Int J Basic Sci Med. 2021;6(4):132-138 Original Article

http://ijbsm.zbmu.ac.ir/ doi 10.34172/ijbsm.2021.24

# Down Regulation of Chemerin and Resistin in Type II Diabetic Rats Treated With Silver Nanoparticles Synthetized Using *Eryngium thyrsoideum Boiss* Extract

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**Received** August 22, 2021
**Accepted** September 24, 2021
**Published online** December 30, 2021

**Abstract**

**Introduction:** Diabetes is related to the higher production of inflammatory markers such as chemerin and resistin. Hypoglycemic influences of *Eryngium thyrsoideum* Boiss and silver nanoparticles (SNPs) have been established. The present study investigated the impacts of chemically or biologically synthesized SNPs using *E. thyrsoideum* extract on chemerin and resistin gene expressions in type II diabetic rats.

**Methods:** Twenty male Wistar rats weighing 180-200 g were used. Type 2 diabetes was induced by nicotinamide and streptozotocin. Saline and 2.5 mg/kg chemically or biologically synthesized SNPs were injected to diabetic rats for two weeks. Five healthy rats received saline for two weeks. One day after the last injection, fasting blood samples were collected. Mean serum concentrations of glucose, creatinine, urea, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured by spectrophotometry. The gene expression of chemerin and resistin was determined by real-time polymerase chain reaction (PCR).

**Results:** Mean serum concentrations of glucose, urea, ALT, AST, and mean relative gene expression of chemerin and resistin remarkably decreased in the diabetic group receiving SNPs prepared by either the chemical method or using *Eryngium* extract compared to the diabetic control group. Serum creatinine concentration did not change significantly in the control diabetic or diabetic groups receiving SNPs prepared either chemically or using the *Eryngium* extract.

**Conclusion:** Chemically or green synthesized SNPs prevent liver hepatocyte damage. They reduced inflammatory factors via exerting hypoglycemic effects.

**Keywords:** *Eryngium thyrsoideum*, Silver nanoparticles, Chemerin, Resistance

**Please cite this article as follows:** Poureskandar Souha S, Mahmoudi F, Noorizadeh E, Panahi A. Down regulation of chemerin and resistin in type ii diabetic rats treated with silver nanoparticles synthetized using *eryngium thyrsoideum boiss* extract. Int J Basic Sci Med. 2021;6(4):132-138. doi:10.34172/ijbms.2021.24.

## Introduction

Hyperglycemia, insulin resistance and overproduction of inflammatory markers are related to diabetes.[1] Chronic hyperglycemia, in turn, induces impairment of metabolism, oxidative stress, and kidney and hepatic damages.[1] In addition to energy storage resource, the adipose tissue is implicated in the regulation of the function of almost all organs of the body via the production of adipokines, which play vital roles in insulin resistance, cardiovascular dysfunction, metabolic syndrome, or obesity.[2]

Resistin, encoded by the *RETN* gene, is a 114- and 108-amino acid polypeptide in rodents and humans, respectively. In rodents, resistin, at the highest level, is produced in adipose tissues while in humans, its production in the adipose tissue is significantly lower, and it is expressed at high levels in the bone marrow, lung, pancreatic islet cells, muscles, and mononuclear cells.[3] In different species, resistin expression is completely gender dependent. In rats, plasma resistin level in males is higher than in females. Vice versa, in humans, its plasma level in females is higher than in males.[3] Several studies have indicated function of resistin in the progression of diabetes and obesity.[3-5]

Chemerin is encoded by the retinoic acid receptor responder 2 (*Rarres2*) gene.[5] Chemerin exerts its physiological functions related to the inflammatory response via binding to G-protein-coupled chemokine-like receptor 1 (CMKLR1).[5,6] Chemerin is produced at the highest level

in the white adipose tissue and liver and to a lesser extent in other peripheral tissues.[7] Also, CMKLR1 is highly synthesized in adipocytes and immune cells.[6] Chemerin acts as an important link between inflammation, heart failure, obesity, insulin resistance, and diabetes-related complications. Chemerin disrupts glucose uptake and the insulin receptor signaling pathway.[5]

The *Eryngium* genus belongs to the Apiaceae family. *Eryngium thyrsoideum* Boiss is consumed by people of Eastern Azerbaijan of Iran due to its potent hypoglycemic effects.[8] In addition, the antioxidant, anti-inflammatory, antidiabetic, and antimicrobial effects of other species of *Eryngium* have been established by several previous studies.[9-11]

Silver nanoparticles (SNPs) are clinically in interest due to their chemical stability and pharmaceutical roles.[12,13] Different physical or chemical methods are used to fabricate SNPs.[14,15] In fact, biosynthesis methods are attracting much interest due to their simplicity, lower cost, and safety as they generally utilize plant extracts to reduce the metal salts of NPs, instead of some harmful chemical materials.[15,16] This study tries to determine the impacts of chemically or bio-synthetically (using *E. thyrsoideum*) fabricated SNPs on chemerin and resistin gene expressions in diabetic rats.

## Materials and Methods

### *Animals*

Male Wistar rats, weighing 180-200 g (n = 20), were purchased from Iran University of Medical Sciences. Standard laboratory conditions, including standard temperature (22 ± 2 °C) and 12 h light/dark period were used for housing the rats. The guidance of the ethical committee of the Ardabil University of Medical Sciences (IR.ARUMS.REC.1400.082) was followed in this research.

### *Synthesis and Characterization of SNPs*

Chemically synthesized and bio-synthesized SNPs (using *E. thyrsoideum* extract) were prepared as described in our previous study.[17] TESCAN mira3 field-emission scanning electron microscope (FE-SEM, Brno, Czech Republic) and Philips CM30 TEM (Eindhoven, the Netherlands) operating at 300 kV were used for observation of the morphology and TEM images of SNPs, respectively.

### *Induction of Type 2 Diabetes*

Overnight fasting rats received nicotinamide (110 mg/kg, dissolved in distilled water) and streptozotocin (55 mg/kg, dissolved in citrate buffer, 0.1 M, pH: 4.5) via intraperitoneal injection. Streptozotocin was injected 15 minutes after nicotinamide.[18] The 10% glucose solution for one day was provided to the animals to prevent their death due to hypoglycemia. On day seventh, animals with a blood glucose concentration above 250 mg/dL were considered as diabetic.

### *Injections of Drugs*

On day seventh of the experiment, healthy control rats in group one received saline. Diabetic rats in group two also received saline. Rats in groups three and four received intraperitoneal injections of 2.5 mg/kg chemically and bio-synthetically prepared SNPs, respectively. Each group included five rats, and drug injections lasted for two weeks.

### *Biochemical Assays*

One the day following the last injection, the animals were deeply anesthetized by the injection of ketamine (80 mg/kg) and xylazine (10 mg/kg). After decapitation, serum samples were collected by centrifugation at 3000 rpm for 15 minutes. The serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, urea, and glucose were measured using special kits provided by Pars Azmoon Co. (Iran) (Figure 1).

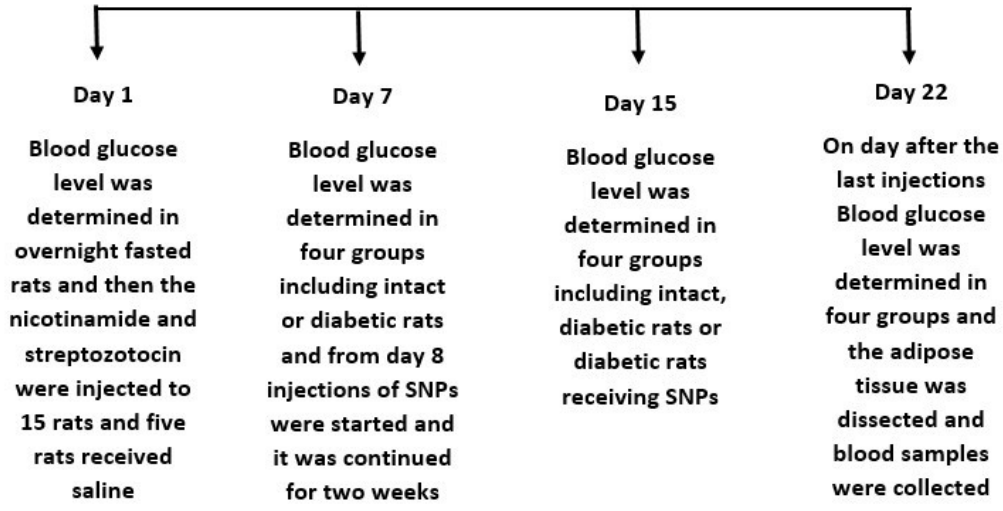


**Figure 1.** The Time Points of Drug Injections and Sampling.

### *Real-time PCR*

The visceral adipose tissue was dissected and stored at -80°C. Total RNA was isolated; cDNA was synthesized, and mRNA levels of *chemerin* and *resistin* were measured using real-time PCR. GAPDH was used as a reference gene to normalize data. PCR cycling conditions were as follows: first denaturation at 95°C for 15 minutes, followed by 40 cycles of denaturation at 95°C for 20 secs, annealing at 60°C for 40 seconds (*chemerin*, *resistin*, and *GAPDH*). Specific oligo nucleotide sequences were used as the forward and reverse primers: chemerin; forward 5′-CTAAAGCAAAGCCATGAAGTGCC -3′, and reverse 5′-TGAGAAGAACAGGTCATCAGC

AC-3′,resistin;forward5′-GACGGTTGATTGAGAACTGA -3′, and reverse 5′- TTGTGTATTTCCAGACCCTC -3′, and GAPDH; forward: 5′-AAGTTCAACGGCACAGTCAAG-3′, and reverse: 5′- CATACTCAGCACCAGCATCAC-3′. The chemerin, resistin, and GAPDH amplified products sized 202, 137, and 120 base pairs, respectively. The expression fold change of each gene was calculated using the equation of $2^{-\Delta\Delta CT}$.

### *Statistical Analysis*

The results were indicated as mean ± SEM (standard error of mean) using SPSS software (version 16) and one-way ANOVA. Comparisons between groups were made by the post hoc Tukey's test. The significance threshold was defined at $P < 0.05$.

## Results

### *Characterization of Morphology and Size of SNPs*

The SEM images of green-synthesized SNPs (GSNPs) using *E. thyrsoideum* (Figure 2a-c) indicated spherical morphology with partial aggregation due to the very small dimensions and high surface energy of the NPs. Also, the chemically synthesized SNPs (ChSNPs) showed spherical morphology; however, their particle sizes were bigger than that of green synthesized SNPs (Figure 2d-f).

TEM images showed spherical SNPs as dark spots with good disparity. There were bright backgrounds around the dark particles, which may be related to the plant extract used for the synthesis of green SNPs. TEM images indicated spherical particles with an average size of 14 nm and 75 nm for GSNPs and ChSNPs, respectively (Figure 3a-c and Figure 3d-f). Most of the green SNPs had the same size and showed a homogeneous distribution.

### *Serum Biochemical Indicators*

Mean serum glucose concentration significantly increased in diabetic rats compared to the control group ($P < 0.05$). A significant decrease was observed in the diabetic rats receiving either ChSNPs or GSNPs in comparison to the diabetic group (Figure 4, $P < 0.05$).

Increased serum concentrations of ALT, AST, and urea were observed in diabetic rats compared to the control group ($P < 0.05$). The injection of ChSNPs or GSNPs to diabetic rats remarkably reduced the concentration of ALT, AST, and urea compared to the diabetic control group ($P < 0.05$). Serum levels of creatinine did not alter in the diabetic control group or the diabetic rats receiving either ChSNPs or GSNPs (Figure 5).

### *Gene Expression Analysis Results*

The mean relative gene expressions of *chemerin* and *resistin* remarkably augmented in diabetic rats compared with the control group ($P < 0.05$). The injection of

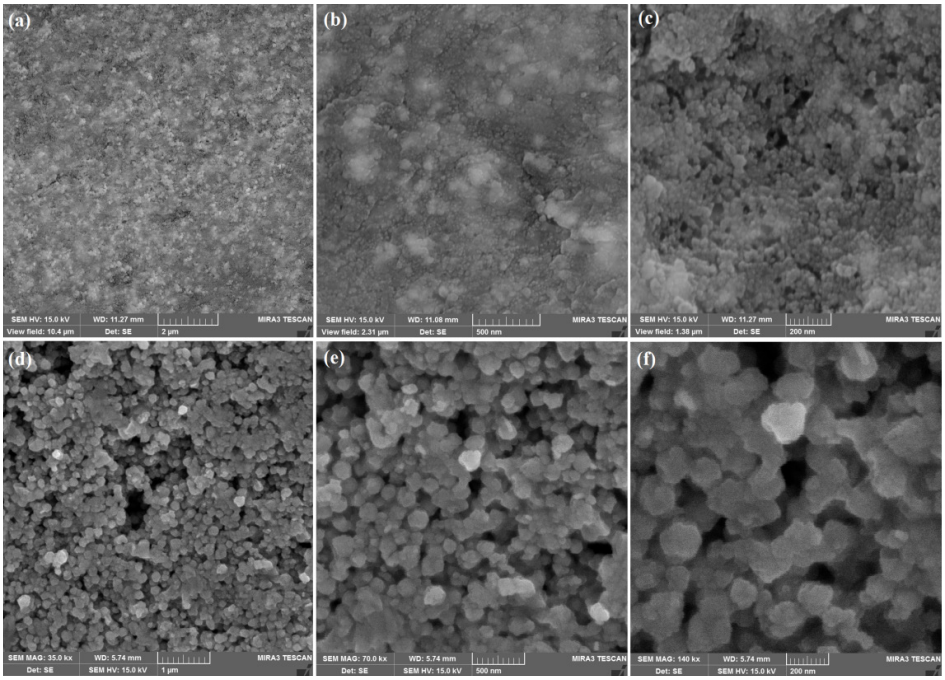


**Figure 2.** SEM Images (a-c) for Green-Synthesized SNPs Prepared Using *E. thyrsoideum* and (d-f) Chemically Synthesized SNPs

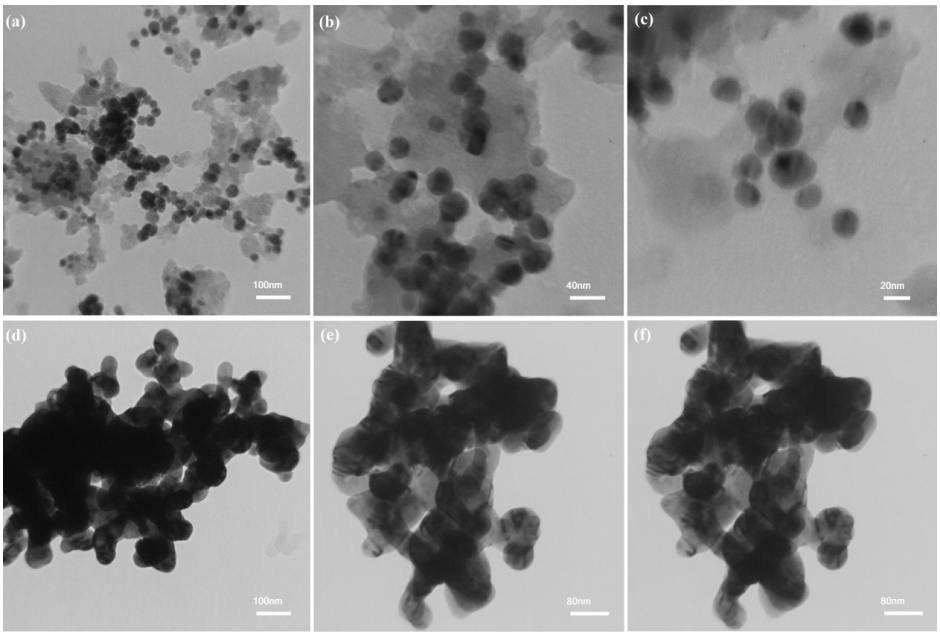


**Figure 3.** TEM Images (a-c) for the Green-Synthesized SNPs Prepared Using *E. thyrsoideum* and (d-f) Chemically Synthesized SNPs.

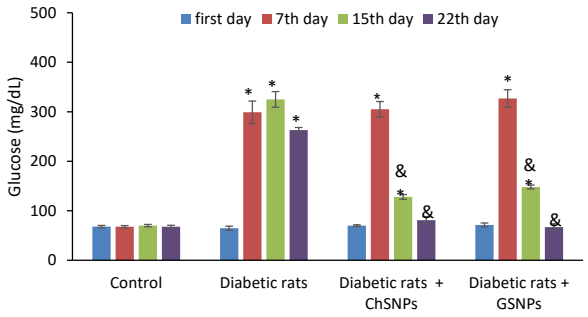


**Figure 4.** The Influences of Chemically-Synthesized SNPs or Green-Synthesized SNPs using *E. thyrsoideum* on Fasting Serum Glucose Concentration. The symbol * shows a significant difference between the control and other groups. The symbol & shows a significant difference between the diabetic control and other groups.

ChSNPs or GSNPs caused a significant decrease in the mean relative gene expressions of *chemerin* and *resistin* compared to diabetic rats (Figure 6, $P < 0.05$).

## Discussion

The present data showed that both chemically or bio-synthesized SNPs (using *E. thyrsoideum*) exerted hypoglycemic effects and significantly reduced the serum concentrations of hepatic enzymes and urea in type II diabetic in comparison to diabetic control rats. The dose of the NPs was selected based on previous research indicating the hypoglycemic influences of chemically or bio-synthesized (using *E. thyrsoideum*) SNPs in type 1 alloxan-induced diabetes.[17,21] *In fact,* SNPs also improved hematological parameters, oxidative stress, and inflammatory markers in diabetic rats.[17,22,23]

It has been revealed that normal insulin secretion inhibits the release of hepatic glucose to blood circulation,[24] and that SNPs have a potent ability to improve insulin production in diabetic animal models.[21] So, the SNPs synthesized by both methods may exert hypoglycemic effects partly via increasing insulin secretion and decreasing the activity of gluconeogenesis and glycogenolysis enzymes.[25] That's to say, reducing blood glucose and increasing plasma insulin secretion in diabetic models by the injection of ChSNPs have been proven in several previous studies.[21]

As oxidative stress and inflammatory responses are main markers in the progression of insulin resistance and following diabetes, so to find the molecular mechanisms of improving the inflammatory complications related to diabetes, we assessed the effects of both chemically or green-synthesized SNPs (using *Eryngium*) on *chemerin* and *resistin* gene expressions in diabetic rats for the first time.

In accordance with several previous studies, the induction of diabetes resulted into the upregulation of *resistin* and *chemerin* genes in the adipose tissue of diabetic rats. These findings are in accordance with several previous reports that have established the hyperglycemic effects of resistin and chemerin in diabetes.[4,26] It has been shown that the mRNA level of resistin elevated in response to hyperglycemia in adipocytes. Resistin also caused a drop in insulin-induced glucose uptake, impaired insulin signaling in the liver, muscles, and the adipose tissue, suppressed glucose transporter type 4 (GLUT4) gene expression, increased the synthesis of gluconeogenic enzymes in the liver, and stimulated hepatic glucose production in previous studies.[3,4,26] In resistin knockout mice, blood glucose concentration reduced due to a fall in hepatic glucose production.[3] The injection of an anti-resistin antibody improved insulin sensitivity. Also, it has been shown that chemerin and resistin alleviate insulin sensitivity.[4]

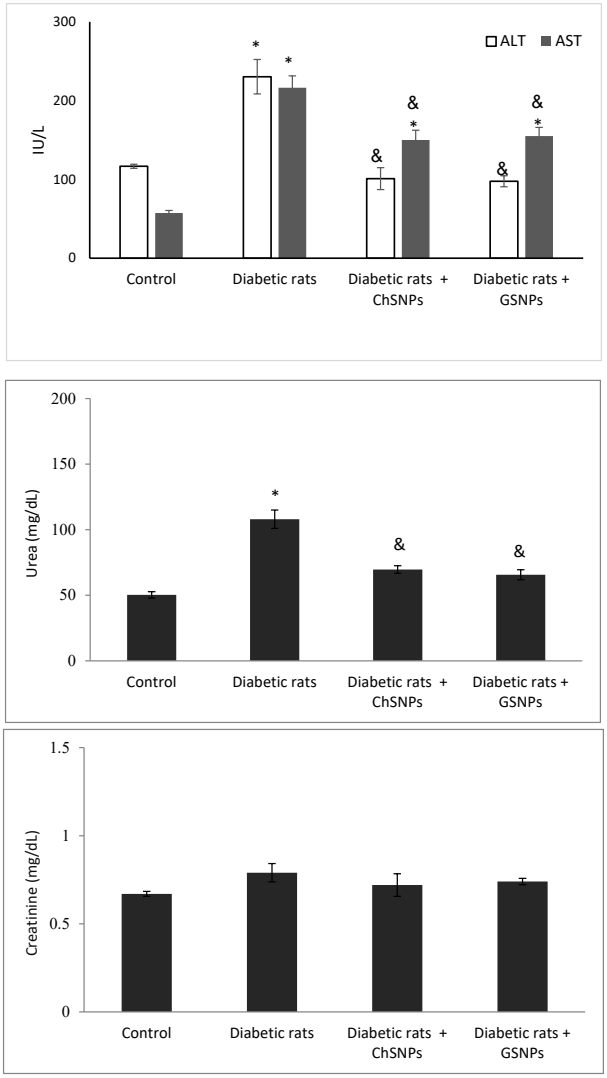


**Figure 5.** The Impacts of Chemically-Synthesized SNPs or Green-Synthesized SNPs Using *E. thyrsoideum* on the Serum Concentrations of Alanine Aminotransferase, Aspartate Aminotransferase, Urea, and Creatinine. The symbol * shows a significant difference between the control and other groups. The symbol & shows a significant difference between the diabetic control and other groups.

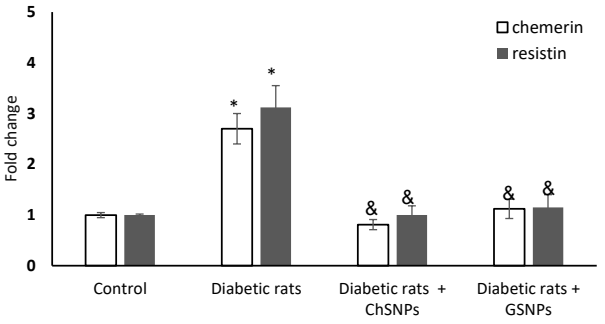


**Figure 6:** The Impact of Chemically-Synthesized SNPs or Green-Synthesized SNPs Using *E. thyrsoideum* on the Gene Expressions of *chemerin* and *resistin*. * Compared to control; & Compared to diabetic rats. The symbol * shows a significant difference between the control and other groups. The symbol & shows a significant difference between the diabetic control and other groups.

Our results demonstrated the suppressive effects of the synthesized SNPs on the gene expression of *resistin* and *chemerin* in the visceral adipose tissue of diabetic rats in comparison to the control diabetic group. Based on previous studies, the production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), induces resistin and chemerin gene expression.[3,5,27] Vice versa, resistin and chemerin result in the upregulation of C- reactive protein (CRP), IL-6, and TNF-α.[3,5,27] On the other hand, TNF-α increases cytokine signaling-3 (SOCS-3) expression via activating MAPK kinase 6,[28] and SOCS-3 is a negative regulator of the insulin signaling pathway. Also, resistin mediates insulin resistance via inducing the over expression of SOCS-3.[4] As previous studies reported, lower doses of SNPs might exert potential anti-inflammatory properties, and they could inhibit the production of IL-12, IL-6, IL-18, and TNF-α.[28-30] So, both chemically or bio-synthesized (using *Eryngium*) SNPs may exert inhibitory effects on chemerin and resistin gene expression somewhat via suppressing TNF-α production in the adipose tissue.

The suppressive effects of SNPs on chemerin are in accordance with several previous studies that demonstrated higher levels of chemerin and CMKLR1 (chemerin receptor) in diabetic people and the positive association of chemerin with insulin resistance.[4] Inflammatory pathological conditions such as obesity or diabetes are related to the synthesis of inducible nitric oxide synthase (iNOS) and then the overproduction of nitric oxide in the adipose tissue. Nitric oxide is implicated in the induction of hyperglycemia and oxidative stress, which in turn leads to the overproduction of inflammatory markers.[31] Also, it has been shown that oxidative stress decreases anti-oxidative enzymes and increases the production of chemerin in diabetes.[32] Also, previous studies demonstrated that SNPs were able to suppress iNOS and decrease ROS production.[33] Thus, suppressing iNOS and stress oxidative may be one possible mechanism through which both chemically or green-synthesized SNPs downregulate chemerin gene expression in diabetic rats. The present study demonstrated the modulating effects of synthesized SNPs (using *E. thyrsoideum*) on pro-inflammatory adipokines in the adipose tissue. However, further studies are needed to investigate the effects of these SNPs on other pro- or anti- inflammatory markers such as leptin, adiponectin, apelin, and so on, which are well-known to be associated with insulin resistance and hyperglycemia.

## Conclusion

Chemically and green-synthesized (*E. thyrsoideum* aqueous extraxt) SNPs' average sizes were 75 nm and 14 nm, respectively. Both chemically and green-synthesized SNPs induced hypoglycemic effects and significantly decreased chemerin and resistin gene expressions in the

adipose tissue of diabetic rats compared to the diabetic control group. As chemerin and resistin are linked with inflammation and insulin resistance, the down-regulation of these pro- inflammatory adipokines may be a potential therapeutic target for the treatment of diabetes-related complications.

**Acknowledgments**

This study was supported financially by University of Mohaghegh Ardabili, Iran.

**Authors' Contributions**

FM developed the idea and designed the experiments. SPS and FM carried out the experiments. FM, EN, AP, and SPS contributed to data interpretation. FM took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analyze the data, and prepare the manuscript.

**Competing Interests**

There is no conflict of interest.

**Ethical Approval**

All experimental procedures were done according to the guidance of the ethical committee of the Ardabil University of Medical Sciences (IR.ARUMS.REC.1400.082).

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