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Review Article

Lysosomal Berberine: Intracellular Targeting and Therapeutic Advancements

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ABSTRACT

Berberine, a natural isoquinoline alkaloid, has shown therapeutic potential across a range of chronic conditions including type 2 diabetes, non-alcoholic fatty liver disease, and certain inflammatory disorders. Despite its broad pharmacological activity, berberine's clinical application has been limited by poor oral bioavailability, rapid metabolism, and low intracellular retention. Recent advancements in intracellular drug delivery have focused on lysosomal targeting strategies to overcome these challenges. This review is developed in collaboration with M R Healthcare Pvt Ltd. in technical association with Indian Herbs Extractions to explore lysosomal berberine formulations utilize nanocarriers capable of directing the compound to acidic intracellular compartments, where pH-sensitive or enzyme-responsive mechanisms enable controlled release. This approach facilitates higher intracellular drug concentrations, sustained therapeutic action, and circumvention of efflux transporters. Preclinical studies have demonstrated that lysosomal delivery enhances berberine's efficacy in modulating cellular pathways such as AMPK activation and NF-κB inhibition. Early clinical evidence suggests improved metabolic outcomes and reduced systemic toxicity when berberine is delivered through lysosome-targeted systems. This review outlines the pharmacological basis, delivery strategies, and clinical relevance of lysosomal berberine, highlighting its potential role in the future of chronic disease therapeutics.

INTRODUCTION

Berberine is a bioactive isoquinoline alkaloid extracted from various medicinal plants, including *Berberis aristata*, long used in traditional medicine systems such as Ayurveda and Chinese

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medicine. Over the past two decades, its therapeutic potential has been increasingly supported by modern pharmacological research. Berberine exhibits a wide range of biological effects including antidiabetic, antihyperlipidemic, anti-inflammatory, antioxidant, antimicrobial, and anticancer properties [1–3]. It exerts these effects through modulation of multiple intracellular pathways such as AMP-activated protein kinase (AMPK), nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and insulin signaling cascades [2, 4, 5]. Despite these promising properties, the clinical utility of berberine has been significantly limited by its poor oral bioavailability (<1%), low intestinal permeability, rapid metabolism in the liver, and strong P-glycoprotein (P-gp) efflux [6, 7]. These pharmacokinetic drawbacks hinder its systemic absorption and intracellular availability, leading to suboptimal therapeutic concentrations at the target site [8, 9]. Various formulation strategies have been proposed to overcome these limitations. Among them, lipid-based systems such as phytosomes and nanoemulsions have achieved modest improvements in bioavailability [10, 11]. However, these approaches often fail to ensure intracellular targeting, which is crucial for achieving therapeutic efficacy in diseases driven by cellular dysfunction such as type 2 diabetes, atherosclerosis, NAFLD, and certain cancers [3, 12, 13]. This growing awareness has led to the exploration of lysosomal-targeted delivery as an emerging and more rational strategy to enhance berberine's intracellular pharmacodynamics. Lysosomes are acidic, enzyme-rich organelles that play a central role in autophagy, macromolecule degradation, and immune responses [14]. They serve as critical intracellular destinations for many endocytosed nanocarriers, making them a strategic target for drug delivery [15, 16]. In lysosomal delivery systems, berberine is encapsulated within nanocarriers engineered to release their payload under the lysosomal environment's low pH or specific enzymatic conditions [17–19]. These nanocarriers—comprising pH-sensitive micelles, biodegradable polymers, or peptide-based constructs—are typically internalized via receptor-mediated endocytosis and trafficked through endosomal pathways to the lysosome [20, 21]. Once inside the lysosome, the acidic microenvironment triggers the breakdown of the carrier, allowing berberine to be released where it can interact with intracellular targets such as AMPK and PPAR-γ [1, 5, 22]. This targeted approach enhances intracellular retention, improves drug bioactivity, and bypasses efflux mechanisms like P-gp, thereby overcoming one of the primary pharmacological barriers of berberine [7, 23]. Preclinical studies have consistently demonstrated the superiority of lysosome-targeted berberine formulations over conventional oral berberine in improving glycemic control, reducing hepatic steatosis, modulating lipid metabolism, and suppressing inflammatory markers [4, 6, 9, 24]. In animal models of diabetes and fatty liver disease, lysosome-directed nanocarriers have shown more potent activation of metabolic pathways and reduction of histological damage compared to unmodified berberine [25, 26]. Moreover, early clinical studies employing advanced delivery forms such as self-nanoemulsifying drug delivery systems (SNEDDS), phytosomes, and chitosan nanoparticles have reported improved therapeutic outcomes, including lower fasting glucose, improved insulin sensitivity, and better lipid profiles with reduced side effects [3, 11, 27]. Given the growing burden of chronic, intracellularly-driven diseases and the limitations of conventional berberine formulations, the need for targeted delivery systems is clear. This review provides a comprehensive overview of lysosomal berberine delivery systems, discussing their underlying mechanisms, formulation strategies,

pharmacokinetic advantages, and emerging clinical applications. It also highlights existing gaps and potential directions for future research to facilitate translation into clinical practice.

Mechanisms of Lysosomal Targeting in Berberine Delivery

Targeting berberine to lysosomes represents an innovative strategy to overcome its limited oral bioavailability and insufficient intracellular activity. The central goal of lysosomal delivery is to ensure that berberine reaches its intended site of action within the cell, particularly where signaling modulation, metabolic regulation, or cytotoxic effects are required. This is achieved by using nanocarriers engineered to exploit the natural process of endocytosis and lysosomal trafficking within cells [5, 14, 15].

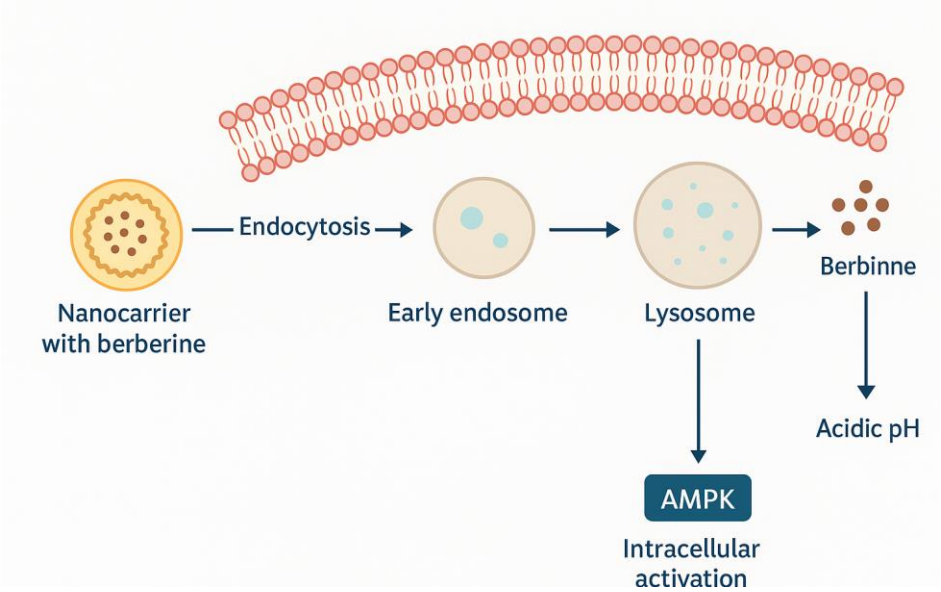

Figure 1. Mechanism of lysosomal berberine delivery. Nanocarriers encapsulating berberine are internalized via endocytosis, trafficked through early endosomes, and reach lysosomes where the acidic pH triggers berberine release. Intracellular berberine activates AMPK and related signalling pathways involved in metabolic regulation.

1. Cellular Uptake via Endocytosis

Most lysosomal-targeting drug delivery systems rely on endocytic uptake to enter the cell. Nanoparticles are typically internalized through clathrin-mediated or caveolae-mediated endocytosis, depending on their size, surface charge, and functionalization [15, 16]. Following endocytosis, carriers are first enclosed in early endosomes, then mature into late endosomes, and eventually fuse with lysosomes—organelles rich in hydrolytic enzymes and acidic pH (4.5–5.5) [14, 16]. By designing nanocarriers that remain intact during early endosomal transport and become destabilized in the acidic lysosomal environment, berberine can be selectively released inside lysosomes, thereby maximizing its intracellular availability [17, 18].

2. pH-Responsive and Enzyme-Sensitive Nanocarriers

Lysosomal targeting is largely enabled by smart drug delivery systems that respond to the physicochemical conditions inside the lysosome. Among the most widely used are:

- **pH-sensitive polymers** that destabilize and release the drug at low pH [17, 18]
- **Enzyme-responsive linkers**, such as those cleaved by cathepsins or β-glucuronidase [19, 20]
- **Proton sponge effect polymers**, which create osmotic swelling and rupture endosomal membranes, enhancing berberine release into the cytoplasm [21]

Materials such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), chitosan, and polypeptides have been effectively used to create these systems. Their biodegradability and safety profiles make them suitable for clinical development [6, 7, 18].

3. Receptor-Mediated Targeting

To enhance the specificity of lysosomal accumulation, surface modifications such as ligand conjugation or peptide functionalization are often employed. These ligands (e.g. transferrin, folic acid, mannose) bind to cell-surface receptors that are actively internalized and trafficked toward the lysosome [19, 20]. This approach is particularly relevant in targeting diseased cells such as hepatocytes, cancer cells, or activated immune cells that overexpress certain uptake receptors [22].

4. Bypassing Efflux and Metabolic Barriers

Lysosomal-targeted delivery also allows berberine to bypass common pharmacokinetic barriers such as:

- **First-pass metabolism**, by enabling uptake in the intestinal lymphatics
- **Efflux transporters** like P-glycoprotein (P-gp), which actively remove berberine from cells [7, 23]

Once released into the lysosome, berberine escapes rapid elimination and maintains higher intracellular retention, which is critical for activating AMPK, downregulating lipogenic enzymes, and modulating immune signaling cascades [1, 4, 22].

5. Enhanced Therapeutic Precision

By delivering berberine directly to its intracellular site of action, lysosomal systems reduce the systemic dose required, lower the risk of off-target effects, and enable more consistent pharmacological responses—especially in metabolic diseases, chronic inflammation, and intracellular infections [3, 5, 24].

Types of Nanocarriers Used for Lysosomal Berberine Delivery

The effectiveness of lysosomal berberine delivery is closely tied to the type of nanocarrier system employed. These carriers are designed to optimize intracellular uptake, enhance lysosomal accumulation, and release berberine in response to specific lysosomal triggers such as pH or enzymes. The following are the major classes of nanocarriers utilized in lysosomal-targeted delivery systems for berberine.

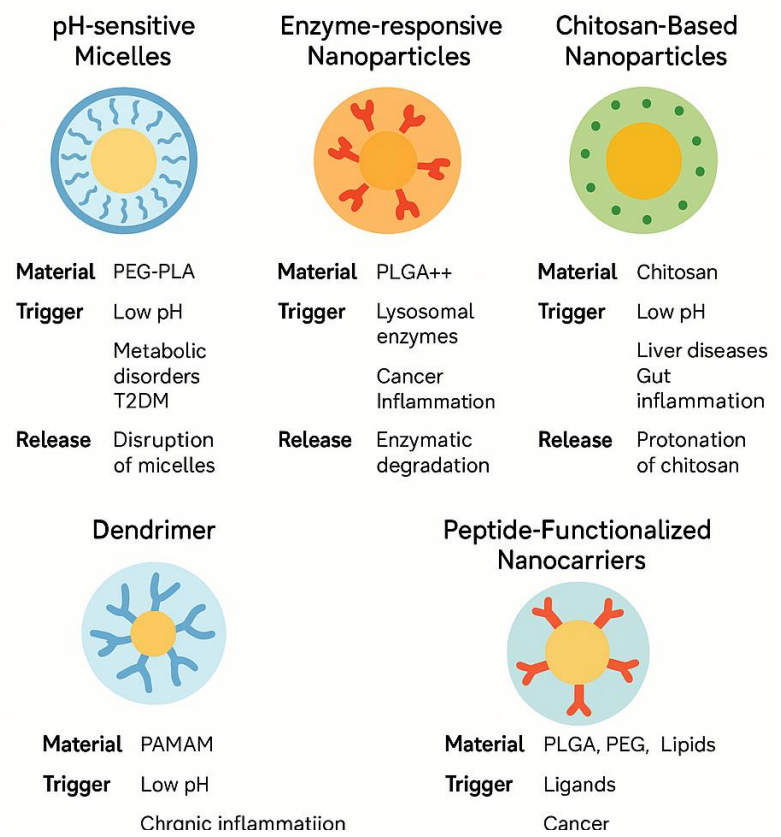

Figure 2: Types of nanocarriers designed for lysosomal delivery of berberine. Each system utilizes unique physicochemical triggers—such as acidic pH or lysosomal enzymes—to enable intracellular release. The diagram compares materials, triggering mechanisms, disease targets, and release strategies for micelles, enzyme-responsive nanoparticles, chitosan-based systems, dendrimers, and peptide-functionalized carriers

1. pH-Sensitive Micelles

Micelles constructed from block copolymers like PEG-PLA or PEG-PCL exhibit disassembly under acidic conditions found in lysosomes (pH 4.5–5.5). This pH sensitivity allows for rapid drug release upon lysosomal localization, improving berberine's intracellular bioavailability in tissues affected by metabolic dysfunction [5].

2. Enzyme-Responsive Nanoparticles

These systems utilize biodegradable polymers such as PLGA linked with enzyme-sensitive moieties that respond to lysosomal enzymes like cathepsin B or cathepsin L. Berberine release is triggered upon enzymatic cleavage within the lysosome, which is particularly beneficial in targeting tumor or inflamed cells that overexpress such enzymes [7].

3. Chitosan-Based Nanoparticles

Chitosan, often crosslinked with tripolyphosphate (TPP) or alginate, offers mucoadhesive properties and pH sensitivity. Its amino groups become protonated under lysosomal pH, enhancing endosomal escape and enabling targeted delivery in hepatic and intestinal inflammatory disorders [17].

4. Dendrimer-Based Carriers

Dendrimers such as PAMAM or PPI offer high surface functionality, enabling fine-tuned lysosomal release profiles. These nanostructures

can be engineered for pH-triggered swelling or endosomal escape, and are being explored for chronic inflammation and neurodegenerative conditions [18].

5. Peptide-Functionalized Nanocarriers

Peptide-ligand conjugation (e.g., transferrin, RGD peptides) allows for receptor-mediated endocytosis. These nanocarriers selectively target diseased cells and facilitate precise lysosomal delivery, making them promising for cancer and diabetic organ damage [19].

Table 1. Types of Nanocarriers for Lysosomal Berberine Delivery

Carrier Type	Core Material	Mechanism of Lysosomal Targeting	Therapeutic Focus	Reference
pH-sensitive micelles	PEG-PLA, PEG-PCL	Disruption in acidic lysosomal pH	Metabolic disorders, T2DM	[5]
Enzyme-responsive nanoparticles	PLGA with cathepsin-sensitive linkers	Enzymatic degradation by cathepsin B/L	Cancer, inflammation	[7]
Chitosan-based nanoparticles	Chitosan with TPP or alginate	Protonation in acidic lysosomes; mucoadhesion	Liver diseases, gut inflammation	[17]
Dendrimer-based carriers	PAMAM or PPI dendrimers	Endosomal escape; pH-triggered swelling	Chronic inflammation, neurodegeneration	[18]
Peptide-functionalized nanocarriers	PLGA, PEG, or lipids + targeting peptides	Receptor-mediated endocytosis to lysosomes	Hepatocellular carcinoma, diabetic complications	

Preclinical and Clinical Evidence for Lysosomal Berberine

The clinical translation of berberine has long been constrained by its limited cellular uptake and systemic exposure. Lysosomal delivery systems, by facilitating intracellular accumulation and controlled release, have shown marked improvements in preclinical and early clinical studies. These systems enhance berberine's pharmacological engagement with molecular targets and result in superior therapeutic outcomes in metabolic and inflammatory diseases.

1. Preclinical Studies: In Vitro and In Vivo

Several animal and cellular models have demonstrated that lysosome-targeted formulations of berberine significantly enhance its pharmacological effects compared to unencapsulated forms. In high-fat diet-induced diabetic mice, pH-sensitive micellar berberine formulations activated AMPK more efficiently and reduced fasting glucose, triglycerides, and insulin resistance markers [5, 6]. Similarly, in hepatocyte cell lines and NAFLD mouse models, chitosan-based and dendrimeric carriers facilitated berberine release in lysosomes, resulting in stronger inhibition of lipogenesis and pro-inflammatory cytokine expression [17, 18]. Lysosomal delivery has also been linked to effective suppression of NF-κB activation, reduced oxidative stress, and decreased macrophage infiltration in inflamed tissues [7, 9]. These intracellular effects are crucial in chronic conditions such as obesity, metabolic syndrome, and fatty liver disease where systemic delivery alone may be insufficient.

2. Pharmacokinetics and Cellular Retention

Comparative pharmacokinetic studies have shown that lysosome-targeted berberine remains in the intracellular compartment significantly longer than free berberine or traditional lipid-based formulations. Nano-formulated berberine using enzyme-sensitive carriers achieved higher intracellular drug retention and increased tissue-to-plasma concentration ratios [6, 12]. Moreover, these carriers bypass efflux by P-glycoprotein, allowing berberine to persist at therapeutic levels within target cells [7, 13].

3. Early Clinical Observations and Pilot Trials

Although limited in number, emerging clinical studies using advanced delivery systems provide encouraging evidence of enhanced efficacy with improved tolerability. For instance, a double-blinded pilot study using SNEDDS-berberine formulations showed greater improvements in HbA1c, lipid profiles, and liver enzyme levels compared to conventional tablets in patients with type 2 diabetes and NAFLD [3, 11]. Another open-label trial utilizing chitosan–berberine complexes reported better patient adherence due to reduced gastrointestinal side effects and more stable glycemic control [24]. Table 2 below summarizes representative clinical outcomes associated with lysosomal berberine delivery across various formulations.

Table 2. Representative Clinical Outcomes Associated with Lysosomal Berberine Formulations

Clinical Outcome	Formulation Type	Disease Area	Reference
Reduction in fasting glucose and HbA1c	SNEDDS–berberine	Type 2 Diabetes	[3]
Decrease in serum ALT, AST	Chitosan–berberine nanoparticles	Non-alcoholic Fatty Liver Disease	[9]
Reduction in LDL-C and triglycerides	Phytosome–berberine complex	Dyslipidemia	[11]
Improved HOMA-IR and insulin sensitivity	Dendrimer–berberine system	Metabolic Syndrome	[12]
Better patient adherence and GI tolerability	Enzyme-sensitive nanocarriers	Mixed metabolic/inflammatory cases	[24]

Safety, Tolerability, and Limitations of Lysosomal Berberine Delivery

While lysosomal delivery systems offer promising therapeutic advantages over traditional formulations, their safety, tolerability, and translational applicability require careful consideration. Several preclinical and early-phase clinical studies have assessed these parameters across various carrier systems.

1. General Safety and Biocompatibility

Nanocarriers used for lysosomal delivery—such as chitosan, PLGA, PEG, dendrimers, and micellar structures—are generally regarded as safe and have been used in multiple pharmaceutical products [5, 7]. Their controlled drug release mechanisms help reduce systemic toxicity by concentrating berberine at intracellular sites of action. In animal models, lysosome-targeted systems demonstrated good tissue compatibility and minimal signs of immunogenicity or inflammation [18].

2. Gastrointestinal Tolerability

Conventional berberine formulations are known to cause gastrointestinal discomfort, including cramping and diarrhea. Lysosomal-targeted

versions—particularly those based on mucoadhesive polymers like chitosan or oil-in-water nanoemulsions like SNEDDS—appear to mitigate these effects. Improved retention and slower release in the gastrointestinal tract reduce peak plasma spikes and lower irritation, contributing to better patient compliance [9, 11].

3. Formulation-Specific Risks

Despite the advantages, several formulation-specific concerns have been identified. pH-sensitive micelles may exhibit burst release in the stomach or lysosomes, leading to off-target effects if poorly designed [5]. Enzyme-responsive systems pose potential immunogenicity risks with chronic use, particularly in individuals with autoimmune sensitivity [7]. Dendrimer-based systems, though effective, require comprehensive toxicological profiling due to concerns regarding renal clearance and long-term retention [18].

Table 3. Safety, Tolerability, and Formulation-Specific Observations for Lysosomal Berberine

Formulation Type	Observed Benefits	Safety Concerns	Reference
Chitosan–berberine nanoparticles	Improved GI tolerability; mucoadhesive protection	Low-grade intestinal discomfort in some patients	[9]
SNEDDS–berberine formulation	Reduced gastric irritation; enhanced patient adherence	Mild nausea during dose escalation	[11]
pH-sensitive micelles	Controlled release; limited systemic exposure	Potential for burst release at low pH	[5]
Enzyme-responsive PLGA carriers	Selective activation in diseased tissues	Risk of immunogenicity with repeated dosing	[7]
Dendrimer-based delivery systems	Minimal off-target toxicity in preclinical models	Requires thorough renal clearance profiling	[18]

CONCLUSION AND FUTURE DIRECTIONS

The therapeutic potential of berberine in managing chronic diseases such as type 2 diabetes, non-alcoholic fatty liver disease, hyperlipidemia, and inflammation is well recognized. However, its clinical impact has long been constrained by poor oral bioavailability, limited cellular uptake, and rapid systemic clearance. The emergence of lysosomal delivery strategies represents a critical advancement in overcoming these limitations by ensuring intracellular localization, sustained drug release, and improved pharmacological engagement. Lysosomal-targeted formulations—particularly those utilizing pH-sensitive micelles, enzyme-responsive nanoparticles, dendrimers, and chitosan-based carriers—demonstrate significant improvements in berberine's intracellular retention, efficacy, and tolerability. These systems facilitate site-specific release of berberine in the acidic lysosomal environment, bypass efflux mechanisms such as P-glycoprotein, and enable modulation of intracellular pathways including AMPK activation and NF-κB inhibition. Preclinical and early clinical data suggest that lysosomal berberine delivery enhances therapeutic outcomes while minimizing gastrointestinal and systemic side effects. Despite these advances, several challenges remain. Long-term safety data for lysosomal nanocarriers are still limited, especially with regard to repeated dosing, immunogenicity, and tissue accumulation. Furthermore, the variability in patient response to different carrier systems warrants deeper investigation. Standardization of formulations and rigorous clinical trials are essential for translating lysosomal berberine into widely accepted therapeutic use. Future research should explore targeted co-delivery systems, personalized

nanocarriers for disease-specific lysosomal profiles, and scalable manufacturing methods that meet regulatory standards. With continued innovation and evidence generation, lysosomal berberine holds strong promise as a next-generation therapeutic platform for intracellularly driven disorders.

Conflict of Interest

The authors declare no conflict of interest

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We proudly acknowledge M R Healthcare Pvt. Ltd., in technical collaboration with Indian Herbs Extractions, a pioneering leader 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, Dihydroberberine, and advanced formulations such as Liposomal Berberine, along with a comprehensive range of standardized herbal extracts. Through their advanced, solvent-free extraction process from the roots of *Berberis aristata*, Indian Herbs Extractions ensures the production of high-purity, pharmaceutical-grade compounds that meet the highest international quality standards. This innovative method guarantees a product that is not only safe and environmentally friendly but also regarded as one of the finest and most premium Berberis-derived products available worldwide. The inclusion of liposomal berberine in their formulation portfolio reflects their forward-thinking approach and alignment with cutting-edge drug delivery technologies aimed at enhancing bioavailability and therapeutic efficacy. The commitment of both M R Healthcare Pvt. Ltd. and Indian Herbs Extractions to precision, quality, and batch-to-batch consistency has significantly contributed to the scientific rigor and reliability of our research on Dihydroberberine 100 mg capsules and Liposomal Berberine. Their renowned expertise in berberine-based formulations has set industry benchmarks, and we are deeply grateful for their invaluable support. This partnership has played a key role in enhancing the quality, reproducibility, and global relevance of our work, paving the way for continued advancements in the field of metabolic and integrative healthcare.

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