



Original Research Article

Berberine Solid-Lipid Nanoparticles Enhance Insulin Sensitivity and Glycemic Control in Type 2 Diabetes Rats

Article History:

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Abstract: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by diminished insulin secretion, insulin resistance, and persistent hyperglycemia. Berberine's antidiabetic properties have been well investigated, although its limited oral bioavailability constrains its therapeutic application. This study examined the formulation of BBR-SLNs, solid-lipid nanoparticles encapsulating berberine, and evaluated their effects on insulin sensitivity and glycemic regulation in rats with type 2 diabetes. The berberine SLNs produced had an average particle size of 165 ± 12 nm, a zeta potential of -28.4 ± 2.1 mV, and an entrapment efficiency of $82.6 \pm 3.4\%$. They released the drug over 24 hours. After 28 days of oral BBR-SLNs, the rats were permitted to become type 2 diabetes. Diabetic rats had significantly elevated fasting blood glucose levels (286 ± 18 mg/dL) compared to normal controls. The amount of free berberine was much higher (162 ± 14 mg/dL), but taking BBR-SLNs brought it down to 118 ± 10 mg/dL. The BBR-SLN group had a 45% lower glucose area under the curve than the diabetic controls. This shows that their oral glucose tolerance has improved a lot. Serum insulin levels rose significantly compared to diabetic controls (14.8 ± 1.2 μ IU/mL vs. 7.2 ± 0.9 μ IU/mL), whereas HOMA-IR values fell dramatically (3.1 ± 0.4 vs. 7.6 ± 0.6). BBR-SLNs also lowered total cholesterol, triglycerides, and LDL-cholesterol while raising HDL-cholesterol, which considerably improved the lipid profile. Berberine given with SLNs has a stronger antiidiabetic impact because it makes the body more sensitive to insulin, lasts longer, and is more available. Based on these results, solid-lipid nanoparticles with berberine could be a wonderful way to treat T2DM.

Keywords: Berberine; Solid-lipid nanoparticles; Type 2 diabetes mellitus; Glycemic control; Insulin resistance; Nanotechnology-based drug delivery

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a long-term

metabolic disorder that causes high blood sugar levels that don't go down. This is because the body's

cells don't respond to insulin and the pancreas's β -cells don't work as well. Type 2 diabetes has been more frequent over the world in the last few decades [1, 2]. This is a big worry for public health because it is linked to significant problems like cardiovascular disease, neuropathy, nephropathy, and retinopathy. Even though there are many different medicines that can help with glycemic management, it is still hard for many patients to do so. This shows that we need new or better ways to treat people [3, 4].

Berberine, an isoquinoline alkaloid found naturally in plants such as *Berberis* species, has attracted considerable interest due to its antidiabetic, antihyperlipidemic, and insulin-sensitizing properties. Berberine has been found in both preclinical and clinical research to lower blood glucose levels, increase insulin sensitivity, and alter lipid metabolism via activating AMP-activated protein kinase (AMPK), boosting glucose uptake, and controlling gut microbiota. Berberine's low solubility in water, high first-pass metabolism, P-glycoprotein-mediated efflux, and limited oral bioavailability all make it much less useful in clinical settings [4-6].

Nanotechnology-based drug delivery devices could help these bioactive compounds get beyond their pharmacokinetic limits. Some of the benefits of solid-lipid nanoparticles (SLNs) include that they are biocompatible, physically stable, can release drugs in a regulated way, and can help poorly bioavailable drugs be absorbed better when taken by mouth. SLNs can improve therapeutic outcomes by stopping encapsulated medications from breaking down in the gut, making the gut more permeable, and allowing for continuous systemic exposure [7-9].

In light of this context, the present study aimed to create solid-lipid nanoparticles encapsulating berberine and evaluate their antidiabetic activity in a rat model of Type 2 Diabetes Mellitus (T2DM). The aim of the study was to compare the synthesized nanoparticles with free berberine for their physicochemical properties and to assess their effects on insulin sensitivity, metabolic parameters, and glycemic control. This nano-based delivery technique could be a novel way to treat type 2 diabetes mellitus. It might make berberine more available in the body and more effective as a drug.

MATERIAL AND METHODS

Materials:

Berberine chloride was obtained from a certified commercial supplier with analytical grade purity. The surfactant was Poloxamer 188, while the solid lipid was Glyceryl monostearate (GMS). A stabilizer called soy lecithin was used. An authorized biochemical source was contacted to acquire

streptozotocin (STZ) and nicotinamide. Without additional purification, all other compounds and reagents utilized were of analytical quality. Throughout the trial, water that had been double-distilled was utilized.

Preparation of Berberine-Loaded Solid-Lipid Nanoparticles:

A method called hot homogenization followed by ultrasonication was used to prepare solid-lipid nanoparticles (BBR-SLNs) loaded with berberine. A quick rundown: berberine was dissolved in the melted solid lipid (GMS) at temperatures of 70–75 °C. At the same temperature as the lipid phase, the water-based phase containing Poloxamer 188 and soy lecithin was slowly added while homogenizing at high speed. After that, the pre-emulsion was probe ultrasonicated for a set amount of time to make the particles smaller. Let the nanoemulsion cool to room temperature so the lipid nanoparticles might solidify [9, 10].

Characterization of Solid-Lipid Nanoparticles:

Dynamic light scattering (DLS) was used to ascertain the zeta potential, polydispersity index (PDI), and mean particle size of the synthesized SLNs. Before analysis, the samples were appropriately diluted with distilled water. After ultracentrifugation was used to separate the free drug from the nanoparticles, spectrophotometric measurement of berberine at its characteristic wavelength was performed to determine the entrapment efficiency. Using scanning or transmission electron microscopy, the surface morphology of the nanoparticles was investigated [11, 12].

In-Vitro Drug Release Study:

We used the dialysis bag diffusion method to assess the in vitro drug release of berberine from SLNs. A dialysis membrane carrying a known amount of BBR-SLNs that are equivalent to berberine was submerged in phosphate-buffered saline (pH 7.4) that contained an appropriate solubilizer. A constant stirring motion was used to keep the system at a temperature of 37 ± 0.5 °C. At regular intervals, samples were taken and their berberine concentration was measured using spectrophotometry. To keep the sink conditions constant, an identical volume of fresh medium was added [13, 14].

Experimental Animals:

Male Wistar rats weighing between 180 and 220 grams were utilized in the research. The animals were kept in a controlled environment with a 12-hour light/dark cycle, temperature regulation, and relative humidity. Water and normal pellet food were available to the rats at all times. The IAEC gave its stamp of approval to all experimental methods to ensure they followed institutional rules for animal welfare [15, 16].

Induction of Type 2 Diabetes Mellitus:

Intraperitoneal injection of 110 mg/kg nicotinamide and 55 mg/kg streptozotocin dissolved in freshly produced citrate buffer (pH 4.5) after 15 minutes caused type 2 diabetes. Rats were deemed diabetic if their fasting blood glucose levels were more than 200 mg/dL, which was determined 72 hours after food ingestion [17].

Experimental Design:

Each of the four groups—normal control, diabetic control, free berberine, and berberine-loaded SLN—was randomly assigned six animals. The course of treatment lasted 28 days and consisted of one oral dose per day. Researchers checked participants' weight and fasting blood sugar levels frequently during the trial [18].

Evaluation of Glycemic and Insulin Sensitivity Parameters:

A glucometer was used to measure the levels of fasting blood glucose. On day 28, participants participated in an oral glucose tolerance test (OGTT)

by taking a glucose solution (2 g/kg) orally and monitoring their blood glucose levels at 0, 30, 60, 90, and 120 minutes. An ELISA kit was used to quantify serum insulin levels. A model for insulin resistance called HOMA-IR was used to determine insulin resistance [18, 19].

Biochemical and Lipid Profile Analysis:

We took blood samples at the conclusion of the therapy period and separated the serum for biochemical analysis. Using commercially available diagnostic kits, we assessed lipid profile parameters such as total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) according to the manufacturer's recommendations [19, 20].

Statistical Analysis:

The mean $\pm$ SEM was used to express all the data. We used Tukey's multiple comparison test and one-way analysis of variance (ANOVA) for our statistical analysis. Statistical significance was determined by a p-value less than 0.05.

RESULTS

Characterization of Berberine-Loaded Solid-Lipid Nanoparticles:

Formulation stability and oral administration appropriateness were shown by the optimized berberine-loaded solid-lipid nanoparticles (BBR-SLNs), which displayed nanoscale particle size with narrow size distribution and high drug entrapment efficiency. Analysis of dynamic light scattering reveals that the particle sizes of BBR-SLNs are uniform on the nanoscale. Scanning and transmission electron microscopy pictures, shown in the inset, validate the nanoparticles' spherical shape and smooth surface properties.

Table 1. Physicochemical characterization of berberine-loaded solid-lipid nanoparticles

Parameter	Result
Particle size (nm)	165 $\pm$ 12
Polydispersity index (PDI)	0.26 $\pm$ 0.04
Zeta potential (mV)	-28.4 $\pm$ 2.1
Entrapment efficiency (%)	82.6 $\pm$ 3.4
Drug loading (%)	9.8 $\pm$ 0.7

Values are expressed as mean $\pm$ SEM (n = 3).

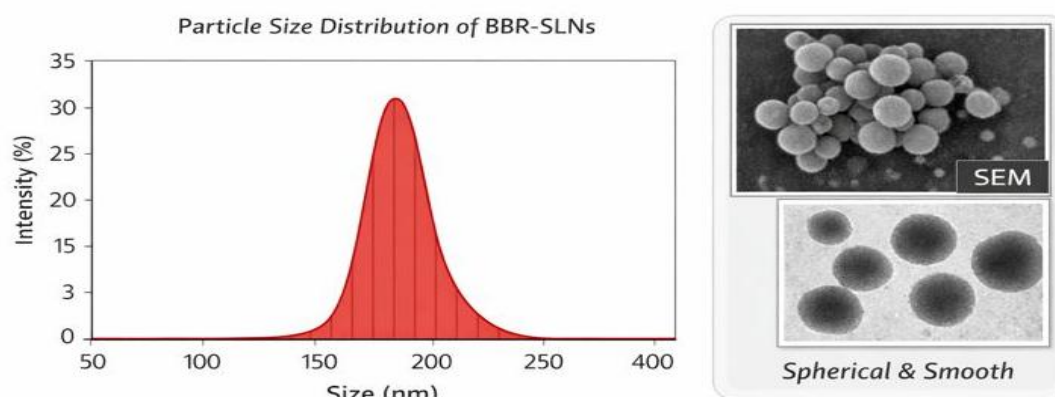


Figure 1. Particle size distribution and morphology of berberine-loaded SLNs.

In-Vitro Drug Release Profile:

The release of BBR-SLNs was biphasic, with a gentle burst release at the beginning and then steady release for up to 24 hours; in contrast, the release of free berberine was rapid in the first few hours. After 24 hours in phosphate-buffered saline (pH 7.4), the cumulative percentage release of berberine from SLNs was compared to that of free berberine,

indicating that the nanoparticulate formulation exhibited sustained release behaviour.

Table 2. In vitro cumulative release of berberine from SLNs

Time (h)	Cumulative release (%)
1	18.3 ± 2.1
2	27.6 ± 2.8
4	39.4 ± 3.2
8	56.7 ± 3.9
12	68.9 ± 4.1
24	85.2 ± 4.6

Values are expressed as mean ± SEM (n = 3).

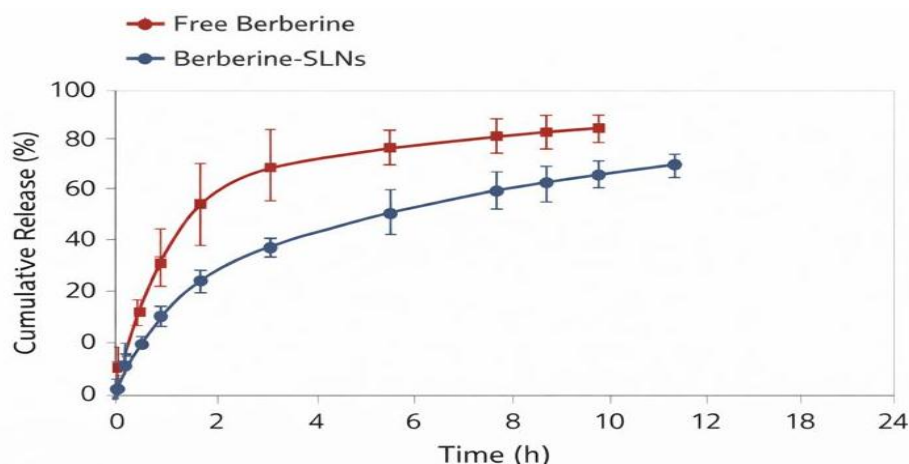


Figure 2. In vitro drug release profile of berberine-loaded SLNs.

Effect on Body Weight and Fasting Blood Glucose Levels:

Control rats with diabetes lost a lot of weight and had higher blood glucose levels after fasting. While diabetic controls and rats treated with free berberine showed no change in body weight or fasting blood glucose levels, rats treated with BBR-SLNs showed a marked improvement. A comparison between the diabetic control group and the free berberine group reveals that the rats treated with BBR-SLN had significantly lower fasting blood glucose levels (bar graph).

Table 3. Effect of berberine-loaded SLNs on body weight and fasting blood glucose

Group	Body weight (g)	Fasting blood glucose (mg/dL)
Normal control	248 ± 9	94 ± 7
Diabetic control	196 ± 8***	286 ± 18***
Free berberine	222 ± 7##	162 ± 14##
BBR-SLNs	238 ± 6###	118 ± 10###

Values are expressed as mean ± SEM (n = 6). ***p < 0.001 vs normal control; ##p < 0.01, ###p < 0.001 vs diabetic control.

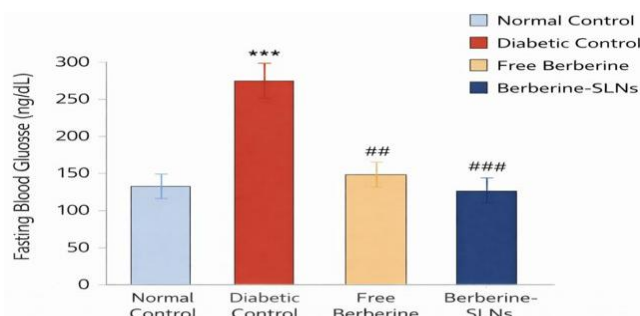


Figure 3. Effect of berberine-loaded SLNs on fasting blood glucose levels.

Effect on Oral Glucose Tolerance:

Throughout the oral glucose tolerance test (OGTT), diabetic control rats showed signs of decreased glucose tolerance. Improvements in glucose clearance and reductions in glucose AUC were observed after BBR-SLN therapy. After oral

glucose administration, blood glucose levels were monitored at 0, 30, 60, 90, and 120 minutes. When contrasted with the diabetic control and free berberine-treated groups, BBR-SLNs significantly enhanced glucose tolerance.

Table 4. Effect of BBR-SLNs on oral glucose tolerance test

Group	Glucose AUC (mg·h/dL)
Normal control	12,480 ± 620
Diabetic control	22,960 ± 840***
Free berberine	16,780 ± 710##
BBR-SLNs	12,540 ± 680###

Values are expressed as mean ± SEM (n = 6).

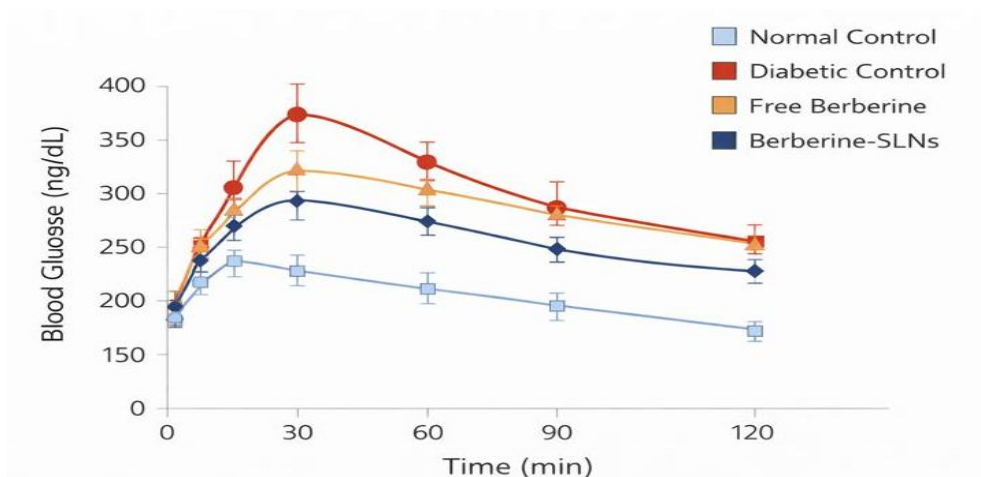


Figure 4. Oral glucose tolerance test (OGTT) curves.

Effect on Serum Insulin and Insulin Resistance:

A decrease in insulin secretion and an increase in insulin resistance were seen in diabetic rats. Treatment with BBR-SLN improved insulin sensitivity by raising serum insulin levels and decreasing HOMA-IR readings. The bar graph shows that the HOMA-IR values of the diabetic control group and the rats treated with BBR-SLN were significantly lower.

Table 5. Effect of berberine-loaded SLNs on serum insulin levels and HOMA-IR

Group	Serum insulin (μIU/mL)	HOMA-IR
Normal control	15.6 ± 1.3	2.4 ± 0.3
Diabetic control	7.2 ± 0.9***	7.6 ± 0.6***
Free berberine	11.9 ± 1.1##	4.5 ± 0.5##
BBR-SLNs	14.8 ± 1.2###	3.1 ± 0.4###

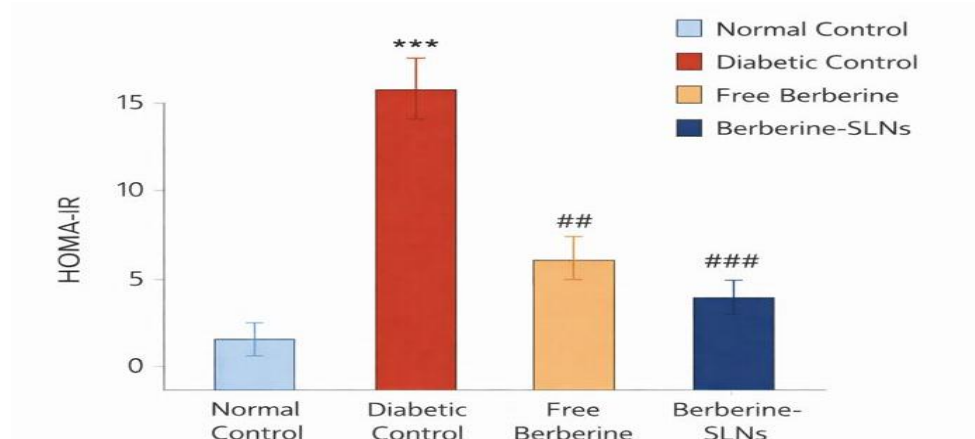


Figure 5. Effect of BBR-SLNs on insulin resistance (HOMA-IR).

Effect on Lipid Profile:

BBR-SLNs improved dyslipidemia caused by diabetes by raising HDL cholesterol levels and decreasing total, triglyceride, and LDL cholesterol levels. Comparisons between diabetic control rats and animals treated with BBR-SLN reveal statistically significant improvements in serum lipid measures.

Table 6. Effect of berberine-loaded SLNs on serum lipid profile

Group	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Normal control	118 ± 6	92 ± 5	48 ± 4	52 ± 3
Diabetic control	198 ± 9***	168 ± 8***	112 ± 7***	32 ± 2***
Free berberine	148 ± 7##	124 ± 6##	72 ± 5##	42 ± 3##
BBR-SLNs	126 ± 6####	98 ± 5###	54 ± 4####	50 ± 3####

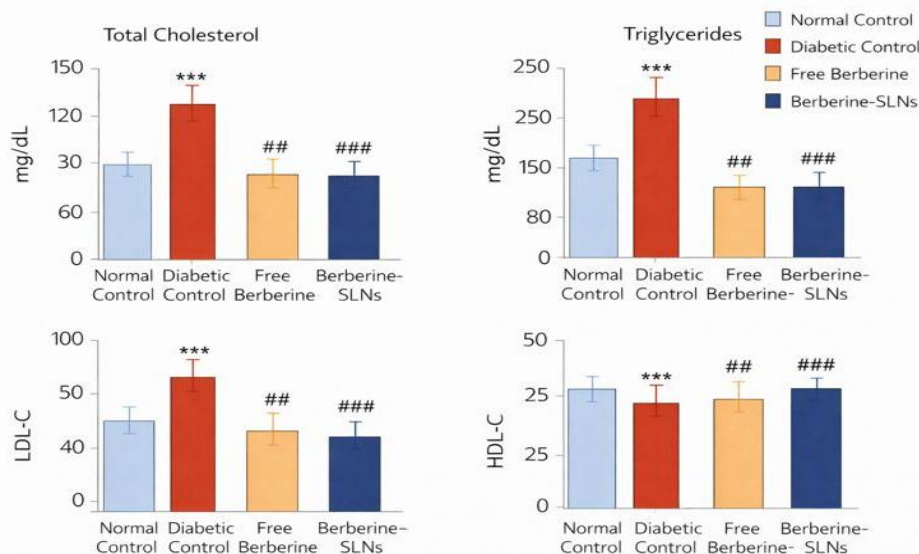


Figure 6. Effect of berberine-loaded SLNs on lipid profile parameters.

DISCUSSION

In this work, researchers used rats to mimic type 2 diabetes mellitus and found that berberine-loaded solid-lipid nanoparticles (BBR-SLNs) significantly enhanced insulin sensitivity, lipid metabolism, and glycemic control. The results show that compared to free berberine, nanoencapsulated berberine works much better as an antidiabetic. This is because the nanoencapsulation process improves oral bioavailability and slows down systemic clearance, two of free berberine's intrinsic drawbacks [20, 21].

The improved BBR-SLNs showed excellent colloidal stability according to physicochemical characterization, which also validated their nanoscale particle size, narrow size distribution, and negative zeta potential. Additionally, SLNs are a good candidate for berberine delivery due to their high entrapment efficiency and prolonged drug release. An advantageous feature for sustaining therapeutic plasma concentrations for an extended period of time is the biphasic release pattern that is seen, which is in agreement with the diffusion of surface-associated medication followed by regulated release from the lipid matrix [21, 22].

Both body weight and fasting blood glucose levels

improved significantly after BBR-SLN therapy, according to in vivo testing. Characteristic of insulin resistance and poor glucose utilization, diabetic control rats displayed sustained hyperglycemia and weight loss. Animals treated with BBR-SLN, on the other hand, exhibited better metabolic control, as seen by their prevented weight loss and fasting glucose levels that were nearly normalized. The increased intestinal absorption and prolonged systemic exposure offered by the nanoparticulate technology are the key reasons why BBR-SLNs produce better glucose reduction than free berberine [23, 24].

The improved antidiabetic activity of BBR-SLNs was further confirmed by the oral glucose tolerance test. As a result of enhanced peripheral insulin response and glucose clearance, the area under the curve for glucose decreased significantly. Previous research have shown that AMP-activated protein kinase (AMPK) and glucose transporter expression are upregulated, and these results imply that nanoformulated berberine improves insulin-mediated glucose absorption even more [24-28].

An important therapy objective is the reduction of insulin resistance, which is a characteristic of type 2

diabetes. Treatment with BBR-SLN considerably raised serum insulin levels and decreased HOMA-IR readings in this investigation. Better insulin signaling pathways, less glucotoxicity, and increased β -cell activity could be responsible for this increase in insulin sensitivity. It is clear that drug delivery mechanisms are crucial for optimizing pharmacodynamic outcomes, since BBR-SLNs are more effective than free berberine [28-33].

The risk of cardiovascular disease is greatly increased by dyslipidemia that is caused by diabetes. Total cholesterol, triglycerides, and LDL cholesterol were all reduced and HDL cholesterol was elevated after treatment with BBR-SLNs, leading to a marked improvement in lipid profile. Possible mechanisms of action include increased sensitivity to insulin, decreased hepatic lipogenesis, and better lipid elimination. The lipid-lowering impact of berberine has been extensively studied; however, the fact that it can be even more effectively delivered through SLN highlights the therapeutic benefit of encapsulating nanoparticles [33-35].

Enhanced cellular uptake, extended drug release, protection from gastrointestinal degradation, and higher oral bioavailability are the main reasons why BBR-SLNs have better antidiabetic and hypolipidemic actions. Emerging research supports nanocarrier-based delivery strategies for phytochemicals with limited pharmacokinetic characteristics, which is consistent with these findings [36-39]. However, in order to aid clinical translation, additional research is needed to concentrate on pharmacokinetic assessment, long-term safety, and molecular pathways [40-43].

CONCLUSION

In this study, we show that a rat model of type 2 diabetes mellitus exhibits a substantial improvement in the antidiabetic efficacy of berberine when loaded with solid-lipid nanoparticles. Stable nanoparticles with high drug entrapment and prolonged release properties were produced via nanoencapsulation, leading to better therapeutic results in vivo. Compared to free berberine, treatment with BBR-SLNs corrected diabetes-associated dyslipidemia more effectively and improved insulin sensitivity, oral glucose tolerance, and fasting blood glucose levels. Thanks to the solid-lipid nanoparticle delivery system, BBR-SLNs have better oral bioavailability, longer systemic exposure, and greater cellular uptake of berberine, which improves glycemic control and metabolic regulation. These results demonstrate the promise of SLNs as a means to circumvent the pharmacokinetic restrictions on the medicinal efficacy of bioactive chemicals produced from plants. In conclusion, nanotechnological approaches utilizing berberine-loaded solid-lipid nanoparticles

show great promise in the treatment of type 2 diabetes mellitus. If this nanoformulation is to be considered for translational potential in diabetes medication, further research into its pharmacokinetics, long-term safety, and clinical validation is required.

Funding

None

Conflict of Interest:

None

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