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Evaluation of the Therapeutic Effect of Curcumin Phytosomes on Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Diabetes Mellitus (DM) has been described as a metabolic disorder that results in chronic high blood sugar level. However, it is difficult to evaluate the effectiveness of natural products such as curcumin on diabetes and its complications, due to the low intestinal bioavailability and the low systemic absorption rate. The study evaluated the efficacy of the phytosome in its ability to enhance the absorption of curcumin and thus its effect on blood sugar level and lipid profile in streptozotocin (STZ)-nicotinamide-induced diabetic rats. Curcumin and combination of curcumin and phytosomes (Cur-P) were administered orally at 150 and 250 mg/kg, respectively, to streptozotocin (STZ)-nicotinamide induced DM rats. Metformin was used as a positive control. The blood glucose level and lipid profile were monitored for 21 days. The results showed a clear decline in the levels of blood glucose, cholesterol, triglycerides, and the low-density lipoprotein (LDL), cholesterol, in addition to a significant rise in the high-density lipoprotein (HDL). The hypoglycemic and hypolipidemic effects caused by treatment with Cur-P were higher than those treated with Curcumin alone at the same dose, indicating that the phytosomes enhances the potential of absorption and bioavailability of Curcumin. The findings suggest that Cur-P may have a potential therapeutic effect on diabetes through enhancing the potential of absorption and bioavailability of curcumin.

Keywords: Diabetes mellitus, Curcumin, phytosomes, hypolipidemic, hypoglycemic.

Introduction

Diabetes can lead to a different number of serious complications such as obesity, dyslipidemia, kidney failure, vision loss, nerve damage and uterine fibroids.[1] It increases the risk of cardiovascular disease by three folds due to the elevation in triglyceride rich remnant lipoproteins and small dense LDL and decrease in HDL cholesterol concentrations.[2,3] The production of reactive oxygen species (ROS) in diabetics leads to several complications including advanced glycation end products (AGEs) formation, expression of their receptors, activation of isoforms of protein kinase C and pathway flux of polyol, the pathway of hexosamine and decreasing the protective role of the antioxidant capacities.[4,5] The World Health Organization has predicted an increase in the number of adults with diabetes to reach 439 million by the end of 2030, from 285 million in 2010.[6] Therefore, it is important to discover antidiabetic drugs in order to decrease the risk of cardiovascular disease.[7]

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A number of studies indicate the efficacy of phytochemicals as an alternative to treat diabetes such as, hydroxycitric Acid, vanillic acid, syringic acid, chlorogenic acid, quercetin, apigenin, hesperidin, and piperine.[8-12] When dealing with all types of plant extracts as antimicrobial, antidiabetic and anticancer, the defining of optimal conditions for treatments is necessary for achieving maximal effectiveness of treatment.[10,11,13-27]

One of the polyphenolic compounds, curcumin, found in the roots of turmeric (Curcuma longa), has major biological and pharmacological roles, including as antioxidant, anti-coagulant and anti-inflammatory.[28,29] Unfortunately, Curcumin is poorly absorbed and rapidly metabolized.[30] Recently, studies in nanotechnology have advanced in different fields such as : data storage,[31] cosmetics,[32] antimicrobial agents[33] and anticancer.[16] On the other hand, Phytosomes is a Nano-vehicle cell-like structure, it consider as a complex between phytochemical molecules and natural phospholipid.[34] Beside that Phytosomes is an advanced form of conventional herbal which can avail safe remedy. It also increases the absorption and the bioavailability of loaded phytochemical, which has been demonstrated by pharmacokinetics studies and pharmacodynamics experiments in animals and in humans.[35] Nevertheless, the role of Curcumin -phytosomes (Cur-P) complex on hyperlipidemic and hyperglycemic condition induced by diabetic condition has never been evaluated before. Therefore, in this study, the hypolidemic and hypoglycemic effects of the Cur-P complex have been investigated in Streptozotocin - induced diabetic rats.

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Materials and Methods

Drugs and Chemicals

Curcumin (BioEnergyTech® /USA, MW,368.38 g/mole). Streptozotocin (Sigma-Aldrich Chemie. GmbH, Germany). Nicotinamide (DUCHEFA BIOCHEMIE B. V / Netherlands). Metformin (Hikma Company /Jordan). Phosphatidylcholine (Soybean Lecithin Cargill, Belgium E 322. MW, 677.93 g /mole). Commercial diagnostic kits of BM100/BM200 analyzers (BioMaxima S.A., ul Vetterow 5, 20-277 Lublin, Poland) were purchased in good state.

Preparation of Curcumin-Phytosome Complex (Cur-P)

Preparation of Cur-P was achieved by using procedure of Awasthi[36] In this procedure, 1 mole of phosphatidylcholine (Soybean lecithin) mixed with 1 mole of Curcumin in an aprotic solvent like acetone. Complex compounds were isolated upon completion of the solubilization through removing the solvent with vacuation and precipitating it with n-hexane.[36]

Transmission electron microscopy (TEM)

A transmission electron microscope (TEM, model: FEI Morgagni 268 100kV TEM) was used to monitor phospholipid complex samples. Samples were dissolved in suitable volume of distilled water in a ratio of 1:20 with 5 minutes sonication. A drop of the mixture was placed over a specific copper grid coated with carbon. After drying, the grid-loaded thin lipid film was stained with 2% uranic acid, then the view was examined using TEM then their picture was taken.

In vivo study

All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee (IAEC). Experiments were performed in the Animals House / Department of Biological Sciences / Mutah University. All animal experiments were conducted according to the guidelines of European Commission Directive 86/609/EEC for laboratory animal care and use.

Median lethal dose (LD_{50}) and acute toxicity

To define the median lethal dose (LD_{50}) and acute toxicity of Curcumin, Curcumin was administered to rats orally by a multi-dose process.[37] An aqueous solution of Curcumin was given to each group (six rats) of the rats in a dose of 250, 500, 1000, and 2000 mg/kg While one of these groups was given only normal saline as a control. Prior to dosing, the rats were fasted for three hours. The mortality rate of rats were monitored for 48 hours with following-up and monitoring the overall influences of dullness, breathing, tremors, standing, and walking.

Chronic toxicity

To assess chronic toxicity, urea levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and blood creatinine were automatically assessed three weeks after receiving the highest dose of Curcumin (250 mg / kg) using commercially available diagnostic kits for BM100/BM200 analyzers (BioMaxima SA, ul Vetterow 5, 20-277 Lublin, Poland). For comparison purpose, the control group received only normal saline. General effects such as confusion, breathing, response to stimuli, tremors, standing, and walking were monitored.

Induction of diabetes

Male Wistar rats, about ten weeks old, weighing 220-250 g, were bred at Animal House, University of Jordan. The animals were housed in plastic cages in a room whose temperature and humidity were set 24 ± 2°C and 45-64%, respectively, in addition to 12-hour day and night cycle. During the experiments, a balanced commercial diet was provided to the animals.

Animals preparation

The rats were divided into a control and experimental groups five days before the start of the experiment, so that the weights of all rats were carefully adjusted. On the day of the injection, all rats fasted for eight hours prior to the STZ injection while leaving water available as usual.

Induction of diabetes with STZ and nicotinamide

In this experiment, a method of simultaneous STZ injection with nicotinamide was used. Nicotinamide (110 mg/mL) was dissolved in 0.9% normal saline. STZ dissolved in the cold fresh 0.05 M sodium citrate buffer (pH 4.5), immediately before injection (for each rat, 50 mg STZ was placed into an Eppendorf tube). The rats were injected with 110 mg / kg of nicotinamide and after 15 minutes, they were injected with 50 mg / kg of STZ. After the STZ injection, the rats were returned to their cages, given 5% D-glucose for 4 days as well as providing them with routine food and drinking water. After four days, the fasted rats were checked for diabetes. Control animals were only treated with an equal volume of citrate solution (pH 4.5). A rat was considered to have diabetes if the blood sugar was greater than 200 mg / dL. This T2DM system was stimulated in rats, which results from insufficient insulin, but is not insulin resistant, is stable and moderately high in blood sugar and is correlated with a loss of 60% of the function of β-cells, thus nicotinamide is used to protect β-cells from STZ.[38,39]

Animal experimental design

The rats were divided into seven groups of 6: group 1, healthy control rats (HCR); group 2, diabetic control rats (DCR); group 3, diabetic rats administered orally metformin at a dose of 100 mg/kg (MT100); group 4, diabetic rats administered orally only Curcumin at a dose of 150 mg/kg (Cur150); group 5, diabetic rats administered orally single Curcumin at a dose of 250 mg/kg (Cur250); group 6, diabetic rats administered orally Curcumin phytosome complex at a dose of 150 mg/kg (Cur-P150); group 7, diabetic rats were administered orally cur-P complex at a dose of 250 mg/kg. Daily dosages were given orally by an intragastric tube for 21 days. Fasting blood glucose, cholesterol, triglyceride, LDL, and HDL were estimated on days: 0, 7, 14, and 21 of the experiment. Blood specimens were collected by retro-orbital plexus method.[40] The day the STZ was injected was counted as day 0 of the experiment.

Automated biochemical analysis

Collected blood specimens were allowed to completely clot for 30 minutes at room temperature. To yield serum, clotted blood specimens were centrifuged for 15 minutes at 3500 rpm. Depending on the principle of colorimetric estimation methods,[41] obtained specimens were collected in Hitachi cups to estimate automatedly total serum glucose, cholesterol, triglycerides, and HDL level, using commercial diagnostic kits of BM100/BM200 analyzers (BioMaxima S.A., ul Vetterow 5, 20-277 Lublin, Poland). LDL cholesterol was calculated using the following equation:[42] LDL = Total cholesterol − (HDL + Trig/5). BioMaxima Quality Control (QC) Protocol was applied to ensure the accuracy of the results of the automated analyzers.

Statistical analysis

Statistical analyzes were performed using SPSS version 26. ± SEM was considered as standard error of the mean. An ANOVA test followed by Tukey's test was used. The significance level of differences between and within groups was considered at $p < 0.05$. The partial eta-square was figured to set the effect of volume, so that the effect of 0.01, 0.06 and 0.14 were considered small, medium and large, respectively. Data were normally distributed and homogenized.

Results and Discussion

Transmission electron microscope (TEM)

The shapes obtained with TEM showed the formation of discrete vesicular structures, which appear as incomplete spheres (Figure 1). When dispersed in the water by shaking slightly, the phytosomes arranged itself orderly in response to surface tension. In addition, the aggregation between vesicles was observed in single-particle shape, forming irregular large sized particles. TEM pictures appear as discretely distributed phytosomes.

Lethal Dose (LD_{50}) and Acute Toxicity An acute toxicity study showed that Curcumin did not cause mortality in any group of rats After 48 hours (Table 1). Thus, the LD_{50} of curcumin was more than 2000 mg / kg. corresponding with the finding of Sharma et al (2007),

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which indicated that the high concentrations of Curcumin are well tolerated.[43]

LD_{50} = higher dose ─ Σ (a x b)/ n where n = No. of animals in each group

LD_{50} = 2000─ 0 = 2000 mg / kg; ED_{50} = LD_{50} / 10 = 2000 / 10 = 200mg / kg.

Chronic toxicity

The chronic toxicity study showed that Curcumin caused no change in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and creatinine level when were orally administered with 250 mg/kg of Curcumin for three weeks compared with the control group (Table 2). Furthermore, during the chronic study, administration of Curcumin at a dose of 250 mg/kg did not affect the dullness, breathing, tremors, standing, walking, and response to stimuli.

Antihyperglycemic effects:

At the end of the experiment, the diabetic control rats (DCR) group showed that the level of fasting blood glucose recorded a significant increase in results ($p<0.001$), while oral administration of single Curcumin and Cur-P complex at 150 and 250 mg/kg to diabetic rats significantly reversed these biochemical changes ($p<0.001$). Glycemic results in healthy control rats were within normal range from day 0 to day 21 (Table 3). The results showed that Cur-P complex at 250 mg/kg had a better antihyperglycemic effect than Cur-P complex at 150 mg/kg, single Curcumin at 250 mg/kg, and single Curcumin at 150 mg/kg respectively. As expected, metformin at 100 mg/kg showed the most antihyperglycemic effect (Figure 2). DM is an abnormal dysfunction that results in chronic hyperglycemia and hamper lipid metabolism process.[44]

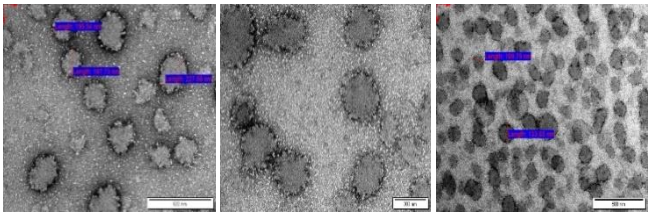

Figure 1: Transmission electron microscopes (TEM) photographs of phytosomes

Table 1: Determination of Curcumin acute toxicity

Group	Dose (mg/kg)	No. of animals	Dose Difference(a)	rats died(b)	Mean	(a x b)
1	N.S	6	0	0	0	0
2	250	6	0	0	0	0
3	500	6	250	0	0	0
4	1000	6	500	0	0	0
5	2000	6	1000	0	0	0

Table 2: The effects of Curcumin in serum ALT, AST, Creatinine, and Urea level

	ALT (U/l)		AST (U/l)		Creatinine (mg/*dL*)		Urea (mg/*dL*)	
	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental
Average value	76.5	71.7	107.7	164.7	0.81	0.82	35.8	44.5
Max. value	95	92.4	123.3	187.3	0.92	0.92	45.5	51.4
Min. value	68.1	63.0	88	141.0	0.71	0.76	31.3	34.7

Cholesterol and triglycerides

The effects of different doses of Cur, Cur-P complex, and metformin on total cholesterol level were measured in different groups. The results showed that, the DCR group exhibited a significant increase in the level of blood cholesterol ($p<0.001$), while the oral administration of curcumin and Cur-P complex at 150 and 250 mg/kg in diabetic rats significantly reversed all of these changes ($p<0.001$). At the same time, serum cholesterol level in HCR group remained unchanged from day zero to day 21 (Table 4). The results showed that Cur-P complex at 250 mg/kg caused more decrease in blood cholesterol level than using Cur-P complex at 150 mg/kg, curcumin at 150 and 250 mg/kg and even more than metformin at 100 mg/kg (Figure 3).

The effect of different treatments on serum triglyceride levels showed that DCR group showed an increase in the level of blood triglycerides, while the Oral administration of Cur-P complex at 150 and 250 mg/kg in diabetic rats significantly reversed all of these changes ($p<0.001$).

At the same time, serum triglyceride level in HCR group continued stable from day zero to day 21 (Table 5).

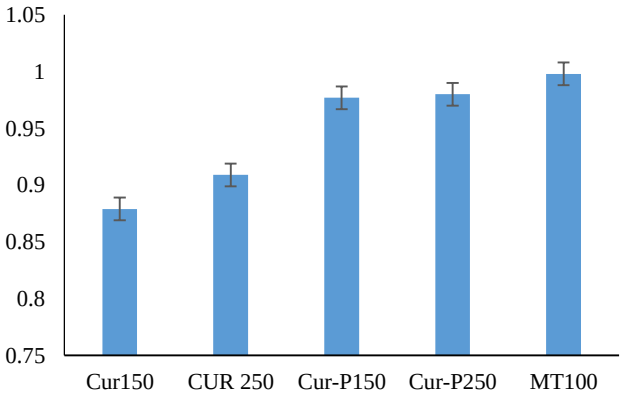

Figure 2: Effect size of different treatment on fasting blood glucose level of different experimental groups. Partial eta square (η^2) scale: 0.01= small effect, 0.06= medium effect, 0.14= large effect.

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Cur-P complex at 250 mg/kg caused a decrease in blood triglycerides level better than using each of the following; 150 mg/kg of Cur-P, 150 and 250 mg/kg single curcumin besides metformin at 100 mg/kg (Figure 4). Hyperlipidemia is a known complication of diabetes, which is accompanied by high levels of cholesterol and triglycerides, beside to changes in the composition of lipoprotein.[45] It appears that reducing blood lipid levels using dietary or drug medication methods is dependent on the reduced risk of vascular disease and correlated complications.[41] Triglycerides are formed in the liver as a result of their stimulation by STZ-induced diabetes so that it is subsequently discharged through the blood in the form of lipoproteins.[46] In this study, an insulin-deficient, not insulin-resistant, T2DM model was induced. The lipoprotein lipase (LPL), a pioneering enzyme in the elimination and degradation of triglycerides from the circulatory system, is diluted due to insulin deficiency induced by STZ.[47] In this study, we induced a model of insulin-deficient, but not insulin resistant T2DM, the lipoprotein lipase (LPL), a key enzyme in the removal and degradation of triglycerides from circulation, is mitigated by insulin deficiency which induced by STZ.[47] Moreover, previous studies demonstrated that STZ causes diabetes in animal models by destroying pancreatic cells through the production of nitric oxide (NO) and reactive oxygen species (ROS).[48] Many studies stated that Curcumin could improve the efflux of cholesterol through the PPARγ-LXRABCA1 pathway. Curcumin activates PPARγ, which drives the stimulation of the ligand X receptor (LXR α) (a further family of transcription factors that have a role in the homeostasis of cholesterol and fatty acids) that results in ABCA1 stimulation.[49-51]

High density lipoprotein (HDL)

The results showed that treatment with different doses of curcumin single, Cur-P and metformin significantly decreased HDL levels in the blood of the DCR group. Oral administration of single curcumin and Cur-P at 150 and 250 mg /kg in diabetic rats significantly reversed all of these low values ($p < 0.001$), while Metformin at 100 mg/kg, had no significant effect. HDL cholesterol results in the HCR group remained stable (Table 6) over the duration of the experiment (0 to 21 days).

The effects of different treatments on the different experimental groups recorded that Cur-P complex at 250 mg/kg showed a better increase in HDL in the blood than using 150 mg/kg Cur-P, single curcumin at 150 and 250 mg/kg and metformin at 100 mg/kg (Figure 5). All this promotes the efflux of cholesterol to the liver and intestines. In another way, curcumin modulates caveolin-1 which synthesizes the cholesterol transporter complex through the cell membrane. Caveolin-1 connects with free cholesterol and transmits extra cholesterol into HDL particles[52]. In the liver, *β*-hydroxy-*β*-methylglutamyl coenzyme A (HMG-CoA) reductase catalyzes the biosynthesis of cholesterol, and its activity correlates with the synthesis rate of tissue cholesterol. It was reported that Curcumin is in charge of relieving the enzymatic activity of HMG-CoA reductase.[53]

Low density lipoprotein (LDL)

The effects of different doses of single curcumin and Cur-P on serum HDL compared with metformin were measured (Table 7). The results showed a significant increase in the level of LDL in the blood of the DCR group. While, the oral administration of curcumin and Cur-P in diabetic rats at doses of 150 and 250 mg/kg led to significant decreases in all these values ($P < 0.001$), while MT100 group showed a significant increase in the blood LDL level ($P < 0.01$).

Low density lipoprotein (LDL)

The effects of different doses of single curcumin and Cur-P on serum HDL compared with metformin were measured (Table 7). The results showed a significant increase in the level of LDL in the blood of the DCR group. While, the oral administration of curcumin and Cur-P in diabetic rats at doses of 150 and 250 mg/kg led to significant decreases in all these values ($P < 0.001$), while MT100 group showed a significant increase in the blood LDL level ($P < 0.01$). Results of LDL blood levels in HCR were within the normal range at all times of the experiment (0 to 21 days). The effect of the different treatment showed that using Cur-P compound at 250 mg/kg let to higher increase in serum LDL level than 150 mg/kg of Cur-P, 150 and 250 mg/kg single curcumin as well as metformin at 100 mg/Kg (Figure 6).

Table 3: Effects of different treatments on fasting blood glucose levels (mg/*dL*) in different experimental groups.

	Treatment	Day 0	Day 7	Day 14	Day 21
1	HCR	99.39 ± 0.58	100.66 ± 0.68	98.61 ± 1.55	97.92 ± 1.29
2	DCR	213.02 ± 1.63 [a]	223.37 ± 1.40 [a]	245.26 ± 7.20 [a]	242.12 ± 0.92 [a]
3	MT100	239.62 ± 0.50 [a]	206.01 ± 0.78 [a]	159.85 ± 0.53 [a]	113.91 ± 1.70 [a]
4	Cur150	231.88 ± 2.22 [a]	223.74 ± 1.53(N.S)	209.68 ± 3.87 [a]	191.63 ± 1.86 [a]
5	Cur250	228.38 ± 1.84 [a]	221.25 ± 3.40(N.S)	201.54 ± 2.78 [a]	183.08 ± 1.53 [a]
6	Cur-P150	230.55 ± 1.31 [a]	222.74 ± 1.98(N.S)	199.63 ± 0.99 [a]	177.30 ± 0.79 [a]
7	Cur-P250	235.15 ± 1.55 [a]	224.71 ± 1.85(N.S)	194.80 ± 2.23 [a]	164.69 ± 1.89 [a]

Values are mean ± SEM; n = 6 in each group; Groups 3-7 were compared with group 2, and group 2 was compared with group 1. Values of significance[a] = $p<0.001$, [b] = $p < 0.01$, [c] = $p < 0.05$

Table 4: Effects of different treatments on serum cholesterol levels (mg/*dL*) in different experimental groups

	Treatment	Day 0	Day 7	Day 14	Day 21
1	HCR	106.10 ± 1.58	105.49 ± 1.48	104.12 ± 0.40	102.45 ± 0.41
2	DCR	117.62 ± 0.74 [a]	117.49 ± 0.41 [a]	118.83 ± 0.74 [a]	120.35 ± 0.45 [a]
3	MT100	105.38 ± 3.10 [a]	105.55 ± 3.49 [a]	106.51 ± 2.95 [a]	107.06 ± 2.25 [a]
4	Cur150	110.24 ± 0.77 [c]	110.60 ± 0.21 [c]	103.79 ± 0.42 [a]	94.66 ± 1.24 [a]
5	Cur250	113.20 ± 0.45(N.S)	111.58 ± 0.43(N.S)	109.05 ± 0.39 [a]	107.12 ± 0.31 [a]
6	Cur-P150	114.38 ± 0.49(N.S)	111.90 ± 0.10(N.S)	102.70 ± 0.82 [a]	94.36 ± 1.37 [a]
7	Cur-P250	117.91 ± 0.44(N.S)	113.05 ± 0.34(N.S)	104.35 ± 0.47 [a]	95.93 ± 1.36 [a]

Values are mean ± SEM; n = 6 in each group; Groups 3-7 were compared with group 2, and group 2 was compared with group 1. Values of significance [a] = $p < 0.001$, [b] = $p < 0.01$, [c] = $p < 0.05$

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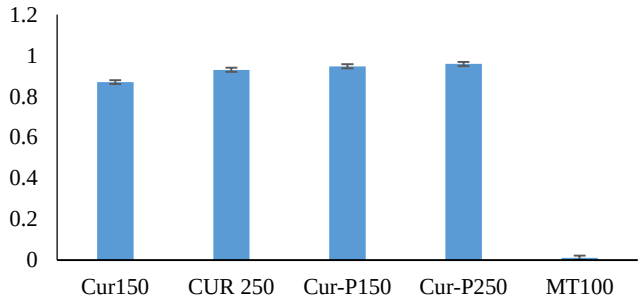

Figure 3: Effect size of different treatments on serum cholesterol levels of different experimental groups. Partial eta square (η^2) scale: 0.01 = small effect, 0.06 = medium effect, and 0.14 = large effect.

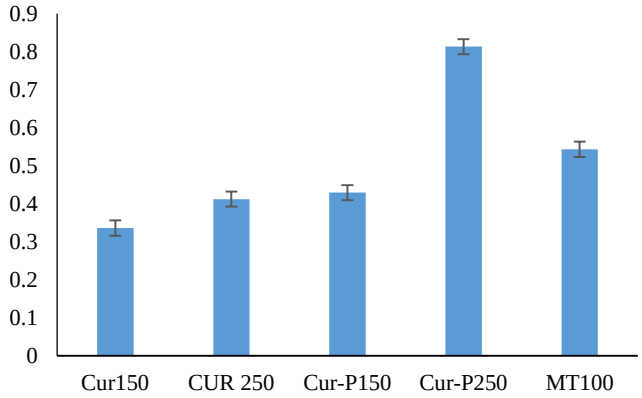

Figure 4: Effect size of different treatments on serum Triglyceride levels of different experimental groups. Partial eta square (η^2) scale: 0.01= small effect, 0.06= medium effect, and 0.14= large effect.

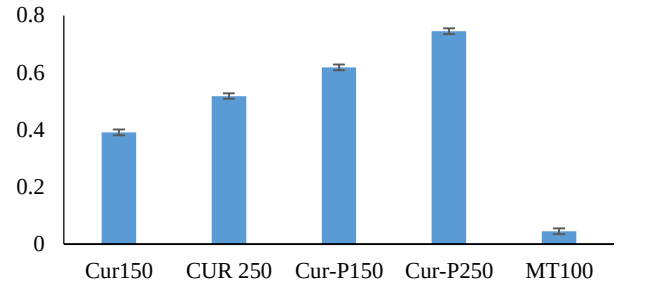

Figure 5: Effect size of different treatments on serum HDL levels in different experimental groups. Partial eta square (η^2) scale: 0.01= small effect, 0.06 = medium effect, and 0.14 = large effect.

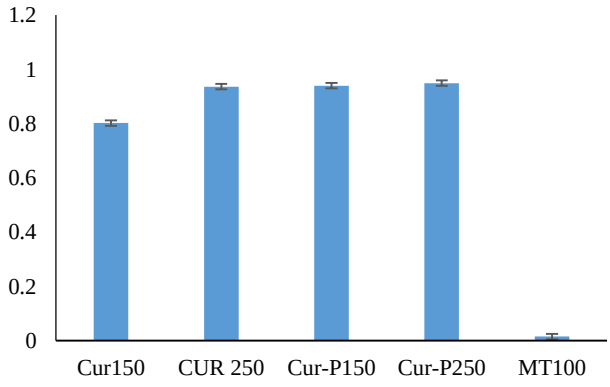

Figure 6 Effect size of different treatments on serum LDL levels in different experimental groups. Partial eta square (η^2) scale: 0.01= small effect, 0.06 = medium effect, and 0.14 = large effect.

Table 5: Effects of different treatments on serum triglyceride levels (mg/*dL*) in different experimental groups

	Treatment	Day 0	Day 7	Day 14	Day 21
1	CR	63.66 ± 0.41	62.14 ± 0.47	61.82 ± 0.22	70.26 ± 0.15
2	DCR	66.29 ± 2.78(N.S)	69.11 ± 3.74(N.S)	69.74 ± 3.76(N.S)	70.26 ± 3.78(N.S)
3	DCMT	71.60 ± 0.83(N.S)	69.62 ± 0.66(N.S)	70.49 ± 0.95(N.S)	71.40 ± 1.22(N.S)
4	CUR150	63.81 ± 0.67(N.S)	62.73 ± 0.84(N.S)	60.16 ± 1.32(N.S)	57.63 ± 1.77 [b]
5	CUR250	66.32 ± 0.45(N.S)	64.78 ± 0.94(N.S)	64.56 ± 0.31(N.S)	63.83 ± 0.33 [b]
6	P.CUR150	64.31 ± 0.25(N.S)	64.55 ± 0.33(N.S)	62.89 ± 0.84 [c]	61.41 ± 0.95 [a]
7	PCUR250	68.55 ± 0.32(N.S)	67.70 ± 0.69(N.S)	63.00 ± 0.75 [c]	56.83 ± 1.68 [a]

-Values are mean ± SEM; n = 6 in each group; Groups 3-7 were compared with group 2, and group 2 was compared with group 1. Values of significance [a] = $p < 0.001$, [b] = $p < 0.01$, [c] = $p < 0.05$.

Table 6: Effects of different treatments on serum HDL levels (mg/*dL*) in different experimental groups

	Treatment	Day 0	Day 7	Day 14	Day 21
1	HCR	34.62 ± 0.44	35.26 ± 0.83	42.87 ± 0.51	48.79 ± 0.23
2	DCR	28.09 ± 0.28 [a]	27.29 ± 0.41 [a]	26.75 ± 0.42 [a]	26.25 ± 0.37 [a]
3	MT100	26.65 ± 0.25(N.S)	26.51 ± 0.17(N.S)	25.68 ± 0.21(N.S)	24.85 ± 0.45(N.S)
4	Cur150	45.06 ± 0.33 [a]	45.20 ± 0.39 [a]	46.08 ± 0.27 [a]	46.81 ± 0.19 [a]
5	Cur250	45.95 ± 0.55 [a]	46.69 ± 0.37 [a]	47.41 ± 0.33 [a]	48.17 ± 0.58 [a]
6	Cur-P150	50.47 ± 0.20 [a]	50.40 ± 0.27 [a]	51.69 ± 0.39 [a]	52.83 ± 0.46 [a]
7	Cur-P250	53.13 ± 0.11 [a]	53.85 ± 0.14 [a]	57.05 ± 0084 [a]	60.25 ± 1.19 [a]

Values are mean ± SEM; n = 6 in each group; Groups 3-7 were compared with group 2, and group 2 was compared with group 1. Values of significance [a] = $p < 0.001$, [b] = $p < 0.01$, [c] = $p < 0.05$.

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Table 7: Effects of different treatments on serum LDL levels (mg*/dL*) in different experimental groups

	Treatment	Day 0	Day 7	Day 14	Day 21
1	HCR	58.53 ± 1.89	58.32 ± 1.09	48.89 ± 0.88	41.40 ± 0.51
2	DCR	76.73 ± 0.53 [a]	76.88 ± 0.88 [a]	77.65 ± 1.13 [a]	79.55 ± 0.94 [a]
3	MT100	66.33 ± 3.80 [b]	67.34 ± 4.26 [b]	68.20 ± 3.53 [b]	69.61 ± 2.96 [b]
4	Cur150	52.41 ± 0.64 [a]	52.85 ± 0.64 [a]	45.68 ± 0.33 [a]	36.32 ± 0.98 [a]
5	Cur250	53.98 ± 0.59 [a]	51.93 ± 0.42 [a]	48.72 ± 0.37 [a]	46.68 ± 0.94 [a]
6	Cur-P150	51.04 ± 0.52 [a]	48.58 ± 0.31 [a]	38.43 ± 0.96 [a]	29.24 ± 1.67 [a]
7	Cur-P250	51.07 ± 0.48 [a]	45.65 ± 0.35 [a]	34.70 ± 1.09 [a]	24.32 ± 1.96 [a]

Values are mean ± SEM; n = 6 in each group; Groups 3-7 were compared with group 2, and group 2 was compared with group 1. Values of significance a = $p < 0.001$, b = $p < 0.01$, c = $p < 0.05$.

One of the therapeutic approaches proposed for the diabetes is based on the retardation of lipid and glucose levels. The results of this study revealed that Curcumin mediates hypoglycemic and hypolidemic effect in STZ-induced diabetes rats. The result also indicated that phytosomes increases the absorption and the bioavailability of Curcumin, leading to the enhancement of the glucose and lipid metabolism.[54] One of the possible mechanism by which treatment can mediates hypoglycemic and hypolidemic effect is enhancing the insulin secretion.[19] it was reported that administration of Nano Curcumin at 100 and 200 mg/kg significantly rises insulin blood levels in the diabetic rats.[55-57] Curcumin clearly presented hypolipidemic and hypoglycemic effects by preventing the augmentation of glucose,cholesterol, LDL-C and triglyceride levels, the insulinotropic effect of Curcumin can explain such effects as insulin plays an important role in the regulation of lipid metabolism.[53,58-60] Nevertheless, different studies have confirmed that Curcumin has low bioavailability and poor absorption.[61,62] Therefore this study is the first study to evaluate the effect of phytosome in increasing the bioavailability and absorption of Curcumin and study the reflection of that on the retardation of lipid and glucose levels in diabetic rats. It is probably for these reasons that Cur-P complex is more effective in improving lipid and glucose levels than single Curcumin.

Conclusion

To the best of our knowledge, the process of targeting hyperglycemia along with other hematological and physiological parameters such as oxidative stress and dyslipidemia by using curcumin (Cur) combined with phytosomes have not been reported. This study addressed the first data about a promising treatment strategy while combining curcumin (Cur) with phytosomes (P) for managing diabetes complications, especially the physiological disorders that could lead to cardiovascular disease and blood vessels. Using the two compounds at the same dose showed that Cur-P had a stronger effect than curcumin compared to the metformin, due to increasing of the bioavailability of curcumin by phytosomes. More research is needed to be able to understand the mechanisms of action of this compound (Cur-P), which led to the normalization of glucose and lipid levels in the blood. Furthermore, we recommended in the future studies to investigate the effect of Cur-P on the regulation of antioxidant enzyme, which has been strongly linked to the development and progression of diabetic neuropathy.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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