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The effects of the curcumin-loaded selenium nanoparticles on hepatic stereo-histology, blood glucose, and lipid profile in rats

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Abstract The application of novel pharmaceutical formulations of natural compounds, including those incorporating nanoparticles, represents a promising avenue for therapeutic advancement. The objective of this study was to examine the impact of curcumin-loaded selenium nanoparticles on the hepatic histological structure, as well as on blood glucose and lipids in rats. A total of 75 adult male rats were randomly assigned to one control group and four treatment groups. The control group was administered no medication, while the four treatment groups received the following: 50 mg/kg of curcumin (Group 1), 3.5 mg/kg of selenium nanoparticles (Group 2), combination of 50 mg/kg of curcumin plus 3.5 mg/kg of curcumin-loaded selenium nanoparticles (Group 3), and 5% DMSO (Group 4). On days 3, 7, and 14, blood samples were collected for biochemical testing and liver tissue samples were obtained. The hepatic tissue structure of the control, curcumin, and solvent groups exhibited no significant differences on days 3, 7, and 14. It was observed that the selenium nanoparticles group exhibited notable alterations in tissue structure, which were markedly diminished in the curcumin-loaded selenium nanoparticles group. Notable stereological findings were observed in the selenium nanoparticles group in comparison to the control group, including an increase in the volume density of hepatocytes and sinusoids, accompanied by a reduction in the volume density of central veins. No significant alterations were observed in the triglyceride and cholesterol levels in the experimental groups. It can be concluded that the administration of curcumin-loaded selenium nanoparticles to rats demonstrated notable hepatoprotective effects against selenium nanoparticles.

Introduction

The body's natural response to a range of physical, chemical, and biological injuries that result in tissue damage and the release of inflammatory mediators is the onset of inflammation. The continuation of the inflammatory response is primarily attributed to the body's inability to effectively eliminate the inciting agents or to manage the ongoing damage. A variety of substances, including chemicals, toxins, metabolites, medications, and even viruses, have the potential to induce hepatotoxicity or injury via a number of mechanisms, including apoptosis, elevated cytokine concentrations, oxidative stress, and lipid peroxidation mediated by reactive oxygen species [5]. Today, the indication of natural compounds in new pharmaceutical forms, such as loading with nanoparticles, has brought forward new therapeutic prospects [6].

Anti-inflammatory and antioxidant compounds, such as selenium, are often recommended as ingredients in anti-inflammatory medications. Selenium is an essential micronutrient that plays a pivotal role in a multitude of physiological processes. Selenium nanoparticles (SeNPs) display notable characteristics, including chemical stability, high biocompatibility, and low toxicity [1, 2]. Additionally, they enhance the activity of pivotal antioxidant enzymes, including serum glutathione peroxidase, superoxide dismutase, glutathione S-transferase, and thyroxine reductase. They also possess potent antioxidant properties, which inhibit oxidative processes and markedly reduce the synthesis of malondialdehyde [3]. Turmeric, a member of the Zingiberaceae family, has been employed in Asia for over three millennia. The principal active constituent of turmeric, curcumin, is widely recommended in traditional medicine for the treatment of a range of conditions. Additionally, recent research has underscored the anti-inflammatory, antioxidant, antiviral, antibacterial, and anticancer properties of turmeric [4]. The objective of this study was to synthesize curcumin-loaded selenium nanoparticles and evaluate their impact on the liver's histological structure, as well as on blood glucose, triglyceride, and cholesterol levels in rats.

Materials and Methods

Nanoparticles synthesis

The synthesis of nanoparticles was conducted in accordance with the methodology delineated by Kaboutari et al. In summary, 50 mL of a 44 mM ascorbic acid solution (Merck, Germany) was added dropwise to a 500 mL aqueous solution of 1 mM selenium oxide (Sigma-Aldrich, USA) to prepare the selenium nanoparticles (S.N.). Subsequently, 10 mg of curcumin (Sigma-Aldrich, USA) was dissolved in 5 mL of acetone (Sigma-Aldrich, USA) and then added to 150 mL of the S.N. The mixture was stirred and blended thoroughly for 24 hours in the refrigerator to facilitate the loading of curcumin onto the selenium nanoparticles. Subsequently, supplementary tests were conducted, including morphological examination, zeta potential, FTIR, loading efficacy and capacity, and in vitro release characterization, on the synthesized nanoparticles [3].

Animal experiments

A total of 75 healthy adult male Wistar rats, weighing between 200 and 250 grams, were housed in polypropylene cages under standard conditions. These conditions were based on the recommendations of the international and institutional ethical committee (IR.SKU.REC.1401.016) [7]. Following a one-week period of acclimatization, the subjects were randomly assigned to one of five groups, with each group comprising five subjects and three replicates. The control group was administered no medication. In the four treatment groups, the following doses were administered: 50 mg/kg of curcumin (Group 1), 3.5 mg/kg of selenium nanoparticles (Group 2), combination of 50 mg/kg of curcumin plus 3.5 mg/kg of curcumin-loaded selenium nanoparticles (Group 3, Cur@S.N), and 5% DMSO as solvent (Group 4). Each group was administered a single intraperitoneal dose of one milliliter.

On days 3, 7, and 14, a one-millimeter blood sample was collected from each group for biochemical measurements by cardiac puncture. Subsequently, the animals were euthanized via the intraperitoneal administration of 150 mg/kg sodium pentobarbital (Sigma-Aldrich, USA) [7]. The liver was extracted from the abdominal cavity, rinsed with normal saline, and placed in 10% buffered formalin (Merck, Germany). The liver tissue was processed using an Autotechnicon tissue processor (Leica TP1020, Leica Biosystems, USA), and the samples were stained with Hematoxylin and Eosin (H&E).

Biochemical analysis

The colorimetric assay with Karmania Pars Gene (KPG®) kits was employed to quantify blood glucose, triglyceride (TG), and cholesterol levels.

Statistical analysis

The data were expressed as mean ± standard deviation and analyzed using one-way analysis of variance (ANOVA) and the Tukey post hoc test with the use of the SPSS software, version 16. The level of significance was set at P<0.05.

Table 1: The mean quantitative values of volumetric density and absolute volume of hepatocytes in control and experimental rats.

Groups	Hepatocytes					
	'Vv' parameter (%)			'Vt'' parameter (ml)		
Days	3	7	14	3	7	14
Con	62.17	57.94	60.42	5.26±0.25	5.01±0.27	4.95±0.27
Cur	58.31	63.14	57.68	4.89±0.10	5.12±0.13	5.07±0.18
S.N.	64.25	63.71	72.31*[a]	5.98±0.19	6.24±0.22	6.75±0.24*[a]
Cur@S.N.	63.49	63.14	64.23*[b]	5.41±0.21	6.04±0.30	5.86±0.19*[b]
DMSO	60.45	59.20	61.37	5.08±0.31	4.78±.15	4.83±0.23

'Vv': volume density; 'Vt': the total volume; data are shown as mean (SD); p<0.05.

Table 2: The mean quantitative values of volumetric density and absolute volume of sinusoids in control and experimental rats.

Groups	Sinusoids					
	'Vv' parameter (%)			'Vt'' parameter (ml)		
Days	3	7	14	3	7	14
Con	26.82	29.16	28.53	2.20±0.12	2.32±0.31	2.18±0.24
Cur	28.61	26.78	31.22	1.95±0.20	2.19±0.27	2.30±0.13
S.N.	29.41	30.16	35.48*[a]	2.46±0.11	2.52±0.07	3.27±0.08*[a]
Cur@S.N.	28.45	29.13	31.27*[b]	2.28±0.01	2.17±0.32	2.46±0.35*[b]
DMSO	27.46	28.47	28.54	2.16±0.12	1.88±2.41	2.24±0.25

'Vv': volume density; 'Vt': the total volume; data are shown as mean (SD); p<0.05.

Table 3: The mean quantitative values of volumetric density and absolute volume of blood vessels in control and experimental rats.

Groups	Blood vessels					
	'Vv' parameter (%)			'Vt'' parameter (ml)		
Days	3	7	14	3	7	14
Con	10.01	11.90	9.98	1.08±0.32	0.90±0.21	1.02±0.07
Cur	11.86	9.85	10.01	0.95±0.17	1.15±0.25	1.06±0.14
S.N.	10.34	11.04	13.27*[a]	0.98±0.27	1.08±0.26	2.43±0.06*[a]
Cur@S.N.	9.68	10.74	11.89*[b]	1.02±0.24	1.34±0.07	1.41±0.14*[b]
DMSO	11.09	11.35	9.84	1.21±0.05	0.92±0.30	1.10±0.20

'Vv': volume density; 'Vt': the total volume; data are shown as mean (SD); p<0.05.

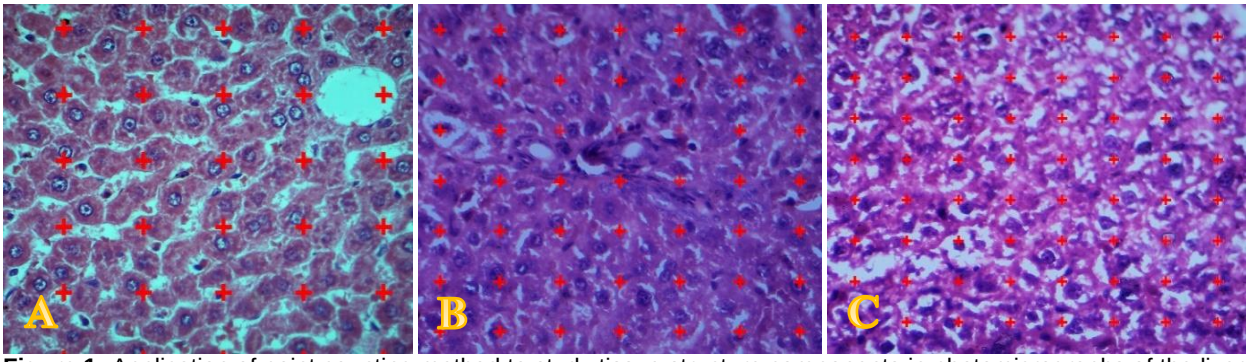

Figure 1: Application of point counting method to study tissue structure components in photomicrographs of the liver. Presentation of methodology in 3 control groups (A), nano-selenium+curcumin (B) and nano-selenium (C) are mentioned, (H&E, ×400 magnification).

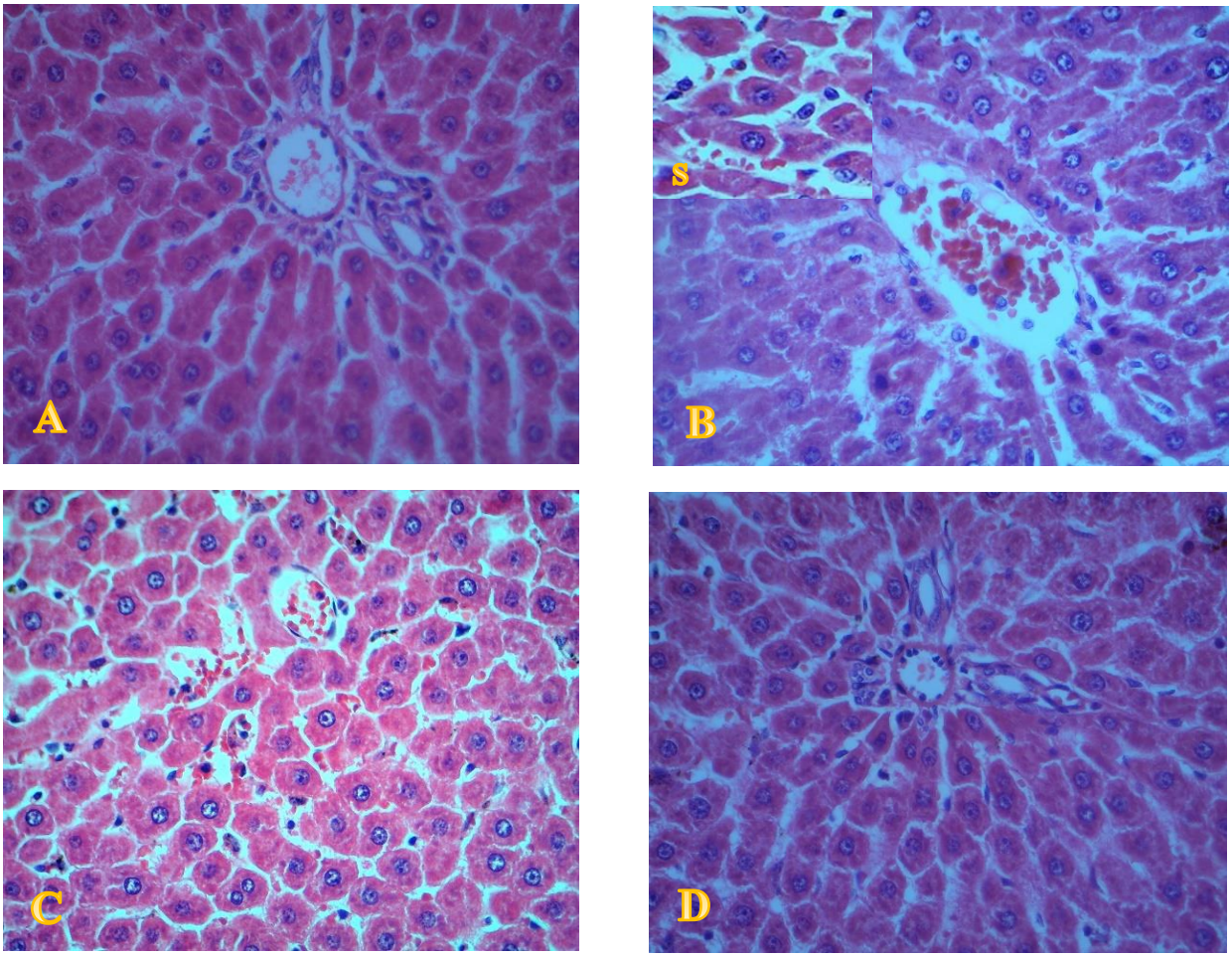

Figure 2: Photomicrograph of liver structure in different groups. A: control group with normal structure; B and C: combination of 50 mg/kg of curcumin plus 3.5 mg/kg of curcumin-loaded selenium nanoparticles, Higher magnification of the B figure; S: hepatic sinusoid, D: 3.5 mg/kg of selenium nanoparticles, (H&E, ×400 magnification).

Results

Histological findings

No statistically significant differences in body weight or mortality were observed among the experimental groups ($P > 0.05$). The light microscopic examination revealed that the hepatic lobule structure exhibited normal histological structure and arrangement in the control, curcumin, and solvent groups on days 3,

7, and 14. In the control group, hepatocytes were observed to predominantly manifest as polygonal structures, exhibiting one or more nuclei with an oval or circular nuclear profile. Additionally, polygonal lobules were noted. Epithelial cells were observed in the branch plates in proximity to the veins, which were ultimately separated by capillary sinuses (Figure 1, A; Figure 2, A; Figure 3, A and B). In the S.N. group, the disintegration of hepatocytes was observed, accompanied by a lateral position nucleus and nuclear hypertrophy. Additionally, there was dilation of interlobular ducts, widespread spaces between hepatocytes, excessive expansion of the sinuses in many structural areas of the tissue, and vasodilation (Figure 2, B and C). In the (Cur@S.N) group, the hepatic tissue alterations were less pronounced compared to the S.N group, and an improvement in the histological changes was observed. Hepatocytes exhibited a more or less normal pattern and shape, while the dilatation of the hepatic vein remained evident (Figure 2, D).

Stereological results

The volume density of hepatocytes (Table 1), sinus space (Table 2), and blood vessels (Table 3) in the control, curcumin, and solvent groups demonstrated no statistically significant difference on days 3, 7, and 14 ($P > 0.05$). On the 14th day, a significant increase in the volume density of hepatocytes (Table 1) and sinusoids (Table 2) in the S.N group, in addition to a significant decrease in the volume density of hepatic blood vessels (Table 3) compared to the control, was observed ($P < 0.05$). In the (Cur@S.N) group, a significant decrease in the volume density of hepatocytes (Table 1) and sinusoids (Table 2) was observed in comparison to the S.N group. Additionally, a significant increase in blood vessel volume density values (Table 3) was noted on day 14 ($p < 0.05$). Conversely, no significant difference in the relative volume of hepatocytes was identified in comparison to the control ($p < 0.05$).

Blood glucose

No significant difference was observed in the experimental groups on days 3 and 7 ($p > 0.05$). However, on day 14, a non-significantly increased level was noted in the S.N. group ($p > 0.05$) (Table 4).

Table 4: The effect of curcumin on blood glucose level in the control and treatment groups.

Parameter		Glucose				
Groups		Con	Cur	S.N.	Cur@S.N	DMSO
Days	3	93.23± 7.81	91.10 ±7.42	110± 8.25	94± 5.34	96.14 ±6.94
	7	89.74± 6.43	88.95 ±6.44	107± 7.46	100± 6.98	87.23 ±7.46
	14	97.23± 6.86	95.23 ±7.87	118± 9.08	97± 6.85	98.23 ±7.55

Lipid indices

No significant differences were observed in the triglyceride and cholesterol levels of the experimental groups ($p > 0.05$) (Tables 5 and 6).

Table 5: The effect of curcumin on triglyceride level in the control and treatment groups.

Parameter		Triglyceride				
Groups		Con	Cur	S.N.	Cur@S.N.	DMSO
Days	3	187.8 ±10.7	178.8 ±12.3	198.4± 11.7	172.1± 8.7	192.2± 10.4
	7	185.1 ±9.7	178.6 ±10.8	194.3± 10.1	178.6± 9.1	189.3± 10.8
	14	188.4 ±10.1	192.1 ±9.3	196.3± 9.4	184.3± 10.1	177.9± 9.65

Table 6: The effect of curcumin on cholesterol level in the control and treatment groups.

Parameter		Cholesterol				
Groups		Con	Cur	S.N.	Cur@S.N.	DMSO
Days	3	89.3± 6.3	87.4± 5.5	95.4± 7.5	91.2± 6.4	89.4± 7.5
	7	86.3± 4.52	85.7± 7.3	96.3± 6.8	92.7±5.6	87.1± 6.4
	14	81.2± 3.91	89.2± 5.1	94.4± 7.8	90.4± 6.4	88.6± 7.6

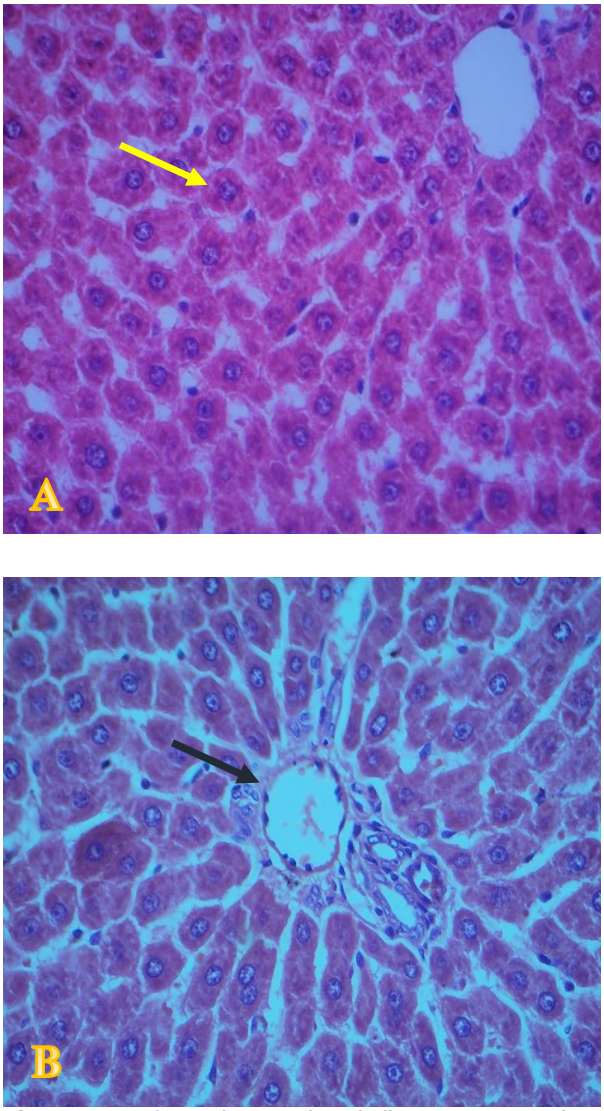

Figure 3: Photomicrograph of liver structure in untreated groups. A: control group and B: DMSO group, hepatocyte (yellow arrow), portal vein (black arrow), (H&E, ×400 magnification).

Discussion

The administration of slow-release curcumin-loaded selenium nanoparticles (Cur@S.N.) to rats demonstrated notable hepatoprotective effects and enhancements in hepatic structure, blood glucose regulation, and lipid profile against selenium nanoparticles. The structural alterations observed in the selenium nanoparticle-treated group suggest the occurrence of partial damage to the general structures of hepatocytes, sinusoids, and blood vessels. In contrast, the hepatocytes in the Cur@S.N group exhibited a well-preserved structure. Despite the presence of minor histological alterations, the experiment did not reveal any notable infiltration of inflammatory cells with pronounced pathological changes.

Some researchers have determined that S.N exhibit low toxicity in the nutritional dose range in comparison to selenite, selenomethionine, and methyl selenocysteine [9]. Furthermore, other researchers have demonstrated that a nutritional dose (0.4 mg/kg) of S.N is unable to induce toxic effects on serum liver enzymes [10]. Conversely, the administration of 5 mg/kg of S.N has been demonstrated to induce hydropic hepatic degeneration, while a dose of 8.0 mg has been shown to result in focal hepatic degeneration and necrosis [8]. Furthermore, the administration of 4 and 8 mg/kg of S.N has been demonstrated to induce toxic effects on the liver, kidneys, lungs, and testes, as well as to suppress thymus growth [11].

The distinctive attribute of Cur@S.N is its capacity to mitigate the deleterious histological consequences induced by S.N. The biological activity of turmeric is attributable to curcumin. It has been demonstrated that curcumin can suppress both acute and chronic inflammation by reducing histamine levels and potentially increasing the production of natural cortisone by the adrenal glands. The anti-inflammatory effect of curcumin may be attributed to its ability to inhibit the PLA2 enzyme, thereby reducing COX2 gene expression. Additionally, curcumin has been demonstrated to inhibit the 5-LO enzyme and suppress NF-κB activity, which ultimately results in the downregulation of proinflammatory genes [12, 13].

The principal mechanism underlying S.N.'s anti-inflammatory activity is the inhibition of COX-2 activity and PGE2 production. Furthermore, it reduces the migration of TNF-α, monocytes, and granulocytes, enhances the activity of glutathione peroxidase and thioredoxin reductase enzymes, inhibits leukotriene and prostaglandin synthesis, and prevents the infiltration of inflammatory cells [14-18].

Group (Cur@S.N) has been demonstrated to exert a beneficial influence on hepatic structure and morphology. Curcumin, renowned for its anti-

inflammatory and antioxidant properties, has been demonstrated to mitigate hepatic damage induced by a wide range of damaging factors and to improve overall hepatic structure. (Cur@S.N) enhances the bioavailability of curcumin, thereby augmenting its therapeutic efficacy. (Cur@S.N) has been demonstrated to diminish inflammatory cell infiltration and facilitate the restoration of normal hepatocyte structure, while also reducing fibrosis and necrosis. These findings suggest that it may serve as a protective measure against hepatotoxicity. The combination of curcumin's biological activities with selenium's antioxidant properties results in a synergistic effect that further promotes hepatic health and regeneration [18].

Group (Cur@S.N) demonstrated efficacy in mitigating hyperlipidemia induced by S.N. This may be attributed to the antioxidative properties of curcumin, which may facilitate the removal of reactive oxygen and nitrogen species, metal chelation, and the regulation of pro-inflammatory enzymes. The reduction of cholesterol and triglycerides by flavonoids has been well documented previously. However, the mechanisms involved in this process may be complex [19]. Additional research substantiates the efficacy of curcumin in lowering lipid profile in hypocholesterolemic models [20]. The inhibition of 3-hydroxy-3-methylglutaryl CoA reductase in the liver by reducing the expression of nuclear transcription factors may prove to be a significant factor in the anti-hyperlipidemic effects of curcumin [21].

The antihyperlipidemic effect of (Cur@S.N) may be mediated by a number of mechanisms, including the regulation of lipid metabolism, the effect on lipid transport proteins, and antioxidant and anti-inflammatory activity. Curcumin has been demonstrated to inhibit key enzymes involved in lipid metabolism, including HMG-CoA reductase, which plays an essential role in cholesterol synthesis. Consequently, curcumin has the potential to reduce overall cholesterol levels. Moreover, it may activate AMPK, a crucial regulator of cellular energy homeostasis that enhances fatty acid oxidation and inhibits lipogenesis. The incorporation of selenium nanoparticles into curcumin formulations has been demonstrated to enhance the antioxidant capacity of the latter, thereby reducing oxidative stress. This reduction contributes to the mitigation of lipid peroxidation, which may result in an improvement of lipid profile. The antioxidant efficacy may be mediated through the Nrf2 pathway, which activates the expression of various antioxidant genes [22-25]. The anti-inflammatory properties of curcumin contribute to the downregulation of pro-inflammatory cytokines, such as TNF-α and IL-6, which are frequently linked to dyslipidemia. This results in a reduction of inflammation within adipose tissue, thereby facilitating lipid metabolism. Inhibition of the NF-κB pathway by curcumin has been demonstrated to result in further reduction of inflammation and improvement of the lipid profile. It is possible that curcumin exerts an influence on the expression of lipid transport proteins, such as CD36 and FABP4, which are involved in the uptake and transport of fatty acids in adipocytes and hepatocytes. This may contribute to the establishment of more optimal lipid homeostasis [22-25]. (Cur@S.N) exerts its effect on blood glucose via a complex mechanism that includes the improvement of insulin sensitivity, the increase of glucose transporter proteins, the regulation of gluconeogenesis, and a number of general mechanisms, including anti-inflammatory, anti-oxidative, and improvement of lipid profile effects. Curcumin has been demonstrated to enhance insulin sensitivity by activating the AMPK pathway, thereby improving glucose uptake in skeletal muscle and enhancing glucose utilization. Furthermore, it has been demonstrated that curcumin can inhibit key enzymes involved in gluconeogenesis, such as glucose-6-phosphatase and fructose-1,6-bisphosphatase, which subsequently leads to a reduction in hepatic glucose synthesis [26-29]. Chronic inflammation represents a pivotal risk factor in the pathogenesis of insulin resistance. The anti-inflammatory properties of curcumin have been demonstrated to reduce pro-inflammatory cytokines and inhibit the NF-κB pathway. This may lead to improvements in insulin signaling pathways and glucose metabolism [26-29].

The antioxidant activity of curcumin is enhanced by selenium nanoparticles, which may be mediated through the Nrf2 pathway. This results in the upregulation of various antioxidant enzymes, which reduces oxidative stress and improves insulin resistance. It is possible that curcumin may increase the expression of glucose transporter proteins, particularly GLUT4, in muscle tissues, thereby facilitating glucose uptake from the bloodstream. Dyslipidemia is frequently associated with insulin resistance and type 2 diabetes. Consequently, enhancing lipid metabolism through the use of Cur@S.N can indirectly improve blood glucose levels [26-29]

Conclusion

The administration of curcumin-loaded selenium nanoparticles (Cur@S.N.) to rats demonstrated notable hepatoprotective effects and enhancements in hepatic structure, blood glucose regulation, and lipid profile. These findings indicate that (Cur@S.N) may represent a promising therapeutic approach for liver health and metabolic disorders.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

This research was conducted in accordance with the relevant international standards and in compliance with the institutional ethical code: IR.SKU.REC.1401.016.

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