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Original Article

Investigation of *Sonchus maritimus* Loaded Niosomes Relieves Hematological Alterations and Cardiac Oxidative Stress Caused by High-Fructose Diet in Rats

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Abstract

This study aimed to evaluate the therapeutic effect of niosomes loaded with *Sonchus maritimus* extract conjugated with linoleic acid on hematological changes and cardiac dysfunction in albino Wistar rats caused by a high fructose diet. Four boxes of six male Albino Wistar rats were randomly divided into four groups. The control group was fed a standard diet, the HFD+SmE-N group received Sonchus maritimus extract-loaded niosomes, and the HFD+Met group received metformin. Growth parameters, hematological profile, oxidative stress markers, and histological analysis were examined for each group. The obtained results demonstrated that HFD significantly decreased (P<0.001) final body weight, water intake, and food intake while significantly increasing (P<0.001) the relative heart weight of rats compared to control rats. According to the hematological parameters, the eurytrogram and leukogram profiles of the HFD group significantly decreased (P<0.01), whereas the blood platelet level significantly increased (P<0.001), compared to the control. Furthermore, in a significant increase (P<0.001) of heart malondialdehyde (MDA) levels while a significant decrease (P<0.01) of reduced glutathione (GSH) and total thiol (-SH) levels, in addition to a significant inhibition (P<0.05) of glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities heart homogenate of HFD group. The histological examination revealed alterations of heart tissue section of HFD group. However, the treatments of *Sonchus maritimus* extract –loaded niosomes and metformin showed an important improvement of the mentioned markers when we compared to HFD group. Globally, the therapeutic effect of SmE-N was better than metformin treatment. Niosomes loaded *Sonchus maritimus* aqueous extract provided therapeutic potential for treating cardiac dysfunction and hematological changes induced by consumption of high-fructose diet through improving the antioxidant defense system, hematological profile, and even the histological profile of affected heart.

Keywords: Cardiac dysfunction, Hematological changes, Oxidative stress, *Sonchus maritimus*, Niosomes.

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1. Introduction

Among the complicated conditions associated with metabolic syndrome are low-grade inflammation and cardiac dysfunction [1]. That raises the possibility of hypertension,

cardiovascular complications, and even mortality [2].

A diet high in fructose is becoming increasingly common due to worldwide modernization and altering lifestyle nutritional patterns because of excessive consumption of products containing high-fructose corn syrup. Consequently, it is essential to assess the cardioprotective mechanism of medicinal substances in cardiac failure generated by a high-fructose diet and confirm their cardioprotective impact on the heart [3, 4]. Additionally, a high-fructose diet causes metabolic disorders that induce oxidative stress and chronic inflammation, both of which impair the metabolism at different levels of the body [5–7]. In recent years, phytotherapy has shown promise in treating and preventing many diseases. Medicinal plants contain compounds like terpenes, flavonoids, and polyphenols that have biological activities. These compounds may work in concert to solve a disease's pathomechanism by enhancing the effectiveness of one another or producing a synergistic effect that maximizes the benefits of a single compound element [8, 9]. The Asteraceae species, to which *Sonchus maritimus* belongs, are among the most valuable plants in terms of medicinal and commercial applications [10, 11]. *Sonchus maritimus* is rich in bioactive substances that are effective against bacterial infections and have antioxidant properties, such as coumarins, flavonoids, tocopherols, and fatty acids [12, 13]. Much attention has been attracted to the use of natural materials as pharmaceuticals.

In particular, research has indicated the advantageous characteristics of polyunsaturated fatty acids, including linoleic acid, in their capacity as bioactive lipids through maintaining metabolic homeostasis and managing energy metabolism [14, 15]. One of the 21st century's most remarkable technological advancements is nanotechnology due to the observation, measurement, and production of materials at the nanoscale level [16–18]. Because of the wide range of uses for nanoparticles in medicine, chemical technology, catalytic processes, and electronics, there has been a significant increase in their requirements in the industry [19, 20]. The production of intelligent nanocarriers, which can target the affected site using specific biosubstances, improve drug solubility, protect medicinal substances from enzymatic damage, as well as regulate blood circulation, which is one of the primary uses of nanotechnology in medicine [21]. The niosome is one kind of vesicular nanocarrier used to administer drugs since it can contain both hydrophilic and hydrophobic substances. They can protect adjacent healthy tissue while destroying damaging cells [22]. The objective of this study was to evaluate the therapeutic efficacy of niosomes containing *Sonchus maritimus* extract and conjugated with linoleic acid in mitigating cardiac dysfunction and hematological alterations caused by a high fructose diet in albino Wistar rats.

2. Materials and Methods

2.1. Sonchus maritimus collection and aqueous extract preparation

Sonchus maritimus was collected in November from Djamaa in El-Oued state, Algeria. To produce the *Sonchus maritimus* leaf aqueous extract (SmE), 10 g of dried leaf powder was mixed with 100 mL of distilled water. The mixture was macerated for 24 hours at room temperature, filtered via filter paper, and dried in a heated oven [23].

2.2. *Niosomes formulation*

A round-bottom flask was filled with a 2:1 volume ratio of ethanol and chloroform in order to dissolve 100 µg of tween 80, 30 mg of cholesterol, and 50 µg of linoleic acid to formulate niosomes involving *Sonchus maritimus* extract. The organic solvents have been removed to make a thin layer on the wall flask using a rotary evaporator, BUCHI R-210 Rotavapor® manufactured in Switzerland, operating under vacuum. The residual solvents underwent removal in a vacuum oven operating at a temperature of 30 °C. Following the dispersion of the layer with 10 mL of an aqueous extract solution, the resulting mixture underwent sonication for one hour at a temperature of 50 °C using a digital ultrasonic cleaner (UC-230D, Spain) to form niosomes conjugated with linoleic acid and loaded with SmE. After being given time to develop at room temperature for the entire night, the phytoniosome suspension was refrigerated to get ready for further analysis [24].

2.3. Animals

Twenty-four males' albino Wistar rats weighing 173.08±3.48 g at 7-8 weeks of age were acquired from the Pasteur Institute in Algiers. At El Oued University in Algeria's animal home of the Faculty of Natural and Life Sciences, the rats were kept in plastic containers. Standard conditions were maintained for the animals, including a (12/12 h) daylight/dark cycle and an ambient temperature (25 ± 2 °C). The animals were kept in the same environment during the study and had free access to standard food and water. To ensure that all experimental methods complied with international norms, the department of Cellular and Molecular Biology at El-Oued University in Algeria cited the local Ethics Committee (06 EC/DCMB /FNSL/ EU2021).

2.4. Experimental Design

After two weeks of acclimation, twenty-four rats were separated into four groups randomly: The control group, which received a standard diet; the HFD group, which received a diet with high-fructose; the HFD+SmE-N group, which received a diet with high-fructose and treated by SmE-loaded niosomes; and HFD+Met group which received a diet with high-fructose and treated by metformin. During 13 weeks, 35% fructose was provided as part of the high-fructose diet received [25]. The rats were given intraperitoneal injections of 50 mg/kg b.w./day of SmE-loaded niosomes [26] and 50 mg/kg b.w./day of metformin [27] for the last four weeks of experience. Each week, the rats were given a weight.

2.5. Sacrifice, blood sampling, and tissue collection

After a 12-hour fast, the rats were put to death at the end of the therapeutic phase. During the rat's decapitation, the blood sample was placed in an EDTA tube identified with the rat's number. Each rat's plasma sample was separated using a centrifuge (1500 rpm/10 min), and it was then reserved at -20 °Cuntil the hematological parameters were estimated. The heart was carefully removed and then cleaned with sodium chloride (NaCl 0.9%) after weighing and freezing at -20 °C for preparing homogenates [23], which are ready to measure oxidative stress, lipid peroxidation markers,

and protein levels in the heart using Bradford method [28].

2.6. Hematological and Oxidative stress parameters

The Rayto Automatic Touch Screen Hematology Analyzer (RT-7600) was utilized to determine the hematological parameters. Malondialdehyde (MDA) and reduced glutathione (GSH) levels in the kidney and testis were determined using described methods [29, 30]. Total thiol in the sample was assessed according to Elman [31]. The enzymatic antioxidant markers, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities in the heart's homogenate, were estimated by standard protocols [32, 33].

2.7. Histopathological analysis

The hearts of rats were submerged in buffer solution (pH = 7.6) and formaldehyde (10%) as a fixative agent for two nights, followed by ethanol dehydration in increasing degrees, toluene cleaning, and immersion in paraffin blocks. Using a rotary microtome, the immersed samples were cut into 5 µm thick slices and subsequently stained by hematoxylin-eosin. For the histopathological evaluation, a light microscope of Optika B-293, manufactured in Italy, with an imaging system of Optika C-B5, manufactured in Italy was utilized; Optika software for image processing was employed to evaluate photomicrographs.

2.8. Statistical analysis

Our findings were presented as Mean ± Standard Error of Mean (Mean ± SEM), and the statistical comparison of the studied groups was carried out via the Student's t-test. All analysis and calculations were processed using MINITAB (Version 19).

3. Results and Discussion

3.1. Growth parameters

Compared to the control group, there was a high significant decline ($P<0.001$) in water intake, food intake, and final body weight of rats, while a very high significant increase ($P<0.01$) in the relative heart weight of rats receiving a high fructose diet. Treatment by Sonchus maritimus-loaded niosomes and metformin demonstrated a significant augmentation ($P<0.05$) of final body weight, water, and food intake, with a very high significant decrease ($P<0.01$) of relative heart weight compared to HFD rats. Except for the food intake of the SmE-N group, which was not statistically changed (**Table 1**).

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

Parameters	Control	HFD	HFD+SmE-N	HFD+Met
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}
Food intake (g/rat/day)	9.500±0.0990	5.160±0.0317***	6.160±0.0317^{***c}	5.500±0.0990^{***b}
Water intake (mL/rat/day)	20.815±0.004	8.250±0.205***	8.373±0.304***	9.305±0.377^{***a}
Relative Heart Weight (g/100g b.w)	0.2472±0.0045	0.3273±0.005***	0.2735±0.0036^{***c}	0.2672±0.0057^{**c}

Values are provided as (mean ± SEM): n=6; * $P<0.05$, ** $P<0.01$, *** $P<0.001$: comparison with the control group; a $P<0.05$, b $P<0.01$, c $P<0.001$: comparison with HFD group.

According to earlier research, mice who were administered a diet rich in fructose for ten weeks lost their final body weight and took fewer liquids and food overall [34]. Consuming more calories means that one's body weight cannot remain constant. However, differences in the amount of energy cells use are associated with maintaining a lower or higher body weight [35]. Moreover, fructose supplementation has been shown to reduce food intake [36].

Because the heart's tissue mass has increased, the relative heart weight has also increased [37, 38] due to inflammation and necrosis of the tissue [39], which was confirmed by histological analysis of HFD. The *S. maritimus* aqueous extract's niosomes enhanced all of the mentioned parameters, but among them was the body weight, which increased when food and water intake increased because of the extract's phytochemicals. Previous research has demonstrated that a plant's aqueous extract can restore body weight [40]. The conjugated linoleic acid with SmE-N improves the body's structure through increased muscle mass, which clarifies its widespread application in physique configuration [41]. The capacity of our customized drug delivery technology to distribute the plant extract's phytochemicals of the plant extract has the potential to inhibit the pathogenesis of disease by decreasing free radicals in the tissue.

Thus reducing lipid peroxidation and inflammation, as demonstrated by the beneficial impact of our therapeutic system, which contains *Sonchus maritimus* extract and helps to reduce and enhance the relative heart weight [42, 43].

3.2. Hematological parameters

The results from **Table 2** hematological parameters revealed a highly significant decrease ($P<0.01$) of red blood cells (RBC), hematocrit (HCT), hemoglobin (HBG), and white blood cell (WBC) while a very significant augmentation ($P<0.01$) of platelet in HFD rats compared to control rats. In contrast, all treated groups proved a significant increase ($P<0.05$) in parameters of the eurytrogram profile and improved immune system performance by increasing number of WBC; however, the platelet was significantly ($P<0.05$) decreased by SmE-N treatment and did not change by metformin and treatment compared to the HFD group. Hematological analysis is crucial to assessing the health status; it provides images of the erythrogram and leukogram since any parameter variation suggests evidence of a particular disease [44].

Table 2. Hematological parameters of control, HFD, and treated groups**.**

Parameter	Control	HFD	HFD+SmE-N	HFD+Met
Red blood cell (10^{12}/L)	8.02±0.03	6.03±0.21***	7.59±0.13^{*c}	7.12±0.18^{**b}
Hemoglobin (g/dL)	13.2±0.14	10.13±0.33***	12.22±0.30^{*c}	12.38±0.21^{*c}
Hematocrit (%)	42.43±0.58	32.11±1.31***	39.98±0.74^{*c}	36.94±1.56^{*a}
Platelet (10^{9}/L)	808.3±14.6	1303±4.4***	1112.7±14.3^{***c}	1295.7±18.3***
White blood cell (10^{9}/L)	4.33±0.20	2.62±0.31**	4.12±0.19^{c}	4.36±0.28^{b}

Values are provided as (mean ± SEM): n=6; * $P<0.05$, ** $P<0.01$, *** $P<0.001$: comparison with the control group; a $P<0.05$, b $P<0.01$, c $P<0.001$: comparison with HFD group.

According to our data, HFD induced a significant decrease in erythrogram results, including red blood cells, hemoglobin, and hematocrit, which agrees with a previous study that suggested that induced metabolic disorders in rats can stimulate erythrocyte hemolysis and a decrease in erythrocyte number in the blood, which referred to elevated production of peroxide species and oxidative stress, which could destroy plasma membrane and cytosolic constituents, leading to oxidative hemolysis of red blood cells and dropped survival of oxidized RBCs in the circulation [45]. Comparable results in a rodent model have revealed that a metabolic syndrome also shows a reduction in cellular immunity. At the same time, the primary probable reason for a decrease in leukocytes may be associated with an induced metabolic syndrome that increases the secretion of corticosteroids and IL-6, which reduces the number of peripheral lymphocytes and increases the mobilization of bone marrow-derived neutrophils [46]. Stress usually causes an increase in inflammatory mediators, which causes inflammatory damage to proteins, lipids, and DNA in cells. This damage is caused by excess reactive nitrogen and oxygen species, further aggravated by damage to mitochondria. Ultimately, this leads to a decline in physiological functions, especially those of the immune, neurological, and endocrine systems that regulate homeostasis [47]. Platelets can repair the endothelium by stimulating hemostatic responses. Metabolic disorders like those related to a high-fructose diet can alter platelet function and increase the tendency towards thrombus formation and arterial blockage, possibly owing to platelet hyperactivation and hyperaggregability [48].

The antioxidant properties of niosomes-loaded *S. maritimus* extract may help to provide hematoprotective capacity due to the anti-free radical properties of phytocomponents such as phenolic molecules, flavonoids, steroids, and tannin, as well as essential metal elements found in *S. maritimus* including zinc, iron, calcium, phosphorus, and potassium, which to ensure the restoration of RBC, hematocrit, and hemoglobin levels in the blood [49]. Niosomes treatment reversed the consequences of a diet rich in fructose on leukogram changes by suppressing the transcription of the genes encoding the inflammatory cytokines, hence preventing the production of those cytokines; this effect is attributed to flavonoids, specifically kaempferol and apigenin [50]. A current study reports on the immunomodulatory function of Sonchus plants due to their bioactive compounds [51]. Based on an existing study, the extract's flavones cause a platelet count drop, proving our results for the SmE-N group [52].

3.3. Oxidative stress markers

The obtained results showed that the MDA levels of the HFD group were significantly higher (P<0.001) than those of the control group. Furthermore, the received amount of high-fructose diet caused a significant diminution (P<0.05) of GSH and total thiol levels, in addition to a significant reduction of GPx and SOD activities, as well as for GPx/GSH and GSH/total thiol rates, and a significant decline (P<0.001) of total antioxidant capacity in heart tissue compared to the control group. The therapeutic system using the niosomes -loaded *Sonchus maritimus* and the metformin significantly increased the rates of GPx/GSH and

GPx/Total thiol in parallel with the significant increase of total thiol and GSH levels and the enzymatic antioxidant markers. Conversely, our treatments significantly decreased the heart MDA levels compared to the HFD group. However, the total thiol level and the SOD activity were not statistically ameliorated by the metformin compared to the HFD group (**Table 3**).

Excessive intake of fructose leads to an imbalance in the antioxidant defense system and an increase in the production of free radicals in various tissues [53, 54]. Reactive species generation is increased by administering a diet rich in fructose, which causes metabolic syndrome in rats, modifies the antioxidant balance, and permits the cells to accumulate more reactive species [55]. Glutathione (GSH), often known as the "master antioxidant," is known to improve the elimination of reactive nitrogen and oxygen species as well as other free radicals [56].

The functional thiol group present in cells is represented by glutathione. In addition to their production and elimination from cells through glutathione redox reaction cycles and pairing with xenobiotics, their basic antioxidant action processes also control the number of cellular thiols [57]. A popular co-factor-reducing reagent for the mammalian GPx enzyme is GSH [58]. Because of these factors, the high-fructose diet in our study decreased the total thiol amount and changed total antioxidant activity in rats, and inhibited SOD and GPx activities. Our research has shown that rats' cardiac MDA levels significantly increased when they consumed excess fructose. According to Chenni *et al.*, deficiencies in the enzymatic antioxidant system can decrease total glutathione, increasing peroxidation and oxidative damage. These changes can also be an indicator of perioxidative stress [59].

Moreover, it has been determined that individuals with metabolic syndrome (MetS) exhibit a relationship between the production of abundant ROS and the breakdown of endogenous protective antioxidants, which has been closely linked to the development of some cardiovascular disorders [60].

According to certain concepts, in the Mets rat model, the antioxidant efficacy of polyphenols in the heart lowered the generation of ROS by scavenging power and promoting the expression of antioxidant-defending enzymes (SOD and GSH-Px). Furthermore, the order of flavonoids' ability to lower lipid peroxidation was quercetin, kaempferol, apigenin, and luteolin [61].

Table 3. Oxidative stress markers of the heart of control, HFD, and treated groups**.**

Parameters	Control	HFD	HFD+SmE-N	HFD+Met
MDA (nmol/mg of prot)	5.802±0.252	10.449±0.617***	7.684±0.485^{*b}	8.176±0.372^{***b}
GSH (nmol/mg of prot)	1.1424±0.0205	0.7732±0.0753**	1.0133±0.0262^{**c}	1.1571±0.0501^{c}
SOD activity (mUI/mg of prot)	12.94±0.54	9.72±0.86*	10.63±0.30^{***a}	10.38±0.55**
GPx activity (µmol/mg of prot)	24.472±0.329	20.43±1.26**	22.920±0.667^{*b}	19.763±0.125^{***c}
Total thiol (mmol/mg of prot)	0.5216±0.0126	0.4572±0.0200**	0.4860±0.0124^{*a}	0.4575±0.0120***
(GPx /GSH) $\times 10^{3}$	21.546±0.164	19.782±0.725*	22.579±0.556^{c}	17.624±0.201^{***c}
(GSH/total -SH) $\times 10^{-3}$ (%)	0.2625±0.0146	0.1830±0.0108***	0.24121±0.006^{*c}	0.2467±0.0101^{c}
Total antioxidant capacity (%)	84.302±0.536	78.89±1.12***	84.354±0.520^{c}	85.576±0.287^{***c}

Values are provided as (mean ± SEM): n=6; * P<0.05, ** P<0.01, *** P<0.001: comparison with the control group; a P<0.05, b P<0.01, c P<0.001: comparison with HFD group.

3.4. Histopathological analysis

Under a microscope, the control group's heart tissue had a typical cell structure, and myofibrillar had normal striations and branches; a few collagen profiles were visible. However, the HFD group showed alterations in tissue involving inflammatory cell infiltrations, hemorrhage, necrosis, and cytoplasmic vacuolization, in addition to large bundles of collagen accumulation in the tissue. The heart section of the treated groups by SmE-N and Met demonstrated an amelioration in the tissue architecture, with a significant improvement in the distribution of collagen, as shown by the reduction of the deposition degree of collagen in cardiac tissue. (**Figure 1** and **Table 4**).

The long-term exposure of rats to a high-fructose diet had detrimental effects on their heart structural sections, as demonstrated by the histopathological investigation of the present study.

Previous findings indicate a potential role of metabolic syndrome, which can be induced by HFD, for the development of cardiac disease in rats, which manifests as heart tissue deterioration resulting from fibrotic cells and hypertrophic cardiac cells and the presence of inflammatory cells in heart tissue. The change in the histology is evidence of chronic inflammation, which begins as an adaptive response in the myocardium and progresses to activate free radicals and cell hypertrophy through increased protein synthesis and alterations in the configuration of the sarcomeric structure. Prolonged inflammation raises TNF-α production, which triggers IL-6 release, which causes cell hypertrophy and inflammatory cell infiltration [62, 63].

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

Parameters	Control	HFD	HFD+SmE-N	HFD+Met
Inflammation	-	++	-	-
Hemorrhage	-	++	-	-
Necrosis	-	+++	-	-
Cytoplasm vacuolization	-	+++	-	-
Collagen Accumulation	-	+++	+	+

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

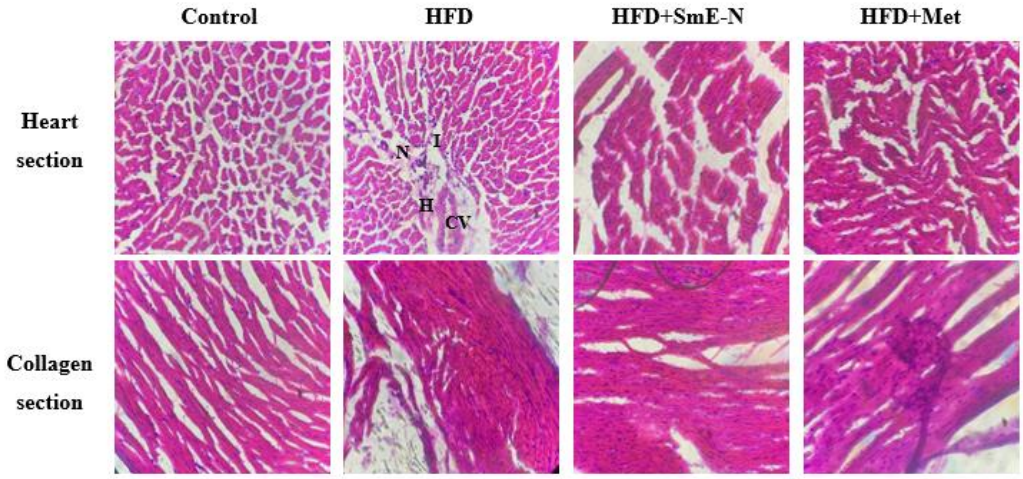

Figure 1. Histological photomicrographs of heart section and collagen of control, HFD, and treated groups at magnification ×400. *Inflammation (I); Necrosis (N); Hemorrhage (H); Cytoplasm vacuolization (CV)*.

Several studies have demonstrated a link between enhancing health and disease prevention and the organic bioactive compounds found in food. Medicinal plants possess large amounts of potassium, phosphorus, magnesium, and other minor minerals like copper, zinc, iron, calcium, and manganese, as well as bioactive substances like phenolic compounds, unsaturated fatty acids, phytosterols and their derivatives, triterpenoids, flavonoids, and saponins. The mentioned minerals and the bioactive can act simultaneously at different or concurrently at the same target areas, offering physiological advantages, improving health, and reducing oxidative stress associated with heart disease [64, 65].

4. Conclusion

Niosomes loaded *Sonchus maritimus* aqueous extract provided the therapeutic potential for treating cardiac dysfunction and hematological changes induced by a diet rich in fructose by improving the antioxidant defense system, hematological profile, and even the histological profile of the heart. These ameliorating effects were due to bioactive substances in the *Sonchus maritimus* leaves aqueous extract. In addition, the formulation of the smart nanocarrier niosomes "SmE-N" helps to prevent cardiac damage and hematological alterations through its ability to deliver the bio-substances of *Sonchus maritimus* extract.

Conflict of interest

The authors declare to have no conflict of interest.

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