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Nano formulation of Berberine (Brb): Transforming a natural alkaloid into advanced therapeutics

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ABSTRACT

A naturally occurring isoquinoline alkaloid "Berberine" (Brb) is found in various plant species of the genus *Berberis*, such as *Berberis vulgaris*, Berberis aristata, *Berberis microphylla*, and so on. This component has been studied extensively by various researchers and scientists for its diverse therapeutic properties, including anticancer, antiviral, antimicrobial antidiarrheal, and anti-inflammatory effects. One of the most remarkable applications of berberine is its efficacy in managing type-II diabetes, which is attributed to its capability to initiate adenosine monophosphate, glycolysis stimulation, protein kinases activation, inhibit mitochondrial function and thus collectively enhance the lipid and glucose metabolism. Also, Berberine has shown promising outcomes in addressing other health conditions, such as hypertension, cardiac arrhythmias, and congestive heart failure. In spite of its numerous benefits, extensive usage of berberine has been hindered by some challenges such as low bioavailability, limited absorption, and poor water solubility. Nano formulation has emerged as an auspicious approach to overcome these obstacles. This review highlights the advancements of using nano technology to overcome the limitations of berberine (Brb) associated with its absorption, dissolution, and bio-distribution, which are critical for its active application of pharmacology. While previous studies have explored the use of nano-carriers for transfer of drug, this review uniquely underlines an inclusive evaluation of several nanocarrier, together with lipid-based nanoparticles (SLNs, NLCs, micelles, and liposomes), polymeric-based nanoparticles (chitosan, alginate, dextran, and PLGA) and advanced materials (graphene, dendrimers, gold (Au), and silver (Ag) nanoparticles). It emphasizes their specific applications in treating conditions like diabetes, osteoarthritis, microbial infections, and melanoma, with special attention on innovative applications such as thermal therapy with AuNP-Brb and bio-imaging with Brb-based carbon dots. In conclusion, nanotechnology has shown an outstanding result in improving the therapeutic strength and delivery of berberine, more investigation is necessary to interpret these nanoparticle carriers into clinical applications. The detailing of specific therapeutic effects and this breadth of comparison highlight the novelty of this review, which sets a foundation for future research to translate these findings into clinical applications.

INTRODUCTION

"Ayurveda" is one of the earliest sources of natural medicine, utilized for thousands of years globally to treat diseases and promote recovery [1]. Its usage of botanical preparations aims not only to treat or prevent diseases but also to repair disease-related damage. Artificial drugs can cause a variety of adverse reactions and limit their clinical utility. Due to the generally low toxicity of herbal medicines, they can enhance patient's quality of life and reduce the need for multiple pharmaceutical actions [2]. Apart from the massive variety of outdated medicinal plants in India, there are about 700 Ayurvedic and Unani plants, as well as 600 Siddha and Aamchi plants [3], that have been used for their therapeutic properties. This rich botanical diversity underlines the deeply rooted tradition of herbal medicine in Indian culture, which offers a plethora of remedies for various diseases and health conditions.

The recent focus by researchers on medicinal herbs such as *Berberis aristata, Berberis thunbergia, Berberis*

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vulgaris, Berberis asiatica, Berberis petiolaris, and Berberis aquifolium, highlights their potential in pharmaceutical applications. Several scientists have identified bioactive compounds in the stem, roots, and rhizomes of these plants, with "berberine" emerging as the chief component [4–6]. It has been found that berberine content is present more in the species *Berberis aristate* that is 5% (Fig. 1 and Fig. 2). A yellowish isoquinoline alkaloid Berberine (Fig. 3) has many pharmacological applications such as antimicrobial, antiviral, antidiabetic, anti-inflammatory, and antidiarrheal [7–9]. Berberine shows significant anti-tumor properties and can be active in the treatment of various cancers such as human colon cancer cells [10] and hepatocellular carcinoma [11]. The anti-inflammatory effect of berberine works by inhibiting activator protein-I, and is a noteworthy factor of transcription involved in the process of inflammation [10].

Berberine also has the capability to treat infections of the intestine by hindering the growth of *Helicobacter pylori* [12,13]. Furthermore, activation of glycolysis stimulation, adenosine monophosphate active protein kinase, and mitochondrial function inhibition occurs significantly in the case of berberine with regard to type- II diabetes, which subsequently improves both glucose and lipid metabolism [14,15]. Berberine shows its antitumor efficacy by four main mechanisms: inhibiting proliferation, inducing apoptosis, inhibiting angiogenesis, and suppressing metastasis. When the tumor cells increase, berberine acts by inhibiting nuclear feature triggered B-cells (*NF-κB*) and matrix metalo-proteinases-1, 2, and 9, that reduces cyclooxygenase-2 actions and activates the adenosine monophosphate active protein kinase signaling [16]. Various literature surveys show that berberine component rises arachidonic acid to prostaglandin E-2 ratio in hepatocellular cancer cells which successfully inhibits the arachidonic acid pathway. Also, it works by hindering the expression of cyclooxygenase-2 gene with phospholipase A-2, which averts tumour growth [17].

Berberine also inhibits the action of a protein so-called focal adhesion kinase in certain cancer cells, such as squamous cell carcinoma and rectal cancer cells. Taking advantage from this, some researchers combined chemotherapy with the administration of berberine to avert tumor degeneration in ovarian cancer [18,19]. As berberine also, has been stated to have useful properties in managing conditions such as hypertension, cardiovascular arrhythmia, and congestive heart failure [13]. Although, berberine offers abundant benefits but its clinical utility is hindered by several limitations, the absorption by the gastrointestinal tract and an unfortunate aqua solubility but 'absorption by the intestinal tract' is the foremost among them leads to the low bioavailability (around 5%) of berberine, and classifying it as a class-4 medicine. Thus, this little bioavailability can be attributed to the high binding of berberine to plasma- proteins, resulting in a short-unbound segment available to reach and penetrate target tissues, as well as the first-pass effect that berberine undergoes [13,16].

Berberine containing various nanoparticles (Fig. 4) have been used to improve berberine's bioavailability, thus this review article explores how these nanoparticles can enhance the beneficial effects and reduce the limitations or side-effects associated with Berberine. The main objectives of this study are (a) To provide an outline of the therapeutic latent and mechanisms action of berberine (b) To highlight the challenges allied with the practice of berberine, such as poor solubility, limited absorption, and low bioavailability (c) To explore the application of various nano-carriers for the delivery of berberine and encapsulation. (d) To assess the efficacy of these nanocarriers in increasing the berberine absorption, solubility, and bioavailability.

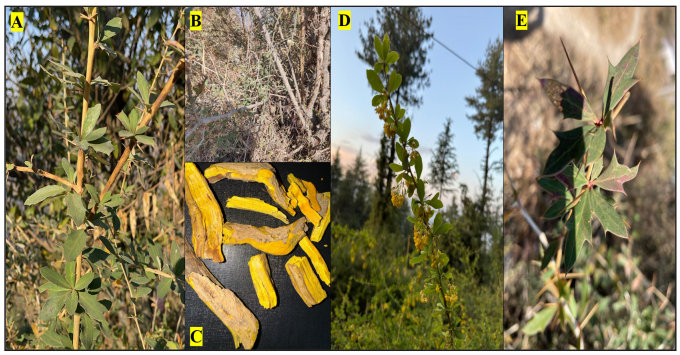

Figure 1. Plant parts of *Berberis aristata*: A- Plant; B- Stem; C- Roots; D- Flowers; E- leaves.

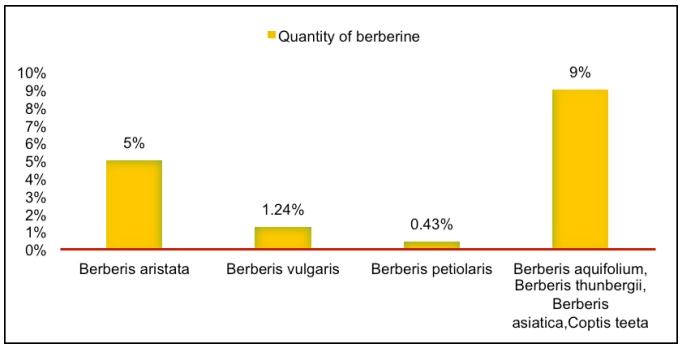

Figure 2. Quantity of Berberine component in *Berberis* species [4–6].

NANO-SCALE BERBERINE

Low solubility is a major limitation of the drug Berberine. To overcome this limitation, researchers employed two bottom-up methods, evaporative precipitation

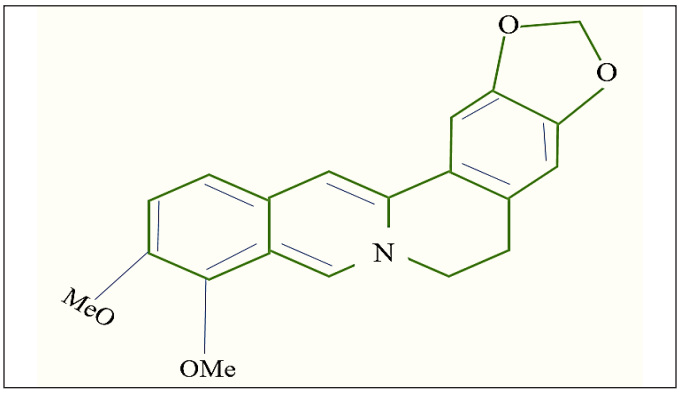

Figure 3. Chemical structure of berberine compound.

Table 1. Overview of polymer-derived nanoparticles containing berberine.

Nanoparticles	Mean size (nm)	Properties	Reference
Alginate nanoparticles Alginate nanoparticle	71.1 278 ± 1.5	Anti-bacterial Wound healing	[30]
Heparin nanoparticle	175.2 ± 5.4 <200	Sustained release of berberine, ability to prevent cell death, and efficacy in improving osteoarthritis symptoms	[31]
Polymer lipid hybrid nanoparticles (PEG–lipid–PLGA NPs	149.6 ± 5.1	Augmented bioavailability Sustained/precise release of berberine	[32]
Dextran nanoparticles	238 ± 18	Anti-diabetic	[33]
Poly lactic-co-glycolic acid	48–211	Good acidic pH releaser	[34]

of nanosuspension (EPN), and anti-solvent precipitation with a syringe pump (APSP), to produce Brb nanocrystals. The EPN method involved making a saturated ethanol extraction of Brb and quickly adding an anti-solvent that is hexane, followed by solvent evaporation. The APSP method involved injecting a saturated Brb solution in ethanol into deionized H_2O as an anti-solvent, via different water-to-solution ratios. The obtained suspensions were then evaporated to form nanocrystals. The mean particle sizes obtained were 71.53 nm for EPN and 102.6 nm for APSP. Dissolution and solubility studies showed that reducing the particle size to the nanoscale effectively resolved the solubility issue of Brb. Formulating drugs as nanosuspensions without carriers is a capable way to enhance the bio-availability and absorption of lipophilic drugs with solubility limitations [20–23]. This limitation can be accomplished by various methods, such as high-speed homogenization, nano-precipitation, sonication, pearl milling, and high-pressure homogenization. Among these methods, the high-pressure homogenization method is highly preferred due to its high productivity and low risk of contamination [24].

Wang *et al*. [25] in their study prepared berberine nanoparticles, i.e., berberine-nanosuspension, by means of a high-pressure homogenization method in which they attained nanoparticles with a particle size < 200 nm. The consequences showed that the solubility and bioavailability of berberine were improved, and the nanoparticles presented an outstanding anti-diabetic activity in diabetic mice models. These nanoparticles confirmed higher hypoglycaemic and reduction of body weight effects compared to berberine alone, and they had very rarer hostile possessions. Xie *et al*. [26] also examined the effect of berberine nanoparticles on renal ischemia-reperfusion injury, which is the utmost common reason for severe renal failure. The berberine nanoparticles prepared by them were injected into a renal ischemia-reperfusion damage rat model which demonstrated the defensive effects of berberine nanoparticles [27,26,28].

POLYMERIC-DERIVED NANOPARTICLE CARRIERS

There are various polymeric systems that have been used for the delivery of drugs, which can be broadly classified into two main groups: natural polymers and artificial polymers. The group of natural polymers includes bio-polymers, i.e., obtained from natural sources, for example, agarose, collagen, albumin, alginate, gelatin, hyaluronic acid, dextran, cyclodextrins, and carrageenan. These are biofriendly and biodegradable polymers, which makes them attractive for drug delivery applications. We have reviewed a few uses of polymers in berberine transportation as shown in Table 1. Furthermore, the synthetic polymer group includes polymers that are chemically created in the laboratories. Examples of synthetic polymers include poly-glycolic acid, poly-lactic acid, polyvinyl pyrrolidone, poly (ε-caprolactone), and polymethacrylates [29]. Both natural and artificial polymers showed an imperative part in the expansion of innovative drug delivery, leveraging their unique properties to achieve efficient and effective drug delivery.

MAGNETIZED MIDPOROUS SILICON-BUILT NANOPARTICLES

The microenvironment of tumor is acidic, which makes the pH-sensitive transporters very effectual and more superior to others for delivering drugs to cancerous cells. Some researchers created pH-sensitive mid-porous nanoparticles composed of iron oxide (Fe_3O_4) as the head group and silica (SiO_2) as the body group. Virtuous super-paramagnetic properties have been shown by these nanoparticles and might transmit a high quantity of the berberine drug and send it to hepatocellular carcinoma (liver cancer) tissues. The berberine-loaded Fe_3O_4-mSiO_2 nanoparticles could weaken the endo/lysosomal membranes in tumor cells, hence enhanced the release of berberine into the cytosol. The researchers developed pH-sensitive nanoparticles that can carry a high amount of the anti-cancer berberine drug and release it inside the hepatocellular cancerous cells. These nanoparticles display effectiveness because they can take advantage of the acidic environment of tumors to deliver the drug exactly to cancer cells [35].

LIPID-BASED NANOPARTICLE TRANSPORTERS

Lipid-based nanoparticles are nanosized carriers composed of lipids, which have gained significant attention in the field of biomedical applications and drug delivery. These nanocarriers offer several benefits, including biocompatibility, biodegradability, and the ability to encapsulate and deliver a wide array of healing mediators, such as small molecules, proteins, nucleic acids, and tomography agents. These lipid

Table.2. Overview of lipid-derived nanostructures integrating berberine.

Nanoparticles	Mean size (nm)	Properties	Reference
Nanostructured lipid careers	189.3 ± 3.7 160	Enhanced bio-availability and heightened Brb plasma concentration, improved antineoplastic efficacy.	[36]
Solid lipid nanoparticle	81.4 ± 8.4	Improves anticancer efficacy, control Brb release and mitigates hepatosteatosis	[37]
Liposomes	121.6 ± 1.5 146.9 ± 3.2 264	Heightened antitumor activity, increased stability in blood	[38,25,39]
Micelles	36 ± 21	Boosted oral bioavailability and anti-diabetic efficiency	[40,41,42]

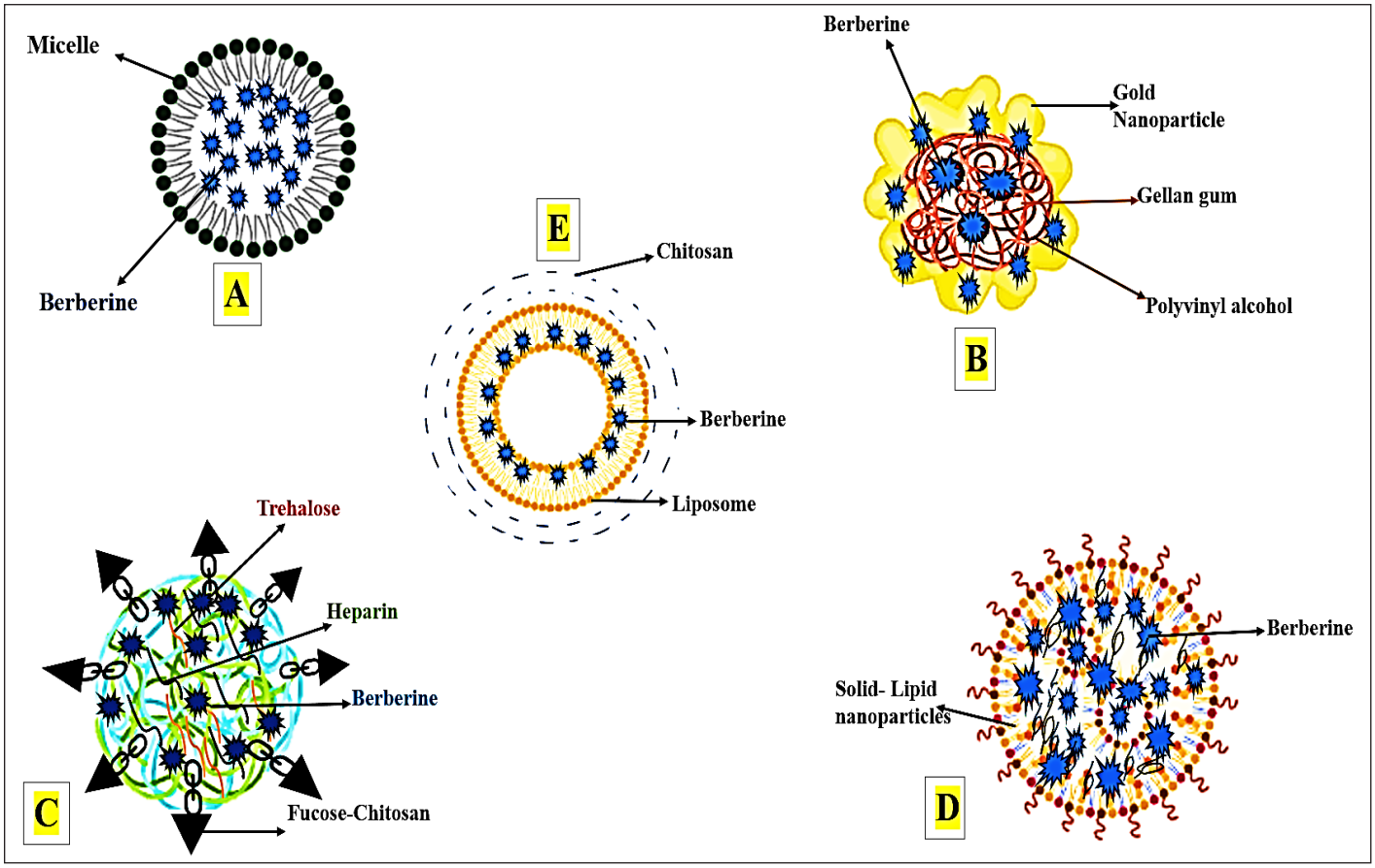

Figure 4. Various nanoparticles containing berberine: (A) Micelle nanoparticle with loaded berberine, (B) gold nanoparticle with berberine, (C) polymeric nanoparticles containing berberine, (D) solid-lipid nanoparticle (SLN) with loaded berberine, and (E) liposome nanoparticle containing berberine [35,44,46,51].

nanoparticles are divided into different types on the basis of their composition and structure which includes Liposomes, Solid lipid nanoparticles, nanostructured lipid careers, and micelles. Table 2 summaries the presentation of lipid-derived nanoparticles utilized as berberine transport [36].

GOLD AND SILVER-BASED NANOPARTICLES WITH BERBERINE

Gold nanoparticles were first manufactured by Michael Faraday in the nineteenth era, and holds a unique properties like the capacity to bind to aminoalkane and thiol groups, superficial plasmon resonance, and the possible for surface modification. These properties are useful for biomedical applications such as cancer therapy, contrast agents, drug delivery, radiosensitizers, and photochemical agents. Investigators have explored using gold nanoparticles in combination with supplementary particles like polyvinyl alcohol and gellan gum for the enhancement of berberine delivery. These nanoparticle-based formulations have confirmed high drug loading efficacy and controlled release possessions which make them promising drug delivery carriers. Further, the unique thermal and optical properties of gold (Au) nanoparticles, such as heat dissipation and surface plasmon resonance, have been

exploited for applications like photo-thermal therapy. In another approach by investigators, biologically modified gold particles have been used as careers for the targeted distribution of berberine to solid tumors. Researchers have attained high berberine at acidic pH (5.8) and 86% drug loading release of berberine, by assigning targeting ligands like folic acid and employing natural resources like tropical fruit peels [43–46].

Silver (Ag) nanoparticles possess some unique properties, like as thermal, optical, and high electric conduction, which make them valuable for innumerable applications, as an anti-bacterial agents, anticancer agents, ophthalmic sensors, and medical device coatings. Some researchers have explored the antibacterial activity of silver-based nanoparticles synthesized by means of the natural isoquinoline alkaloid "berberine". As Chandra *et al*. [46] investigated the synergistic effects of berberine-silver nanoparticles with antibiotics, which revealed their potential in combating antibiotic-resistant bacterial infections. One more investigation has been done by Tahan *et al*. [47] on the antibacterial activity of silver nanoparticles (AgNPs) against multidrug-resistant (MDR) bacterial strains. In their study, they synthesized AgNPs by means of Berberine and evaluated their efficiency against MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains. Biosynthesis of AgNPs has been confirmed using various characterization techniques including XRD, UV-Vis, DLS, FTIR, and zeta potential analysis. Disk diffusion agar and nominal inhibitory concentration tests revealed that the biosynthesized AgNPs proved powerful anti-bacterial activity against the tested MDR strains, inhibiting microbial growth at lower concentrations of AgNPs as compared to conventional antibiotics. Particularly, on combining AgNps with standard antibiotics, a synergetic effect was observed, as established by the checkerboard method. This synergistic action shows that AgNPs can boost the efficacy of present antibiotics against MDR bacterial strains [48]. These studies collectively highlight the promising role of berberine-based silver nanoparticles as substitute anti-microbial agents in varied biomedical applications.

They can also increase the anticancer effects of many medications. In a study by some investigator, they assessed the impact of silver nanoparticles on the feasibility and proliferation of squamous cell carcinoma-25(SSC-25) oral cancer cells, both alone and in a mixture with berberine. The results were found that while silver nanoparticles alone had an effect of anti-proliferative, this outcome was reduced in the presence of Berberine compound. Berberine stimulated the expression of the pro-proliferative Bcl-2 gene and upheld the capability of SCC-25 cancer cells [49]. This non-synergistic phenomenon was attributed to the force of electrostatic between the "+ve" charge of Berberine and the "-ve" charge of silver nanoparticles. Bhanumathi *et al.* [50] developed novel bio-genic silver nanoparticles as a drug delivery carrier for Berberine. Some *in-vitro* studies exhibited dose-dependent toxicity of berberine-loaded silver nanoparticles against MDA-MB-231 breast cancer cell lines and Michigan cancer foundation-7, and *in-vivo* studies confirmed their skill to suppress tumor growth [50,51].

CONCLUSION AND FUTURE SCOPES

This review revealed that although berberine (Brb) consumes many valuable belongings, but it faces certain confines in its dissolution, absorption, and bio distribution. Nanotechnology is proposed as a useful approach to overcome these limitations. Several studies have demonstrated improved pharmacological effects of Brb when it is encapsulated in different nanocarriers. The major findings were polymeric nanostructures made of alginate, dextran, and PLGA were used for drug delivery and controlled discharge of Berberine, exhibiting therapeutic effects against osteoarthritis, diabetes, and microbial infections. Lipid-built nanomaterial carriers, such as solid lipid nanoparticles, nanostructured lipid carriers, micelles, and liposomes, encapsulating Brb showed antidiabetic and antitumor activities. Combinations of Berberine with nanocarriers like dendrimers, gold nanoparticles (AuNPs), and silver nanoparticles were found to be useful in cancer therapy. AuNP-Brb conjugates were investigated for thermal treatment, and carbon dots berberine demonstrated bio-imaging capabilities. The following are some future scopes:

- By leading more wide investigation on the biodistribution, toxicity, and biochemicals of Berberine-loaded nanocarriers will ensure their scientific conversion.
- By the exploration of the potential of Brb-nanocarrier for targeted drug delivery to specific tissues or organs, we can improve therapeutic efficacy and reducing side effects.
- We can further investigate the synergetic properties of Berberine in grouping with another therapeutic nanocarriers for improved therapeutic consequences.
- Conduct clinical trials to assess the berberine-nanocarrier formulation efficacy and protection of auspicious in anthropoid subjects.

Therefore, in general, while nanotechnology has shown hopeful results in improving the therapeutic potential and delivery of berberine, further examination is necessary to interpret these nanoparticle carriers into clinical applications.

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AUTHOR CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All the sources of data provided in this manuscript have duly been referred in the references which are freely available in public domain.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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