THERAPEUTIC POTENTIAL OF BIOCONJUGATED NIOSOMES: SONCHUS MARITIMUS EXTRACT PROTECTS AGAINST HIGH-FRUCTOSE DIET-INDUCED NEPHROTOXICITY

Sara Chetehouna[1], Samir Derouiche[1,2*], Islam Boulaares [1], Yassine Réggami[3]

[1]Department of Cellular and Molecular Biology, Faculty of Natural and Life Sciences, El Oued University, El Oued 39000, Algeria;
[2]Laboratory of Biodiversity and application of biotechnology in the agricultural field, Faculty of natural and life sciences, El Oued University, El-Oued 39000, Algeria.
[3]Department of Natural and Life Sciences, Faculty of Sciences, University 20 August 1955 - Skikda, SKIKDA 21000, Algeria;

**Corresponding*

Abstract
This study evaluated the therapeutic potential of Sonchus maritimus extract-loaded niosomes (SmE-N) against high-fructose diet (HFD)-induced genito-urinary dysfunction in rats. The stability of SmE-N formulations was assessed through standard physicochemical protocols, while morphological features were characterized using scanning and optical microscopy. Male rats were randomly divided into four groups (n=6 each): Control, HFD, HFD+SmE-N, and HFD+metformin. Biochemical, histological, and oxidative stress markers were analyzed in kidney tissues. In vitro characterization revealed that SmE-N were stable, spherical vesicles with an average size of ~200 nm and an encapsulation efficiency of 61.4%, maintaining excellent stability for up to 60 days. In vivo, HFD significantly elevated urea and uric acid levels. Oxidative stress was evident through increased malondialdehyde (MDA) and decreased levels of glutathione (GSH), total thiols, and antioxidant enzymes (GPx, SOD) in renal homogenates compared to controls. Histological examination confirmed tissue alterations in kidneys. Treatment with SmE-N or metformin markedly improved biochemical, oxidative, and histopathological parameters relative to the HFD group. SmE-loaded niosomes bioconjugated with linoleic acid demonstrate strong nephron-protective effects and may serve as a promising therapeutic strategy for managing HFD-induced metabolic complications.

Keywords: *Sonchus maritimus* extract, Niosomes, Linoleic acid bioconjugation, HFD, Nephroprotection

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1. Introduction

It has been suggested urinary disorders is a complication of metabolic syndrome can result in alterations of renal function and structure, involving an increase in urine microalbumin and a decreased glomerular filtration rate through a complex pathogenesis, when chronic kidney disease and MetS a are related and have an effect on each other [1]. During MetS, the pro-inflammatory cytokines promote the inflammatory effects, oxidative stress, endothelial dysfunction, and augmented sympathetic activity, which encourage alteration of renal function and structure including augmented renal volume weight and hyperfiltration, with harming the GFB [2]. The primary causes of urological difficulties in people with MetS are common etiological factors and physiological communication between the kidneys [3]. The nutritional composition of our lifestyle, which includes high fructose corn syrup products, is the factor that causes the incidence of metabolic disorders to rise due to excess fructose consumption [4]. Daily high-fructose diet intake

results in metabolic syndrome, which includes metabolic disruptions that lead to oxidative stress and chronic inflammation, which in turn cause renal dysfunctions [5–7]. Phytotherapy has proven beneficial in the past few decades for the treatment or prevention of various diseases; due to the presence of substances with biological activities in medicinal plants like terpenes, flavonoids, and polyphenols that may interact to solve the pathomechanism of diseases by increasing the effectiveness of each other or having a synergistic effect that yields more benefit from only one compound element. [8,9]. One of the main plants with both therapeutic and commercial value is the species of the Asteraceae family, when *Sonchus maritimus* is a member of it [10,11]. *Sonchus maritimus* contains a range of bioactive compounds, including asphenols, coumarins, flavonoids, fatty acids, and tocopherols, which have demonstrated efficiency against bacterial infections as well as antioxidant characteristics [12,13]. The use of natural materials as medications has garnered a lot of interest. Particularly, polyunsaturated fatty acids, like linoleic acid, have been shown to function well as bioactive lipids. It controls energy metabolism, upholds metabolic homeostasis [14,15]. Nanotechnology is one of the most amazing technologies of the 21st century. It encompasses the ability to work with, monitor, quantify, and create elements at the nanoscale level [16–18] The industrial need for nanoparticles is on the rise recently due to their broad spectrum of applications in the sectors of medical, chemical engineering, catalytic reactions, and electronics [19,20]. One of the main applications of nanotechnology in the field of medicine is the development of smart nanocarriers that are able to target, using particular biosubstances, the affected site, increase the solubility of drugs, protect therapeutic compounds from enzymatic damage, and control the blood circulation system [21]. One type of vesicular nanocarrier used for drug administration is the niosome, which can hold both hydrophilic and hydrophobic compounds. They have the ability to destroy cell damage while shielding nearby healthy tissue [22]. The purpose of this study was to assess the therapeutic impact of niosome-loaded *Sonchus maritimus* extract conjugated with linoleic acid on urinary disorder in albino Wistar rats that was generated by a high fructose diet.

2. Material and Methods

2.1. Collection, identification and extraction of plant material

Sonchus maritimus was obtained in November from Djamaa in El-Oued state, Algeria; and its taxonomy was confirmed by a botanist (Pr. Halis Youcef) in CRSTRA Touggourt. The leaves aqueous extract of *Sonchus maritimus* (SmE) was prepared according to Derouiche *et al*; 10 g of *Sonchus maritimus* dry leaves powder was mixed with 100 ml of distilled water. The mixture was next macerated for 24 hours at ambient temperature before being filtered through filter paper and drying in a stove [23].

2.2. Preparation of niosomes

Niosomes containing *Sonchus maritimus* extract were prepared using non-ionic surfactants (Tween 80). 100 µg of tween 80, 30mg of cholesterol and 50 µg of linoleic acid as stabilizer were dissolved in 2:1 volume ratio of ethanol: chloroform in a round-bottom flask. Under vacuum in a rotary evaporator (BUCHI R-210 Rotavapor®, Switzerland) the organic solvents were removed to form a thin layer on the flask. The residual solvents were evaporated at 30 °C in vacuum oven, t. Then, 10 mL of aqueous extract solution was added to disperse the layer and sonicated the mixture in an ultrasonic bath (DIGITAL ULTRASONIC CLEANER UC-230D, Spain) at 50 °C for 1 hour to produce niosomes conjugated by linoleic acid and loaded with SmE. The phytoniosome suspension was left to mature overnight at room temperature and was then stored in refrigerator for further studies [24].

2.2.1. Morphology characterization of niosomes

Morphology analysis was carried out by Optical microscope (Optika B-293, Italy) equipped with camera (Optika C-B5, Italy) at magnification ×400 for the structural evaluation such as lamellarity and uniformity of shape that performed using a thin layer of the diluted niosomes formulation was disperse between glass slide and lamella. Scanning Electronic Microscope (SEM) used to determine the shape and average size of prepared niosomes, the phytoniosomes suspension were centrifuged followed by three washes to obtain the an encapsulated SmE.

2.2.2. Encapsulation efficiency of niosomes

encapsulation efficiency (EE%) of SmE in niosomes was determined by separation of nonencapsulated SmE from encapsulated SmE in niosomes through centrifugation of the aqueous niosomes suspension at 15700g for 30 min at 4°C. The supernatant was recuperated and the pellet was dissolved in isopropyl alcohol [25]. Using Follin-Ciocalteu method, the amount of bioactive compounds in the supernatant and pellet were measured, the analysis was carried out three times [26]. Encapsulation efficiency was calculated as following:

$$EE\% = 100 \times \frac{\text{amount of encapsulated compound}}{\text{Initial amount of compound}}$$

2.2.3. Physical stability of niosomes

Stability of niosomes was assessed in term of phytoniosomes encapsulation efficiency which was estimated during 24 hours, 1 week, 1, 2 and 3 months after preparation of niosomes after being was stored under condition of 4°C with relative humidity of 25% [25].

2.3.Animals

Twenty-four males of albino Wistar rats, aged 7-8 weeks and weighing 173.08±3.48 g, were received from the Institute Pasteur of Algiers. At animal house of natural and life sciences faculty of Echahid Hamma Lakhdar-El Oued university in Algeria, the rats were kept in plastic cages. Standard conditions were given to the animals (temperature of 2. 2 °C, 12/12-hour cycle of darkness and light). The animals were kept in this condition throughout the study and were given ad libitum access to standard food and water. The local Ethics Committee cited (06 EC/DCMB/FNSL/EU2021) of the Department of Cellular and Molecular Biology, Faculty of Natural Sciences and Life, University of El-Oued, Algeria, ensured that all experimental methods were carried out in accordance with international norms.

2.4. Experimental Design

Twenty-four rats were acclimatized for two weeks before being randomly assigned to four groups of six rats each, control group and received water (control); high-fructose diet group (HFD); high-fructose diet group treated by SmE- loaded noisomes (HFD+SmE-N); high-fructose diet group treated by metformin (HFD+Met). For 13 weeks, the high-fructose diet groups were provided diet contains 35% of fructose [27]. The rats treated by 50 mg/Kg b.w/day of Metformin [28] and by 50 mg/Kg b.w/day of SmE- loaded noisomes [29], using intraperitoneal injection for the last four weeks. The rats were weekly weighted.

2.5. Sacrifice, blood sampling and tissue collection

At the end of the treatment phase and following a 12-hour of fast, the rats were sacrificed while being slightly anesthetized with chloroform (94%) provided by inhalation. The blood samples were received in EDTA tubes with the rat's number during the decapitation. Using the centrifugation for 1500 rpm for 10 min, the plasma sample of each rat was separated and stored at -20 °C until the estimation of biochemical parameters. Kidneys were carefully removed and washed by sodium chloride (NaCl 0.9%); the homogenates of each organ were prepared for determine the protein, lipid peroxidation and oxidative stress markers, after being weighed and stored in the freezer at -20 °C.

2.6. Plasma biochemical parameters

Urea, uric acid and creatinine were determined using (Mindray BS-200, China) and testosterone using (Mindray BS-900i, Germany) by commercial reagent kits (Bio Lab, France and Spin, Spain)

2.7. Preparation of homogenate and determination of protein

Tris buffer saline solution (TBS, pH=7.4) was used to homogenize a part of kidney or testis tissue. The obtained homogenate was centrifuged for 15 min at 5000 rpm at 4 °C, the supernatant was used to lipid peroxidation and oxidative stress markers [23]. The protein level in the both homogenates was determined according to Bradford method using the bovine serum albumin (BSA) as standard [30].

2.8. Oxidative stress parameters

Malondialdehyd (MDA) and reduced glutathione (GSH) levels in kidney and testis were determined using described methods [31,32]. Total thiol in sample was assessed according to Elman Ellman (1959). The enzymatic antioxidant markers including superoxide dismutase (SOD) (EC 1.15.1.1) and glutathione peroxidase (GPx) (EC 1.11.1.9) activities in the both homogenates were estimated by standard methods [34,35].

2.9. Histological analysis

The kidneys of each rat were immersed in phosphate buffer solution with pH=7.6 and formaldehyde 10% as fixative solution for 48h, dehydrated in ethanol ascending grades, cleaned by toluene, submerged in blocks of paraffin. Using a rotary microtome, 5 µm thick sections were cut from the submerged specimens, and then colored by hematoxylin-eosin. The histopathological examination was done using an optical microscope (Optika B-293, Italy) equipped with (Optika C-B5, Italy) camera. the image processing software, Optika was used for the analysis of photomicrographs.

2.10. Statistical analysis

The results are expressed as means ± standard deviations (Mean ± SD), and an ANOVA test was performed to identify statistically significant differences. The Student's t-test was used to compare the groups on study, and the findings of the in-vivo tests were presented as Mean ± Standard Error of Mean (Mean ± SEM). The MINITAB (Version 19) analysis and processing program was utilized for all calculations. Office EXCEL 2019 was used to create histograms.

3. Results and discussion

3.1. Morphological characterization of niosomes

Optical microscopy and scanning electron microscopy (SEM) were used to analyze the size, shape, and morphology of SmE-loaded niosomes which formulated using thin film hydration technique. As seen in the micrographs at a magnification of 400 (figure 1a), our preparation showed that niosomes were small vesicles in size, had a spherical and round form and exhibited some aggregation. Niosomes were loaded *Sonchus maritimus* extract without changing their morphology or structure. The SEM analysis of niosomes also demonstrated the formulation of like spherule structure with an appropriate size about 200 nm (Figure 1b).

In the present study, optical microscopy evaluation of SmE-loaded niosomes as a new bioactive drug delivery system showed a spherical and round shape. In similar paper of Asthana et *al.*, which found that their prepared clarithromycin loaded-niosomes were spherical in shape, too using optical microscopy [36]. The niosomes were indicated to be like spherule structure under scanning electron microscope and with excellent average size, these morphological results were supported by previous study, whereas the formulations of green tea extract-loaded pH-responsive niosomes were also ranged between 100-200 nm in size [37].

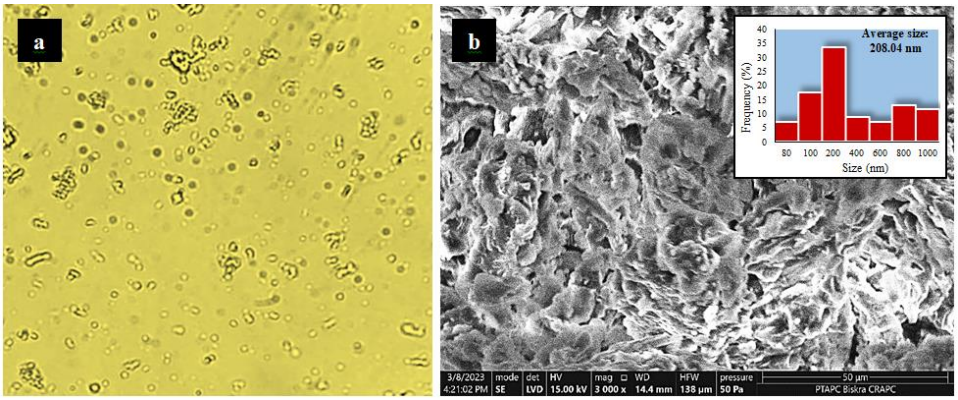

Figure 1. Optical microscopic micrographs at magnification ×400 **(a)** and Scanning electron microscopic micrographs with average size of *S. maritimus*-loaded niosomes **(b)**.

3.2. Physical stability of niosomes

The findings demonstrated that, after 60 days of sample storage at 4°C, our niosomal formulation of *Sonchus maritimus* exhibited a high level of physical stability. No significant variation was observed in the encapsulation efficiency percentage during the first, seventh, thirty, and sixty days of storage; however, after ninety days, a significant reduction in encapsulation efficiency was noted, reaching to 54.71%. This demonstrated that *S. maritimus* extract loaded in niosomes did not leak out after two months and that temperature had no effect on it, as illustrated in figure 2.

Recent studies are unanimous that niosomes are formulations used for create delivery system through encapsulation of bioactive compounds [13]. An important amount of bioactive molecules of extract were entrapped in niosomes up to 61.4% which is indicative of their formulation. Obeid et *al*. also informed that encapsulation of curcumin in their formulation using Tween 85 was around 60% [38]. Stability of encapsulation efficiency of our formulated niosomes over month is in accordance with results of other study presented a no significant modification in EE% of quercetin-loaded niosomes after 30 days of cold storage condition [39].

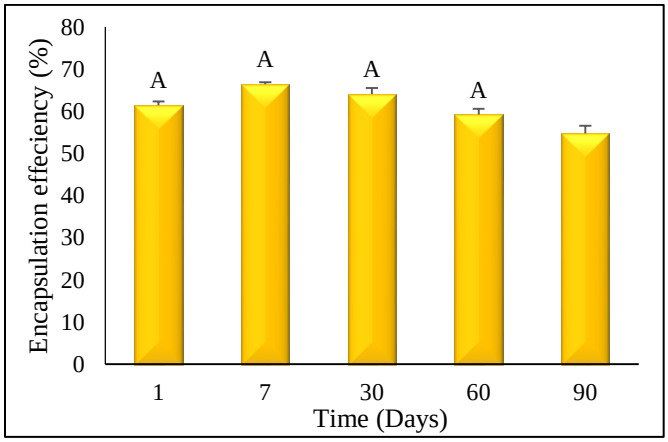

Figure 2. Physical stability of S. maritimus extract -loaded niosomes at 4 °C
Mean EE % was studied as stability parameter. Mean not labeled with the letter A are significantly different from the control level mean

3.3. Growth parameters

The results presented in comparison to control rats, a significant decrease (P<0.001) of final body weight and a significant increase (P<0.001) of relative kidneys and testis weight of all experimental rats exposed

to high fructose diet with exception the relative testis weight of SmE-N group. Treatment by niosomes loaded *Sonchus maritimus* and metformin showed a significant increase (P<0.001) of final body weight and a significant decrease (P<0.01) of relative kidneys and testis weight compered to HFD group. *Sonchus maritimus* decreased significantly the mentioned parameters. The majority of markers were ameliorated by the niosomes better than metformin drug (Table 1).

Previous study consumption of 20% of high-fructose corn syrup for 10 weeks decrease the terminal body weight of rats; this confirmed our obtained results [40]. Increased metabolic requirements are incompatible with maintaining a constant body weight, whereas changes in cellular energy consumption are associated with maintaining a low or high body weight [41]. The relative kidneys weight of the HFD rats was significantly higher than the control. The change may be explained by the higher content of triglyceride in the HFD kidneys [42]. The variation in the HFD group's relative testis weight as a result of testicular reproductive changes [43]. Niosomes of *Sonchus maritimus* enhanced all these parameters, in particular body weight. This was coupled with an increase in intake of food and water because of phyto-compounds present in the aqueous extract, which is consistent with findings of other research showing that plant aqueous extracts can restore total body weight [44], and the inclusion of linoleic acid in SmE-N, which is thought to be among the polyunsaturated fatty acids improving body composition and boosting muscle growth, that explains its widespread application in body configuration[14]. Our niosomal therapeutic structure, which contains *S. maritimus* extract, has been shown to have a positive effect on relative organ weight. This indicates the significance of this drug delivery system for providing the phytochemicals in the extract, which have the potential to reduce the pathogenesis of disease and minimize free radicals in tissues. Consequently, these effects can lower inflammatory processes and peroxidation of lipids [45,46].

Table 1. Growth parameters of control, HFD and treated groups

Parameters	**Control (n=6)**	**HFD (n=6)**	**HFD+SmE-N (n=6)**	**HFD+Met (n=6)**
Initial body weight (g)	179.17±4.72	173.33±6.38	171.67±7.24	172.00±7.18
Final Body Weight (g)	217.50±4.91	127.77±5.41***	153.50±3.67^{***c}	168.75±3.64^{***c}
Relative Kidneys Weight (g/100g b.w)	0.4307±0.0063	0.6007±0.0177***	0.50477±0.0074^{***c}	0.50517±0.0093^{***c}

Values are provided as (mean ± SEM): * P<0.05, ** P<0.01, *** P<0.001: comparison with control group; a P<0.05, b P<0.01, c P<0.001: comparison with HFD group.

3.4. Biochemical parameters

The obtained results showed that there were a very high significant (P<0.001) increase of urea, creatinine, uric acid and protein levels, but a very high significant (P<0.001) decrease in testosterones in rats fed a high fructose diet in comparison with control rats. However, treatment by niosomes loaded *Sonchus maritimus* decreased significantly the mentioned parameters. The majority of markers were ameliorated by the niosomes better than metformin drug (Table 2).

Blood urea, uric acid, and creatinine levels are among the kidney function markers that are elevated by high fructose diet (Lin et al., 2022). Elevated uric acid production is known to reduce endothelial nitric oxide (NO), which therefore results in endothelial dysfunction and reduced insulin utilization in skeletal muscle [47]. Overconsumption of fructose results in an oxidative stress state that damages the kidneys and causes malfunction, which raises the level of biomarkers associated with it (Qiao et al., 2018). As previously demonstrated, rats fed a high-fructose diet suffered oxidative stress, which caused primary hypogonadism and altered testicular cells, resulting in lower serum testosterone levels compared to controls [43]. It has been demonstrated that metabolic disorders can also lead to increase the transcription and the synthesis of pro-inflammatory proteins, which in turn cause oxidative stress in renal tissue and raise the proportion of protein in the kidneys [49]. The results that were obtained concerning the protein

level in the testicular tissue were opposed to the results of other study [50]. The present investigation has demonstrated the efficacy of *S. maritimus* extract in enhancing levels of urea and uric acid. This improvement in biomarker levels may be attributed to the phytochemicals found in the extract, which have an antioxidant effect on the body [51]. In our study, testosterone level was not improved by our therapeutic system, that might be because of testicular destruction severity by HFD. Many studies have been carried out to formally confirm that plants can be used to treat kidney sickness because flavonoids, which are secondary metabolite compounds present in plants, have a significant impact on renal physiology [52]. Previous study reported that the antioxidant capacity and phenolic composition of the *S. maritimus* leaf extract aid in the restoration of the testicles' structure and function, ultimately leading to the restoration of the protein level in the tissue [53].

Table 2. Biochemical markers of control, HFD and treated groups

Parameters	**Control (n=6)**	**HFD (n=6)**	**HFD+SmE-N (n=6)**	**HFD+Met (n=6)**
Urea (g/L)	0.3975±0.0202	0.5325±0.00791***	0.4225±0.0114^{c}	0.585±0.0325**
Creatinine (mg/L)	7.733±0.107	7.9168±0.0658*	7.685±0.142	7.720±0.0790^{a}
Uric acid (mg/L)	14.727±0.961	39.88±3.62***	15.525±0.612^{c}	24.20±1.41^{***c}
Kidney protein (mg/g of tissue)	41.566±0.911	55.954±0.487***	44.02±2.52^{c}	24.14±3.52^{***c}

Values are provided as (mean ± SEM): * P<0.05, **P<0.01, ***P<0.001: comparison with control group; a P<0.05, b P<0.01, c P<0.001: comparison with HFD group.

3.5. Oxidative stress makers

The data showed a significant increase (P<0.01) in kidney and testis MDA levels in the HFD and treated groups as compared to the control. Furthermore, the feeding of a high-fructose diet led to a significant diminution (P<0.05) of GSH and total thiol levels, GPx and SOD activities, as well as GPx/GSH and GSH/total thiol rats, with a decrease in total antioxidant capacity in each kidney and testis in comparison with the control group. However, total antioxidant capacity was not statistically changed in the kidneys in the experimental groups compared to the control group. The treatments using niosome system-loaded *Sonchus maritimus* and metformin significantly augmented the non-enzymatic and enzymatic antioxidant markers, in addition to GPx/GSH and GPx/Total thiol rates. In equal measure, they significantly reduced MDA levels in each of kidney and testis compared to the HFD group. Yet total thiol of kidney tissue was significantly deceased, and SOD activity of testis tissue was not significantly changed by metformin treatment compared to the HFD group (Table 3).

Rats with metabolic disorders were used in a study to demonstrate the existence of oxidative stress in kidney tissue by increasing MDA levels and decreasing antioxidant indicators that had an inverse relationship with MDA levels. When pro-inflammatory mediators activate the inflammatory process, which in turn increases the formation of free radicals, declines the antioxidant activity [54]. Additionally, metabolic disorders can elevate endogenous oxidants by inhibiting SOD, GPx, and GSH and elevating MDA levels, which can lead to severe oxidative stress in the testes [55]. It showed that Sonchus genus extract significantly reduced the markers of oxidative stress and elevated the antioxidant potential in the kidneys, it is possible that the excellent results seen in rats treated with SmE-N are caused by their remarkable capacity to scavenge free radicals and their ability to prevent oxidative stress [51]. Previous findings, which are consistent with our findings in this study, showed that polyphenols in the extract substantially lower the levels of malondialdehyde as well as protein carbonyl, whereas significantly increase glutathione levels and antioxidant enzyme activities in the testis homogenate [56]. This explains the recovery of antioxidant agents' concentrations and activity as antioxidants in tissues because our drug delivery system effectively transports the bioactive components of *S. maritimus* to the sites of injury.

Table 3. kidney Oxidative stress markers of control, HFD and treated groups

Parameters	Control (n=6)	HFD (n=6)	HFD+SmE-N (n=6)	HFD+Met (n=6)
MDA (nmol/mg of prot)	0.3897±0.0116	0.8240±0.0602***	0.4962±0.0777^{b}	0.6999±0.0260^{***b}
GSH (nmol/mg of prot)	0.20458±0.00635	0.18611±0.00536*	0.2371±0.0166^{a}	0.2911±0.0385^{a}
SOD (mUI/mg of prot)	1.66±0.09	1.37±0.01***	1.75±0.14^{a}	1.80±0.13^{a}
GPx (µmol/mg of prot)	3.3322±0.0599	3.1329±0.042***	4.018±0.248^{*b}	5.216±0.792^{*a}
Total thiol (mmol/mg of pro)	0.0925±0.0032	0.0761±0.0019***	0.094±0.006^{a}	0.0047±0.0012^{***c}
(GPx /GSH) $\times 10^{3}$	18.874±0.760	12.302±0.340***	19.074±0.607^{c}	14.584±0.466^{***c}
(GSH/total -SH) x 10^{-3} (%)	0.3204±0.0025	0.2381±0.004***	0.2816±0.002^{***c}	7.300±0.121^{***c}
Total anti-oxidant capacity (%)	97.557±0.030	97.648±0.044	97.323±0.113^{a}	97.591±0.086

Values are provided as (mean ± SEM): * P<0.05, ** P<0.01, *** P<0.001: comparison with control group; a P<0.05, b P<0.01, c P<0.001: comparison with HFD group.

3.6. Histological study

Histological analysis of kidney tissue section presented a normal morphological structure of tissue, similar sizes of glomerulus and bowmen's space, However, histological alterations were showed in tissue section of HFD group that including inflammation, necrosis and hemorrhage with a glomerulus atrophy, bowmen's space expansion, and tubules dilatation. Treatment by niosomes loaded SmE demonstrated a correction of the almost completely morphological alteration of the kidney section better than Metformin treatment which showed slight correction with survival of glomerulus atrophy and bowmen's space the expansion (Figure 3; Table 4).

Further investigation showed that rats fed fructose developed renal impairment characterized by glomerulosclerosis, necrosis, Bowman's space dilatation, and mononuclear cell infiltration in the interstitium. Additionally, the study group's kidneys displayed a larger tubulus proximalis space. It was hypothesized that this increase may have been attributed to inflammatory processes and oxidative stress, which have been found to be significant factors in the development and progression of kidney damage, as well as the high-fructose diet can be induce tubular cell proliferation in rats [57,58][59]. Several studies have shown an association between the maintenance of health and disease prevention and the naturally bioactive compounds found in food. Medicinal plants possess a significant amount of phosphorus, potassium, magnesium, and other minor minerals like zinc, copper, calcium, iron, and manganese, in addition to bioactive components like flavonoids, phenolic compounds, triterpenoids, unsaturated fatty acids and their derivatives, phytosterols, and saponins. The mentioned minerals and biological substances have the capacity to work simultaneously at different or concurrently at the same target places, offering physiological advantages, improving health, and reducing oxidative stress associated with testicular disorders and renal issues [60, 61].

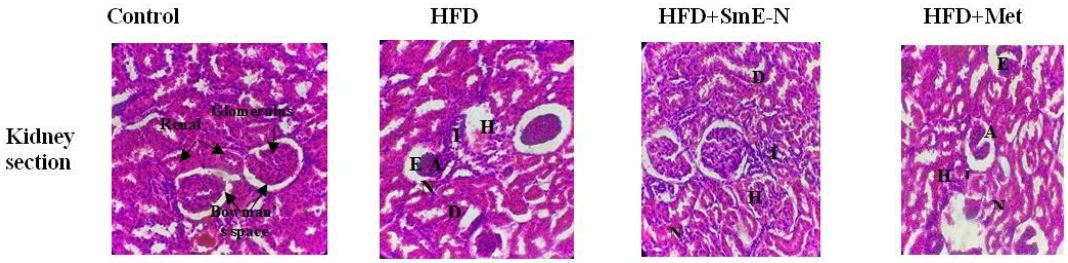

Figure 3. Histological photomicrographs of kidney and teste sections of control, HFD and treated groups at magnification ×400

Inflammation (I); Necrosis (N); Hemorrhage (H); Glomerulus atrophy (A); Bowman's space expansion (E); Renal tubule dilatation (D); Irregular boundaries (IB); Degeneration of spermatogenic cells (DSC); Reduction of flagella condensation (RF)

Table 4. Grading of histological alteration in kidney section of control, HFD and treated groups

Parameters	Control	HFD	HFD+SmE-N	HFD+Met
Hemorrhage	-	+++	+	++
Inflammation	-	+++	+	++
Necrosis	-	+++	+	++
Bowman's space expansion	-	+++	-	+++
Glomerulus atrophy	-	+++	-	+++
Renal tubule dilatation	-	+++	+	+++

none (-); moderate (+); severe (++); very severe (+++)

4. Conclusion

Sonchus maritimus extract-loaded niosomes appeared to provide therapeutic potential for treating urinary disorders which induced by metabolic disorders generated by high-fructose diet, through improving biochemical and histological profile with the antioxidant system. These actions result from the existence of bioactive chemicals in the aqueous extract of *Sonchus maritimus* leaves. In addition, the presence of linoleic acid in niosomes and SmE biomolecules, aids to prevent the damage of affected kidneys and testes.

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