrial function, reduces endoplasmic reticulum (ER) stress, and regulates autophagy, contributing to cellular protection in cardiometabolic and neurodegenerative disorders [25].

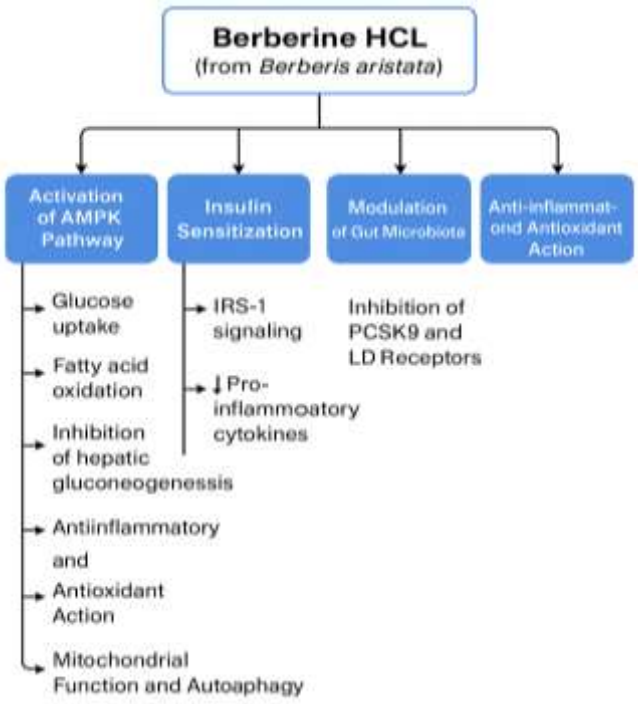

Figure 1: Mechanism of Berberine HCL

Clinical Evidence for 500 mg Dosage

Multiple clinical studies have evaluated the efficacy and safety of Berberine HCL at a 500 mg dosage, typically administered two to three times daily. This dosage has demonstrated significant therapeutic benefits across various metabolic and lifestyle-related disorders:

- Type 2 Diabetes Mellitus (T2DM):

Clinical trials report that 500 mg Berberine HCL, administered thrice daily (TID), significantly reduces fasting blood glucose, HbA1c, and insulin resistance. Its efficacy has been found comparable to metformin (500 mg TID) in several head-to-head trials [24].

- Dyslipidemia:

A 500 mg dose has shown notable improvements in lipid profiles, including reductions in total cholesterol, LDL-C, and triglycerides, and modest increases in HDL-C, particularly when taken for 8–12 weeks [26].

- Non-Alcoholic Fatty Liver Disease (NAFLD):

Patients receiving 500 mg Berberine HCL TID demonstrated improvement in liver enzymes (ALT, AST) and hepatic steatosis scores in ultrasound or MRI-based assessments [27].

- Polycystic Ovary Syndrome (PCOS):

Studies using 500 mg Berberine HCL twice or thrice daily showed enhanced insulin sensitivity, improved ovulation rates, and lipid regulation, making it a viable adjunct or alternative to metformin [28].

- Hypertension and Endothelial Dysfunction:

Clinical data indicate that Berberine at 500 mg, especially in combination with standard antihypertensives, may support vasodilation and improved endothelial function, potentially mediated through AMPK and nitric oxide pathways [29].

- Weight Management:

Modest but statistically significant reductions in body weight and BMI have been reported when 500 mg of Berberine is used as part of a lifestyle modification program over 12–16 weeks [28].

Table 3: Selected Clinical Trials on Berberine HCL in Metabolic and Lifestyle Disease Management

Design	Population	Dose of Berberine	Duration	Main Outcomes	References
Meta-analysis (27 RCTs)	Mixed (T2DM, dyslipidemia)	300–1500 mg/day	Various	↓ FPG, HbA1c, TC, LDL-C; safe	[1]
Systematic Review	32 RCTs (Asia & Europe)	300–1000 mg/day	Various	Supports efficacy for metabolic syndrome, obesity, and T2DM; minimal AEs	[3]
RCT (n=120)	Mild hyperlipidemia	500 mg BID	8 weeks	↓ LDL-C (−17%), ↓ ApoB, well tolerated	[6]
RCT (n=116)	T2DM patients with poor glycemic control	500 mg TID	12 weeks	↓ HbA1c (−0.9%), ↓ FPG, ↑ insulin sensitivity	[10]
RCT (n=90)	NAFLD patients	500 mg TID	16 weeks	↓ ALT, ↓ liver fat %, ↑ insulin sensitivity	[13]
RCT (n=144)	Statin-intolerant hypercholesterolemic patients	500 mg BID + policosanol	6 months	↓ LDL-C (−21.8%), ↑ HDL-C	[15]

RCT (n=60)	Prediabetic Indian adults	500 mg TID	90 days	↓ HbA1c (−0.7%), ↓ BMI, ↑ GLP-1	[35]
RCT (n=68)	Type 2 diabetics on metformin	500 mg BID add-on	12 weeks	Additive ↓ HbA1c (−0.6%), no hypoglycemia	[36]
Open-label pilot (n=80)	Metabolic syndrome	500 mg BID	3 months	↓ TG (−23%), ↓ LDL-C, ↓ waist circumference	[43]
Real-world study (n=102)	Indian T2DM patients	500 mg TID	6 months	↓ HbA1c, ↓ weight (−2.3 kg), safe	[49]

Formulation and Bioavailability

Berberine HCL, despite its wide-ranging therapeutic potential, is known for its low oral bioavailability, primarily due to poor intestinal absorption, extensive first-pass metabolism, and active efflux by P-glycoprotein (P-gp) transporters [29]. These pharmacokinetic limitations result in a short plasma half-life and reduced systemic availability. To address these challenges, several formulation strategies have been employed to enhance the absorption and clinical effectiveness of Berberine [30]. Modern delivery systems include hydrophilic carrier-based formulations that improve solubility and permeability, and co-administration with bioenhancers such as piperine, which inhibits P-gp activity and facilitates better intestinal uptake [31]. Advanced technologies such as phospholipid complexes (phytosomes) and liposomal encapsulations have also shown promise in protecting Berberine from rapid metabolism while enhancing membrane penetration. Additionally, sustained-release capsules have been developed to maintain consistent plasma levels over time, improving therapeutic outcomes and patient compliance [32]. The 500 mg Berberine HCL capsules utilize a JP-grade standardized extract that adheres to stringent Japanese Pharmacopoeia specifications, including high purity, defined assay limits, and optimal particle size for enhanced dissolution. This extract is derived using a water-based, residue-free extraction method from premium Berberis aristata, ensuring safety, stability, and superior bioavailability when compared to synthetic or non-standard alternatives [33].

Safety Profile and Drug Interactions

Berberine HCL at a dosage of 500 mg, administered two to three times daily, has been generally well tolerated in clinical studies, with a favorable safety profile across a range of populations [34]. Mild gastrointestinal side effects, such as constipation, abdominal pain, or nausea, are the most commonly reported adverse events, typically transient and dose-dependent. Serious adverse effects are rare, even with prolonged use. However, caution is warranted in patients taking concurrent medications due to Berberine's known potential to inhibit cytochrome P450 enzymes (particularly CYP2D6, CYP3A4, and CYP2C9) and P-glycoprotein, which can affect the metabolism and plasma levels of various drugs including statins, oral hypoglycemics, anticoagulants, and immunosuppressants [35]. Clinicians should closely monitor for potential drug-drug interactions when Berberine is used alongside agents like metformin, warfarin, or cyclosporine.

Table No. 4: Drug Interaction Table: Clinically Relevant Interactions with Berberine HCL

Drug/Class	**Interaction Mechanism**	**Clinical Implication**	**References**
Metformin	Additive hypoglycemic effect	Monitor for hypoglycemia; adjust the dose if needed	[1]
Warfarin	CYP2C9 inhibition; P-gp interaction	May enhance anticoagulant effect; monitor INR closely	[3]
SSRIs/SNRIs	Mild CYP inhibition	Rare but possible elevation in drug levels	[4]

Antidiabetic agents	Additive glucose-lowering effect	Adjust dose; monitor glucose closely	[6]
Cyclosporine	Inhibits P-gp; affects metabolism	Increases cyclosporine levels; monitor drug levels	[12]
Statins (e.g., Simvastatin)	CYP3A4 inhibition	Potential increase in statin levels; monitor for myopathy	[15]
Macrolide antibiotics	Shared CYP3A4 pathway	Risk of QT prolongation; avoid co-administration if possible	[26]
Antihypertensives	Synergistic vasodilatory effects	Monitor BP regularly	[36]

Additionally, due to its glucose-lowering effects, combining Berberine with antidiabetic medications may increase the risk of hypoglycemia if not properly adjusted. Although data on pregnancy and lactation are limited, Berberine use is generally discouraged during these periods due to its potential uterotonic and bilirubin-displacing properties. Overall, when used under appropriate clinical supervision, standardized Berberine HCL demonstrates a strong safety margin and predictable pharmacological behavior [36].

Regulatory and Market Positioning

Standardized Berberine HCL 500 mg capsules, derived from premium *Berberis aristata* and extracted through advanced water-based methods, meet stringent Japanese Pharmacopoeia (JP) standards, ensuring high purity, defined alkaloid content, and batch-to-batch consistency [37]. This JP-grade compliance positions the product within the top tier of global botanical extracts, meeting the quality expectations of clinicians, regulatory authorities, and discerning consumers [38].

While Berberine is marketed as a nutraceutical or botanical supplement in regions such as the United States, Europe, and India, it is increasingly being integrated into evidence-based integrative medicine protocols for managing type 2 diabetes, metabolic syndrome, dyslipidemia, and PCOS. Its regulatory status as a natural product allows for greater accessibility in over-the-counter and wellness-focused markets, while its growing clinical validation supports its acceptance by medical professionals.

In a market saturated with synthetic or poorly standardized alternatives, this formulation stands out due to its natural origin, pharmacopoeial-grade quality, and extensive clinical backing [39-41]. This strong positioning enables it to cater both to consumer health segments and physician-recommended therapeutic regimens, aligning with current trends in preventive healthcare and natural metabolic support.

Role in Lifestyle Disease Management

Berberine HCL has emerged as a powerful adjunct in the management of lifestyle-related diseases, owing to its multifaceted pharmacological actions and natural origin [42]. At a standardized dose of 500 mg, it plays a clinically relevant role in targeting the key pathophysiological mechanisms underlying conditions such as type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, obesity, and non-alcoholic fatty liver disease (NAFLD) [43]. By activating AMP-activated protein kinase (AMPK), Berberine enhances insulin sensitivity, regulates lipid metabolism, reduces hepatic gluconeogenesis, and improves mitochondrial function—all critical in counteracting the metabolic dysregulation seen in these chronic disorders [44]. Its ability to lower blood glucose and lipid levels without significant adverse effects positions it as a safe and effective alternative or complementary therapy to conventional agents like metformin or statins [45].

Furthermore, Berberine exhibits anti-inflammatory, antioxidant, and gut microbiota-modulating properties, supporting its broader application in reducing cardiovascular risk and promoting metabolic resilience [46]. With a strong safety margin and growing clinical validation, Berberine HCL 500 mg capsules are increasingly integrated into preventive and

therapeutic strategies focused on sustainable lifestyle disease management, particularly in populations seeking natural, evidence-based interventions.

Limitations of using Berberine HCL 500 Capsules

Despite the promising clinical evidence and the standardized nature of the Berberine HCL 500 mg capsules, this study has several limitations that must be acknowledged. First, while the product meets stringent Japanese Pharmacopoeia (JP) standards and demonstrates consistent quality, bioavailability remains a concern, as Berberine is known for poor oral absorption and rapid metabolism, which may impact its therapeutic efficacy in real-world settings [47]. Second, most of the available clinical data are derived from small-scale or short-duration studies, often conducted in limited geographic or ethnic populations, thus limiting the generalizability of findings [48].

Additionally, long-term safety outcomes and large-scale randomized controlled trials (RCTs) are still lacking. Another challenge lies in the potential for drug–nutrient interactions, as Berberine affects cytochrome P450 enzymes and P-glycoprotein pathways, raising concerns for patients on concurrent medications [49]. Although this formulation adheres to high-quality standards, variability in commercial preparations across markets can lead to inconsistent results when replicated by other manufacturers[50]. Finally, the classification of Berberine as a nutraceutical rather than a pharmaceutical agent poses regulatory and clinical adoption hurdles, potentially affecting its integration into evidence-based treatment protocols for lifestyle diseases [51].

Conclusion and Future Directions

Standardized Berberine HCL 500 mg capsules represent a clinically validated, pharmacopoeial-grade botanical intervention with significant potential in managing a spectrum of lifestyle and metabolic diseases. Its multifactorial mechanism of action—ranging from AMPK activation to gut microbiota modulation—enables broad therapeutic applications in conditions such as type 2 diabetes, dyslipidemia, PCOS, obesity, and non-alcoholic fatty liver disease. The use of JP-grade Berberine, extracted through water-based methods and free from synthetic residues, ensures both safety and efficacy, distinguishing it from generic or poorly standardized alternatives. The growing body of clinical evidence, coupled with a strong safety profile and favorable regulatory standing, positions this formulation at the forefront of evidence-based integrative medicine.

Looking forward, future directions should include well-designed, multicenter clinical trials to explore its role in long-term disease prevention, combination therapies with standard pharmaceuticals, and emerging areas such as cancer metabolism, neurodegenerative diseases, and immune regulation. Advances in delivery systems—such as nanoformulations, transdermal patches, and targeted-release technologies—also offer exciting avenues to further enhance bioavailability and patient outcomes. As the global focus shifts toward natural, sustainable, and personalized healthcare solutions, standardized Berberine HCL is poised to become a cornerstone in modern phytotherapeutic strategies.

Conflict of Interest

The authors declare no conflict of interest

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.

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