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ADVANCEMENTS IN BERBERINE-LOADED MICROEMULSION FOR ORAL DELIVERY: A COMPREHENSIVE REVIEW

Priyanka Singh Rajora[1*], Dr.Jitendra Singh Rajawat[2]

[1*]Research Scholar, Bhupal nobles' University, Email Id: singhpriyanka20355@gmail.com
[2]Associate professor, Bhupal nobles' University, Email Id: jeetupharma@gmail.com

***Corresponding author:** Priyanka Singh Rajora
*Research Scholar, Bhupal nobles' University, Email Id: singhpriyanka20355@gmail.com

Abstract
Berberine, a natural alkaloid with a wide range of pharmacological effects, has received a lot of attention due to its possible medicinal benefits. However, its low oral bioavailability and solubility in water pose significant obstacles to achieving effective treatment effects. This review study investigates recent advances in the creation and characterisation of berberine-loaded microemulsion-based oral formulations as a possible approach for improving berberine oral delivery. The scope of this study includes a thorough examination of the literature on the formation of berberine-loaded microemulsions and their prospective applications. The paper examines the principles and benefits of microemulsion as a diverse drug delivery technology, as well as the many formulation factors that are critical in guaranteeing the microemulsion's stability and bioavailability. A search of reliable sources, such as PubMed, Scopus, and Web of Science, yielded research papers, review articles, and patents on the creation of berberine-loaded microemulsions for oral administration. Key findings from the reviewed literature reveal that microemulsion-based formulations offer a promising approach to improve berberine's oral bioavailability and solubility, enhancing its therapeutic efficacy in various medical conditions.

Keywords: Berberine, Microemulsion, Oral formulation, Drug delivery, Bioavailability, Pharmacological properties.

INTRODUCTION
The worldwide cost of vascular disorders is steadily increasing. These conditions include coronary artery disease cerebrovascular disease, hypertension, and diabetes complications. Individuals' quality of life is being jeopardised as the global expense of vascular disorders rises. [1]
Vascular illnesses are caused by a number of reasons, involving vascular dysplasia, oxidative stress, and abnormal lipid metabolism. In general, strategies aimed at reducing inflammation and oxidative stress, as well as normalising lipid metabolism, are utilised to cure and avoid vascular disorders. Common treatment agents include statins, Anti-inflammatory medications that are nonsteroidal, and new biological agents. [2]
However, due to the substantial expenses and negative impact characteristics of these treatments, it is critical to identify less expensive option with little adverse reactions and equivalent or better therapeutic benefits. “Traditional Chinese medicine (TCM)” therapies have long been employed as a substitute and supplementary remedies to treat vascular disease in China. These chemicals have

recently sparked scientific attention due to their reduced toxicity and fewer adverse responses when compared to those identified and utilised in western medicine. [3]

Berberine, a natural isoquinoline alkaloid derived from various plants, has been recognized for its diverse pharmacological properties and therapeutic potential. [4] Traditional medicine has used it for millennia in numerous cultures. It is primarily derived from the roots, rhizomes, and stems of several plants, including Berberis species (such as Berberis vulgaris), Coptis species (such as Coptis chinensis), and Hydrastis canadensis (Goldenseal). [5]

In traditional Chinese medicine (TCM), berberine-containing herbs, such as Huanglian (Coptis chinensis) and Huangbo (Phellodendron amurense), have been used for their medicinal properties dating back over 2000 years. In Ayurvedic medicine, berberine-containing plants like Daruharidra (Berberis aristata) have been used to treat various ailments. [6] [7]

BERBERINE: Physical and Chemical Properties

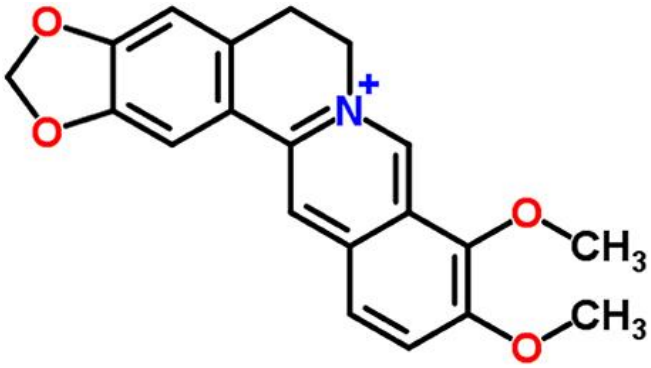

Figure 1 Structure of Berberine

"Molecular formula": $C_{20}H_{19}NO_5$
"Molecular weight": 353.36 g/mol
Appearance: Yellow-orange powder
Solubility: Soluble in water, methanol, and ethanol
Melting point: 175-177°C
Boiling point: 310°C
Storage: Store in a cool, dry place

Berberine has two rings: a "dihydroisoquinoline ring" and an "isoquinoline ring." The skeleton is separated into four rings labelled A, B, C, and D. The C2 & C3 of the A ring create a methylenedioxy group, which is responsible for the majority of berberine's biological actions, including anticancer activity. Berberine's antibacterial activity is dependent on the presence of a "quaternary ammonium structure" in the "C" ring. C9 and C10 are individually connected to a methoxy group in the "D" ring.

Berberine structural modification research has primarily concentrated on the "C" and "D" rings. Hypoglycemic action has been demonstrated by alkyl or acylation in the "D" ring. Cinnamic acid introduced at the 9-O position has also been demonstrated to have substantial hypoglycemia effects. C8 and C13 alkylation has been demonstrated to increase cytotoxicity. Similarly, berberine's anticellular proliferative effect has been demonstrated to be enhanced by changes at positions N7 and C13.

Berberine has an optimal absorbing frequency of 350 nm and a maximum wavelength of emission of 530 nm in a solution of 0.01 mol/L sodium dodecyl sulphate. Berberine content in traditional Chinese medicine (TCM) or medicines can be measured using liquid chromatography-mass spectrometry and isotope labelling.

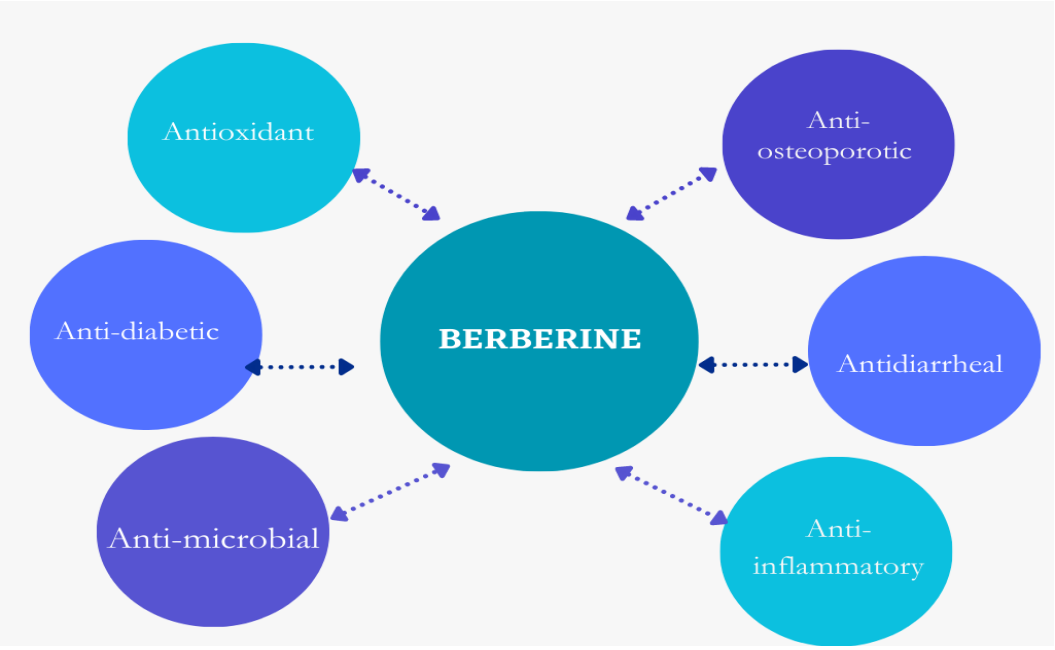

Figure 2 Berberine activities

Berberine has garnered significant attention in the area of pharmacological investigation and medicine due to its remarkable and diverse pharmacological properties. This compound has demonstrated immense therapeutic potential, making it a valuable candidate for the cure of several medical problems & disorders. Diabetes control is one of the main domains where berberine has demonstrated promising results. Berberine has been shown in studies to successfully manage blood glucose levels by increasing insulin sensitivity & stimulating glucose absorption in cells. Berberine has also been shown to inhibit enzymes involved in glucose synthesis in the liver, resulting in better glycemic control. Berberine has attracted interest as a potential supplementary medication for diabetes control as a result of these findings. [8] [9] Berberine's anticancer capabilities have received a lot of interest in the field of oncology. Berberine appears to have “anti-proliferative” & “pro-apoptotic effects” on many cancer cell lines, slowing tumour growth and metastasis. Berberine has also been shown to sensitise cancer cells to radiation therapy and chemotherapy, thereby improving the efficacy of traditional cancer treatments. As a result, research into the role of berberine in preventing and treating cancer is underway, with great potential for future therapeutic techniques. [10] [11]

Berberine's antibacterial effects have also been extensively recognised, with studies demonstrating its effectiveness against a variety of microbiological diseases such as bacteria, viruses, and fungus. As a result, it could be used to fight infectious infections and support the immune system's defence mechanisms. Hence, it exhibits promising effects curing of various diseases, including diabetes, cancer, microbial infections, and inflammatory disorders. [12] [13] Table 1 represents the conventional use of berberine and its various species.

TABLE I Conventional Use of Berberine and its various species

S. No.	Use case	Species	Mentions
1.	Treatment of asthma	Berberis asiatica	Kirtikar and Basu, 1998[16]
2.	Treatment of eye sores	Berberis asiatica	Kirtikar and Basu, 1998
3.	Treatment of jaundice	Berberis asiatica	Kirtikar and Basu, 1998
4.	Treatment of skin pigmentation	Berberis asiatica	Kirtikar and Basu, 1998

5.	Treatment of toothache	Berberis asiatica	Kirtikar and Basu, 1998
6.	Inflammation and edoema are reduced.	Berberis asiatica	Kirtikar and Basu, 1998
7.	Drying ulcers	Berberis asiatica	Kirtikar and Basu, 1998
8.	Conjunctivitis and other ocular disorders Cure	"Berberis aristata, B. chitria, and B. lyceum"	Rajasekaran and Kumar, 2009 [17]
9.	Treatment of enlarged liver and spleen	,,	Rajasekaran and Kumar, 2009
10	Treatment of hemorrhages	,,	Rajasekaran and Kumar, 2009
11	Treatment of jaundice	,,	Rajasekaran and Kumar, 2009
12	Treatment of skin diseases like ulcers	,,	Rajasekaran and Kumar, 2009
13	Treatment of diarrhea	Berberis vulgaris	Chen et al., 2014[18]
14	Treatment of intestinal parasites	Berberis vulgaris	Singh and Mahajan, 2013[19]
15	Treatment of diabetes	Berberis vulgaris	Li et al., 2004[20]
16	Reducing fever	Berberine-containing plants	"Kataoka et al., 2008" [21]
17	Common cold, respiratory tract infections, and viral treatment	Berberine-containing plants	Farnsworth, 2001[22]
18	Use as an "astringent agent" to lighten the skin tone.	Berberine-containing plants	Chen et al., 2014
19	Treatment of mountain sickness, infections, and fever	Leaves and bark of species of the genus Berberis	San Martín, 1983; Houghton and Manby, 1985; [23]
20	Various skin conditions	M. aquifolium	-
21	Reduction of toxins, "damp-heat syndromes", "purge fire", &to "clear heat in the liver"	Coptidis rhizoma	Tang et al., 2009 [24]

However, its limited bioavailability and poor water solubility have posed significant challenges in harnessing its full therapeutic benefits. Consequently, there is an increasing interest in developing innovative medication delivery methods to improve oral drug administration of berberine. [25]

Challenges and limitations of Conventional Berberine formulation

Conventional berberine formulations encounter a number of obstacles and restrictions that limit their therapeutic efficacy & clinical utility:

- **Poor Water Solubility:** Berberine has a low water solubility, which causes problems with dissolving and absorption in the gastrointestinal tract. Because of the restricted solubility, there is less bioavailability and potentially poorer therapeutic outcomes.
- **First-Pass Metabolism:** Berberine undergoes considerable first-pass metabolism in the liver after oral administration, where a significant amount of the chemical is metabolised before

reaching systemic circulation. This metabolism also adds to decreased bioavailability and reduces the quantity of active berberine available to exert pharmacological effects.

- **Gastrointestinal Irritation:** Berberine may produce gastrointestinal pain and irritation at higher dosages or with continuous administration, resulting in poor adherence among patients and restricting the practicality of standard dosing.
- **Limited Targeting:** Traditional formulations frequently lack precise targeting capabilities, leading to non-selective distribution of drugs and possible off-target effects. This limitation may impair therapeutic efficacy while also increasing the risk of undesirable effects.
- **Variable Absorption:** Berberine's varied and unpredictable absorption in the gastrointestinal system might result in variable plasma concentrations, making it difficult to establish a steady and predictable therapeutic impact.
- **Short Half-Life:** Berberine's relatively short half-life complicates dosage methods even further, potentially necessitating numerous injections for sustained therapeutic effect.
- **Berberine formulation stability:** Berberine formulation stability may be a challenge due to its susceptibility to environmental factors including warmth, light, and humidity, pH. These stability difficulties can have an impact on the product's shelf life and efficacy.

To address these issues and improve berberine's therapeutic potential, researchers have been investigating novel drug delivery techniques, such as microemulsion-based formulations, to overcome the limits associated with traditional dosage forms. Microemulsions are a promising method for increasing berberine's solubility, stability, and bioavailability, paving the way for more efficient and effective oral administration systems.

Microemulsion-based formulations have developed as a cutting-edge strategy to overcoming the limits of traditional drug delivery technologies in recent years. Microemulsions are colloidal dispersions of oil and water stabilised by surfactants, which may or may not include co-surfactants. These systems can improve the solubility and bioavailability of lipophilic substances like berberine in the dispersion phase.

The importance of producing an oral formulation for berberine stems from the potential benefits it provides in a variety of applications. To begin, an optimised oral formulation can improve berberine absorption through the gastrointestinal tract, enhancing its systemic availability and therapeutic efficacy. This enhanced bioavailability is critical for delivering therapeutic effects at lower doses, lowering the risk of side effects, and boosting patient compliance.

Second, an effective berberine oral formulation can unlock its potential in treating a wide range of disorders. Berberine's broad pharmacological qualities make it a promising treatment for a variety of medical illnesses, including metabolic disorders, cancer, and infectious infections. Berberine's applicability in various therapeutic areas could be expanded by an improved oral administration mechanism, broadening its clinical impact.

Furthermore, oral formulations based on microemulsions provide advantages in terms of ease of administration, better drug stability, and potential targeting techniques. Because of the adaptability of microemulsions, the formulation can be tailored to specific pharmacological characteristics and release profiles, allowing for fine control over drug release rates.

Hence, the creation of berberine-loaded microemulsion-based oral formulations is a promising step forward in drug delivery technology. Such formulations have the potential to solve the issues associated with berberine oral delivery, resulting in increased bioavailability, greater therapeutic efficacy, and broader clinical applications. The intent of this review paper is to investigate the recent advancements and evaluations of berberine-loaded microemulsions, emphasising their significance and consequences in pharmacological research and healthcare practise. This study adds to the growing body of knowledge and encourages further study in the field of microemulsion-based delivery methods for berberine as well as other poorly soluble medicines by throwing light on recent achievements.

METHOD

This study examines the latest developments in berberine-loaded microemulsion-based oral formulations, with a focus on their development and characterisation. A comprehensive literature search was carried out utilising recognised databases such as PubMed, Scopus, Web of Science, and Google Scholar. Papers published within the last five years that focused on the formulation, characterisation, and assessment of these oral formulations were included in the review. Data extraction and analysis on selected articles were performed, examining specifics on the microemulsion composition, formulation parameters, characterization procedures, in vitro as well as in vivo studies, pharmacokinetic data, and therapeutic effects. To present a consistent flow of information, thematic organisation was adopted, encompassing difficulties, microemulsion principles, formulation creation, characterisation methodologies, in vitro and in vivo research, pharmacokinetics, and prospective medicinal uses.

DEVELOPMENT OF MICROEMULSION-BASED FORMULATION FOR BERBERINE

Microemulsions are isotropic two immiscible liquids dispersed, commonly oil and water, that are stabilised by an interfacial coating of surfactant and cosurfactant. They are normally clean and translucent, with droplet sizes ranging from 10 - 100 nm. [26] The principles and advantages of microemulsions in oral drug delivery are as follows:

1. Enhanced Solubilization and Bioavailability: In their dispersed phase, microemulsions can solubilize simultaneously hydrophobic and hydrophilic medicinal molecules. Microemulsions boost drug bioavailability and expedite absorption across the gastrointestinal tract by increasing solubility, resulting in better therapeutic efficacy

2. Increased Drug Stability: Microemulsions can prevent medications from breakdown under harsh physiological conditions such as acidic stomach pH and enzymatic activity in the gut.

3. Permeability: It has been demonstrated that microemulsions improve medication permeability through biological membranes. Microemulsions' small droplet size and distinct shape increase interactions with cell membranes, resulting in better medication transport and uptake into target cells, tissues, or systemic circulation.

4. Uniform Drug Distribution: Because of their small droplet size and uniform drug distribution, microemulsions enable uniform medication distribution throughout the system.

5. Optimal Drug Release Profile: Depending on the surfactants and co-surfactants used, microemulsions can be customised to achieve certain drug release profiles, such as prolonged release or fast release. This adaptability enables the optimisation of drug release kinetics to meet the therapeutic requirements.

6. Greater Surface Area for medication Absorption: The wide interfacial area of microemulsion droplets in contact with the gastrointestinal mucosa gives a greater surface area for medication absorption.

7. Versatility in Formulation Design: Microemulsions provide significant flexibility in formulation design, allowing the integration of diverse medications, excipients, and lipophilic or hydrophilic agents.

8. Potential for Targeted Drug Delivery: Microemulsions can be designed to provide targeted drug delivery to specific areas in the body with suitable changes.

(Gull et al., 2020) utilised a combination of "cinnamaldehyde (CA)" and "berberine chloride (BER)" to cure acne vulgaris caused by Propionibacterium acnes. CA and BER were initially placed into a "clove oil-based microemulsion," which was subsequently transformed into a hydrogel system using Carbopol 940. [27]

Different CA and BER concentrations were utilised in the microemulsion formulation, and the findings showed that the greatest CA and BER concentrations led to the largest cumulative amount of medication penetrated after 8 hours (68.34%). The microemulsion formulation also outperformed the suspension gel in terms of anti-acne capability, with a 41.85% change in ear thickness as opposed to 27.14% for the suspension gel. The study indicated that "cinnamaldehyde" and

"berberine-loaded CA-BER-ME-Gel" can be an effective prescribed option for the medical cure of acne vulgaris based on these findings.

(Elsheikh et al., 2018) developed a new drug delivery system known as "cremochylomicrons" was developed by combining Cremophor EL (a surfactant routinely utilised in pharmacological formulations) with chylomicrons. Chylomicrons are microscopic lipid-based particles that play a role in the lymphatic transit of dietary lipids. The study's findings showed that the existence of "cremochylomicrons" greatly hindered berberine absorption, resulting in a 43% drop in bioavailability. This data suggests that combining Cremophor EL with "chylomicrons" reduces the drug's capacity to be taken from the gastrointestinal tract and into systemic circulation. This impact can be due to "cremochylomicrons" potentially interfering with medication diffusion through the intestinal barrier, leading to decreased drug uptake.[28]

(Zhu et al.,2015) discovered that berberine microemulsion formulation had various advantages over existing approaches. It boosts bioavailability up to 100-fold, inhibits digestive tract metabolism, enhances biomembrane permeability, lowers dosage, and prevents constipation. Therefore, the microemulsion formulation a viable new alternative for administering berberine, since it allows for greater berberine absorption into the bloodstream, resulting in improved therapeutic benefits. Furthermore, the formulation minimises the required dosage, allowing more berberine to be given to the bloodstream with each administration. Overall, the microemulsion formulation represents a promising new approach for berberine delivery. [29]

(Zhu et al., 2012) discovered that berberine hydrochloride (BBH) oral bioavailability can be improved by using a "self-microemulsifying drug delivery system (SMEDDS)". SMEDDS are stable, isotropic oil-water dispersions stabilised by surfactant and cosurfactant films. The best BBH SMEDDS formulation was discovered to be "40% ethyl linoleate" and "oleic acid (2:1)," "35% Tween-80," and "25% glycerol." In vivo results revealed that the peak plasma concentration and area under the curve were larger than with commercial tablets, and the relative bioavailability of SMEDDS of BBH was increased by 2.42-fold when compared to commercial tablets. This shows that SMEDDS may be a promising new BBH formulation. [30]

(Gui et al., 2008) found that the Berberine's bioavailability was increased by 6.47 times using a microemulsion formulation. This is because the bicontinuous system, which consists of both oil and water phases, allows for the solubilization of both lipophilic and hydrophilic medicines. With a particle size of 24.0 nm, the berberine-loaded microemulsion was found to be efficiently absorbed into the bloodstream, resulting in better therapeutic benefits. The microemulsion formulation is a potential oral drug delivery technology that ensures stable and uncomplicated preparation, making it a promising choice for increasing the efficacy of berberine therapy. [31]

Table II Key Findings of the past work

Method	Findings	Researcher
Clove oil-based microemulsion + Carbopol 940	Highest CA and BER concentrations led to the largest cumulative amount of medication penetrated after 8 hours (68.34%). Microemulsion formulation also outperformed the suspension gel in terms of anti-acne capability.	Gull et al. (2020)
Cremochylomicrons	Existence of "cremochylomicrons" greatly hindered berberine absorption, resulting in a 43% drop in bioavailability.	Elsheikh et al. (2018)
Berberine microemulsion formulation	Boosts bioavailability up to 100-fold, inhibits digestive tract metabolism, enhances biomembrane permeability, lowers dosage, and prevents constipation.	Zhu et al. (2015)
"Self-microemulsifying drug delivery system (SMEDDS)"	Peak plasma concentration and area under the curve were larger than with commercial tablets, and the relative bioavailability of SMEDDS of BBH was increased by 2.42-fold when compared to commercial tablets.	Zhu et al. (2012)
Microemulsion formulation	Berberine's bioavailability was increased by 6.47 times. The berberine-loaded microemulsion was found to be efficiently absorbed into the bloodstream, resulting in better therapeutic benefits.	Gui et al. (2008)

DISCUSSION

The findings suggest that microemulsion-based drug delivery technologies hold tremendous promise for increasing berberine bioavailability and therapeutic efficacy. Several studies have looked into using microemulsions to increase berberine distribution and overcome the constraints of traditional formulations.

Gull et al. (2020) developed a microemulsion-based hydrogel containing cinnamaldehyde and berberine chloride, which displayed increased drug penetration and anti-acne potential. This data supports the ability of microemulsions to improve berberine administration in the cure of "acne vulgaris," highlighting the necessity of new drug delivery systems for specific medical diseases.

Elsheikh et al. (2018) showed reduced berberine absorption, highlighting the need for optimization and exploring innovative carriers to address bioavailability challenges.

Zhu et al. (2015) shed light on the positive aspects of berberine microemulsion formulations over traditional techniques. Berberine bioavailability was significantly increased, biomembrane permeability was enhanced, and the required dosage was reduced, highlighting the promise of microemulsion-based systems in maximising berberine's therapeutic advantages.

Zhu et al. (2012) found that "self-microemulsifying drug delivery systems (SMEDDS)" improved berberine hydrochloride oral bioavailability significantly. SMEDDS could be a viable novel berberine formulation, highlighting the necessity of researching enhanced drug delivery techniques.

And, Gui et al. (2008) found that employing a microemulsion formulation increased berberine bioavailability significantly. This discovery highlights the ability of microemulsions to effectively solubilize berberine, improving absorption and therapeutic effects.

They show that microemulsion-based formulations are a viable and effective way to improve berberine bioavailability and therapeutic effects through oral delivery. These findings emphasise the necessity of future study and optimisation of microemulsion-based drug delivery systems for berberine and other poorly soluble medicines, which offer promising techniques for realising the full potential of these molecules in a variety of medical problems.

CONCLUSION

Advances in berberine-loaded microemulsions for oral administration hold great potential for addressing the limitations associated with berberine's low water solubility and bioavailability. The experiments examined in this study show that microemulsion-based formulations have the potential to improve berberine's therapeutic effectiveness and clinical impact.

Microemulsions have several major benefits, including improved medication solubilization, greater absorption surface area, and regulated drug release profiles. Because these qualities address the constraints of traditional berberine formulations, microemulsions are an appealing and efficient drug delivery technology for berberine as well as other poorly soluble substances.

Several study publications' findings support the idea that microemulsions can greatly improve berberine bioavailability, resulting in greater medication absorption and therapeutic advantages. The research also shed insight on the possibility of microemulsion-based carriers in targeted drug administration and lymphatic targeting, opening up new possibilities for optimising berberine's pharmacological activities. Berberine is a viable candidate for treating a variety of medical disorders, making it critical to investigate novel drug delivery strategies in order to fully realise its therapeutic potential. This review encourages future research and optimisation of berberine-loaded microemulsions for oral administration. To improve berberine's tissue selectivity and therapeutic effects, future research should focus on refining formulation design, studying excipients, and developing innovative targeting techniques. Understanding the cellular and molecular mechanisms of berberine-microemulsion interactions can provide useful insights into medication absorption and pharmacokinetic behaviour. This study adds to our understanding of berberine while also contributing to the larger field of medication delivery research. Harnessing the potential of microemulsions can lead to more effective and efficient therapies, benefiting patients all around the world. Berberine-loaded microemulsion advancements represent an intriguing frontier in pharmaceutical research, providing a viable option for enhancing medication solubility,

bioavailability, and therapeutic efficacy. The ramifications go beyond berberine and may revolutionise the distribution of other poorly soluble medications, making it an appealing topic for additional research and investment in healthcare solutions.

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