

Original Article

The role of selenium and zinc oxide nanoparticles on mitigating side effects of obesity in rats

O papel das nanopartículas de óxido de selênio e zinco no lado mitigador e efeitos da obesidade em ratos

A. H. Mahmoud^a , H. A. AbdElMonem^a  and M. M. Abbas^a 

^aEgyptian Atomic Energy Authority, Nuclear Research Centre, Biological Application Department, Cairo, Egypt

Abstract

Obesity and related diseases represent greatest threats to human health. Nanoparticles (NPs) serve to reduce toxicity; reinforce bioactivity and improve targeting. This study was intended to investigate the antiobesity and antioxidant activities of selenium and zinc oxide nanoparticles. Methods: Twenty four adult male rats were divided into four groups, group 1 control rats fed normal diet and the other three groups were fed high fat diet (HFD) for 10 weeks to induce obesity and injected intraperitoneally with saline, SeNPs (30µg/kg b.wt) and ZnONPs (5mg/kg b.wt) respectively on the last two weeks of feeding (9th and 10th). Results: HFD increased body weight, oxidative stress as indicated by elevated lipid peroxidation and decreased glutathione and catalase levels, increased significantly serum lipid fractions, leptin, liver enzymes, creatinine and uric acid. While causing a substantial decrease in HDL-C and thyroid hormone T₄ levels. The results confirmed that treatment with SeNPs and ZnONPs significantly reduced body weight, MDA and improved liver and kidney functions, ameliorated serum lipid fractions level and significantly increased glutathione, catalase, HDL-C and thyroid hormone. Conclusion: SeNPs and ZnONPs significantly mitigate hyperlipidemia and oxidative stress. So, they might be potential candidate for obesity amelioration.

Keywords: selenium, zinc oxide, obesity, nanoparticles, antioxidants.

Resumo

A obesidade e doenças relacionadas representam as maiores ameaças à saúde humana. As nanopartículas (NPs) servem para reduzir a toxicidade, reforçar a bioatividade e melhorar o direcionamento. Este estudo teve como objetivo investigar as atividades antiobesidade e antioxidante de nanopartículas de selênio e óxido de zinco. Métodos: Vinte e quatro ratos machos adultos foram divididos em quatro grupos, grupo 1 ratos controle alimentados com dieta normal e os outros três grupos foram alimentados com dieta hiperlipídica (HFD) por 10 semanas para induzir obesidade e injetados intraperitonealmente com soro fisiológico, SeNPs (30µg/kg b.wt) e ZnONPs (5mg/kg b.wt) respectivamente nas duas últimas semanas de alimentação (9^a e 10^a). Resultados: HFD aumentou o peso corporal, estresse oxidativo indicado pela peroxidação lipídica elevada e diminuição dos níveis de glutatona e catalase, aumentou significativamente as frações lipídicas séricas, leptina, enzimas hepáticas, creatinina e ácido úrico. Enquanto causa uma diminuição substancial nos níveis de HDL-C e hormônio tireoidiano T₄. Os resultados confirmaram que o tratamento com SeNPs e ZnONPs reduziu significativamente o peso corporal, MDA e melhorou as funções hepáticas e renais, melhorou o nível das frações lipídicas séricas e aumentou significativamente a glutatona, catalase, HDL-C e hormônio tireoidiano. Conclusão: SeNPs e ZnONPs atenuam significativamente a hiperlipidemia e o estresse oxidativo, então eles podem ser candidatos em potencial para a melhora da obesidade.

Palavras-chave: selênio, óxido de zinco, obesidade, nanopartículas, antioxidantes.

1. Introduction

Obesity is a worldwide health problem, resulting from a consequence of an interaction between different factors, related to genetics environment (Gittner et al., 2017), food habits (Kieliszek and Błazejak, 2016) and micronutrients deficiency (Sánchez et al., 2016) that may be due to lower intake of fruits and vegetables and higher intake of poor-quality foods (Beal et al., 2017). A balanced

antioxidant status has main effect on body balance and has been linked to better symptoms associated with obesity (Sainz et al., 2015).

In obese cases, oxidative stress markers are increased, the increase in reactive oxygen species (ROS) in adipose tissue is associated with increasing NADPH oxidase activity and decline in antioxidant enzyme levels (Furukawa et al.,

*e-mail: dr.amalhanafi.1@gmail.com

Received: May 20, 2022 – Accepted: October 4, 2022



This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

2004). Therefore, elements that reduce oxidative stress are therapeutically effective as antiobesity.

The consumption of high fat diet (HFD) is associated with metabolic syndrome causing obesity (Thanopoulou et al., 2003), resulting in more production of ROS in liver and severe changes in mitochondrial lipids (Vial et al., 2011). So obesity is considered a cause of morbidity and mortality (El-Shiekh et al., 2019).

Leptin is a metabolic hormone, secreted by adipocytes proportionally to the amount of body fats. In HFD leptin level rises due to leptin resistance that resulting from increasing inflammation and oxidative stress (Leon-Cabrera et al., 2013).

In obese patients, an insufficiency of trace elements has been reported mainly, Zinc (Zn) (Berger et al., 1992) and selenium (Donma and Donma, 2016). Selenium is an essential trace element is associated with enhancing immune system (Arthur et al., 2003), and capable of modulating the inflammatory responses as it acts as antioxidant. Selenium is incorporated as selenocysteine in antioxidant enzymes as, glutathione peroxidase (Gpx), thioredoxin reductase and iodothyronine deiodinase. Selenium acts as the redox center of all these enzymes and is essential for their biochemical activities. Several studies have reported a negative correlation between serum selenium and BMI (Stranges et al., 2010; Ortega et al., 2012). A study demonstrated that obesity and its severity were associated with a low dietary selenium intake, every increase in dietary selenium intake by 1 mg/Kg/day causes 3-6% decrease in the mass of body fat (Wang et al., 2016).

Also zinc is an essential metal, widely used due its abundance and non-toxic effect. Zinc plays an important role in preventing inflammations in different biological processes (Chasapis et al., 2012) by scavenging free radicals and acting as antioxidant preventing the formation of (OH⁻) hydroxide ion (Jomova and Valko, 2011) that causes severe chronic localized damage in cellular components (Powell, 2000). Many studies demonstrated that zinc can inhibit postischemic injuries in the brain, kidney, retina by replacing iron and copper from binding sites of metallothioneins (MT). MT's are metal-binding proteins having an affinity for zinc and many other metals. They are included in the reduction of oxidative stress, cytoprotective activity and anti-inflammation (Tapiero and Tew, 2003). Zn is required for the activity of more than 300 enzymes, 1000 transcription factors and has a role in the control of genetic expression (Carrasco-Rando et al., 2016).

Recently, nanotechnology field increases and produces different nanoparticles that can be used in medicine, electronics, consumer products. This technology can provide nano scale size particles (1-100 nm). Decreasing the size to Nano range can change their mechanical, structural, chemical and physical properties, thus nanoparticles are the most important materials in different life aspects, as these particles have one dimension in the range of 1-100nm, that increases surface area and permeability into cells (Mironava et al., 2010) and avoiding adverse gastrointestinal reactions and improve their absorption (Lucas, 2010).

In medicine, the most accepted advantage of nanoparticles is the enhanced safely Selenium nanoparticles

give high functioning potential and have significant effect on increasing glutathione and thioredoxine reductase activities (Torres et al., 2012; Srivastava et al., 2014) and Zinc oxide nanoparticles, as antibacterial (Xie et al., 2011), antioxidant and a therapeutic for treatment of mast cells mediated allergies (Agarwal et al., 2019). In the light of these findings, a promising role for ZnONPs and SeNPs as antioxidants. Thus, this study aimed to evaluate the effects of Se and

Zn oxide nanoparticles supplementation on reducing obesity and metabolic syndrome.

2. Materials and Methods

2.1. Chemical

Zinc oxide nanoparticles (ZnONPs) (CAS Number 1314-13-2) was purchased from sigma aldrich (Saint Louis, Mo, USA). The diameters of the particles <50 nm. ZnONPs was suspended in 0.9% NaCl. The Suspension was sonicated for 20 min. in a bath Sonicator to avoid particles aggregations (Branson,2510) and was mixed using a vortex mixer for 1min before every injection. Selenium nanoparticles (SeNPs) were purchased from Shanghai Stone Nano- Technology Port Co. Ltd., China. This product is based on the liquid Nano-Se as main ingredient for health care supplement. The sizes of Se particles ranged from 60 to 80 nm in form of orange powder. SeNPs was suspended in 0.9% NaCl using magnetic stirrer.

2.2. High Fat Diet (HFD)

It was a mixture of 65% standard chow diet and 35% butter fat oil (Chung et al., 2018). Body weight, body length and tail length were measured every week for 10 weeks, and Lee's index was calculated using the following formula: [Body weight (g) 1/3 x 1000] / body length (cm), and mass index (BMI) was calculated as body weight(g)/ body length (cm²), (Bernardis, 1970).

2.3. Animals

Adult male albino rats (weighing 160-180g.) were obtained from animal house of Biological Application Department at Nuclear Research Center, Inches. The rats were housed in stainless steel laboratory animal cages in a ventilated room, maintained at 25 C° ± 2 C° at 12hr dark/ light cycles. Food and water were provided *ad libitum*. After seven days of acclimatization. Twenty four male rats were assigned into four groups, (6 rats/group).

Group 1: Control group rats fed an ordinary diet.

Group 2: rats fed on high fat diet (HFD) for 10 weeks.

Group 3: rats were fed on HFD for 10 weeks and were intraperitoneally injected with freshly prepared ZnONPs (5mg/kg body weight) (5 days/week) on the last 2 weeks of feeding (9th and 10th) (Bashandy et al., 2018).

Group 4: rats were fed on HFD for 10 weeks and were intraperitoneally injected with SeNPs (30µg/kg body weight) (5days/week) on the last 2 weeks of feeding (9th and 10th) (Emara et al., 2019).

Animal experiments were carried out in accordance with criteria of investigation and Ethics committee of Faculty of science, Ain Shams University, Egypt (REC-FS, ref no. 00033), following the guidelines of the National Institutes of Health guide for the use of laboratory animals (NIH).

2.4. Biochemical analyses

At the end of the experimental period (10 weeks), rats were fasted over night. Animals were decapitated and blood samples were collected in test tubes and centrifuged at 3000 r.p.m. for 10 min and kept under -18°C for biochemical analysis.

Serum concentrations of T_4 and TSH were assessed by radio immunoassay using kits purchased from DIA source Immuno Assay S.A.-Rue du Bosquet, 2-B 1348 Louvain- La-Neuve- Belgium. Serum Leptin was determined using Rat ELISA kits (Siemens health care diagnostics, Cambridge, MA, USA).

Serum total cholesterol, total lipids, triglycerides and high density lipoprotein-cholesterol (HDL- C) levels were measured with enzymatic colorimetric methods using Bio-diagnostic commercial kits. While low density lipoprotein-cholesterol (LDL-C) was calculated according to Friedwald's equation: $\text{LDL-C}(\text{mg/dl}) = \text{TC} - (\text{TG}/5 + \text{HDL-C})$ (Friedewald et al., 1972).

A colorimetric determination of Malondialdehyde (MDA) was carried out according to the method of Ohkawa et al. (1979), Catalase (CAT) activity in serum was determined calorimetrically according to the method of Luck (1974) and reduced glutathione (GSH) level in blood was measured by a process adopted by Beutler et al. (1963) using kits purchased from Bio diagnostic Co, Egypt.

Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, albumin, creatinine and uric acid were determined using colorimetric assay kits from Bio diagnostic Co, Egypt.

2.5. Statistical analysis

Data were statically analyzed using computer program COSTAT. Program 3.03,198. Statically comparisons were performed using one-way (ANOVA) followed by Duncan's Multiple Range test. Significant differences were considered at $P < 0.05$. Results are expressed as Mean \pm standard deviations. Pearson correlation coefficients were calculated for relationship between body weight and some measured parameters.

3. Results

Table 1 showed that rats fed HFD revealed a marked increase in body weight as compared to rats fed normal diet (group1). SeNPs & ZnONPs treatment decreased significantly the percentage of body weight gain, Lee's index and body mass index (BMI) compared to HFD fed rats.

The effect of SeNPs and ZnONPs on thyroid hormones in HFD rats were studied (Table 2). Rats fed on HFD showed a significant decrease in serum level of T_4 and a high increase in TSH level as compared to control group. Treatment with SeNPs alleviate these changes significantly and revealed values comparable to control group. Treatment with ZnONPs increased significantly T_4 level in HFD and decreased level of TSH in values less than SeNPs. Also, Table 2 showed that leptin hormone in HFD rats exhibited a significant

Table 1. Effects of selenium nanoparticles (SeNPs) and zinc oxide nanoparticles (ZnONPs) on variation in body weight gain in rats fed a high fat diet (HFD).

| Groups Parameters | Control Normal diet | High fat diet (HFD) | HFD + SeNPs | HFD + ZnONP |
|-------------------------|--------------------------------|--------------------------------|-------------------------------|---------------------------------|
| Initial body weight (g) | 168.0 \pm 9.9 | 170.6 \pm 6.4 | 169.8 \pm 11.7 | 168.2 \pm 8.4 |
| Final body weight (g) | 330.1 \pm 12.16 ^c | 431.6 \pm 24.99 ^a | 392.8 \pm 2.3 ^b | 364.0 \pm 39.06 ^{bc} |
| Body gain | 95.9 \pm 4.96 ^d | 153.1 \pm 10.75 ^a | 131.62 \pm 9.6 ^b | 110.28 \pm 14.56 ^c |
| Lee's index | 305.96 \pm 8.3 ^b | 337.5 \pm 42.53 ^a | 317.9 \pm 6.43 ^b | 312.44 \pm 8.61 ^b |
| BMI | 0.63 \pm 0.04 ^c | 0.86 \pm 0.01 ^a | 0.75 \pm 0.05 ^b | 0.71 \pm 0.1 ^{bc} |

Values are presented as Mean \pm SD (n=6). Different letters indicate significant difference ($P < 0.05$).

Table 2. Effects of selenium nanoparticles (SeNPs) and zinc oxide nanoparticles (ZnONPs), on thyroid hormone (T_4), thyroid stimulating hormones (TSH) and serum leptin levels in rats fed a high fat diet (HFD).

| Groups Parameters | Control Normal diet | High fat diet (HFD) | HFD + SeNPs | HFD + ZnONP |
|---|-------------------------------|--------------------------------|-------------------------------|-------------------------------|
| T_4 (pmol/L) | 37.13 \pm 4.08 ^a | 6.93 \pm 1.2 ^d | 27.61 \pm 2.6 ^c | 14.59 \pm 2.28 ^b |
| TSH ($\mu\text{U}/\text{mL}/\text{ml}$) | 1.45 \pm 0.54 ^d | 10.629 \pm 1.55 ^a | 3.16 \pm 0.27 ^c | 5.32 \pm 0.61 ^b |
| Leptin (ng/ml) | 8.21 \pm 1.8 ^d | 35.07 \pm 3.2 ^a | 16.33 \pm 2.27 ^c | 25.01 \pm 2.1 ^b |

Values are presented as Mean \pm SD (n=6). Different letters indicate significant difference ($P < 0.05$). T_4 = Thyroxin; TSH = Thyroid stimulating hormone.

increase than control group. SeNPs supplementation significantly decreased serum leptin level in HFD rats, ZnONPs supplementation also decreased leptin in rats fed HFD in an acceptable value.

Table 3 Lipid profile in HFD rats showed that rats fed HFD revealed significant increases in Total cholesterol (TC), Triglycerides (TG), Total lipids (TL) and LDL and a marked decrease in HDL in comparison with control rats fed ordinary diet. Treatment with SeNPs significantly reduced the dyslipidaemia in HFD rats and comparable results were obtained with ZnONPs supplementation to HFD rats but the hypolipidemic effect was more potent with SeNPs.

Table 4. The concentration of MDA displayed a significant increase in HFD rats as compared to control, meanwhile reduced glutathione level and catalase activity were significantly decreased in HFD group. Treating rats with SeNPs significantly reduced MDA concentration resulted

in improvement of antioxidant biomarkers level, also ZnONPs exhibited similar results, significantly reduced MDA and increased catalase activity and GSH level but exerted less effect than SeNPs.

Table 5 showed significant increase in liver enzymes (ALT, AST and ALP) in HFD group as compared to control rats. Intraperitoneal injection of SeNPs and ZnONPs significantly decreased liver enzymes elevation. The concentrations of total protein and albumin were decreased in HFD rats. Treatment with SeNPs and ZnONPs induced significant increase in both total protein and albumin compared to HFD. Rats fed on HFD, showed marked increase in creatinine and uric acid levels compared to control rats. Treatment with SeNPs and ZnONPs improved the increase in creatinine and uric acid levels than the HFD group.

Correlation coefficient (r) values between body weight and lipid parameters showed significant positive correlation

Table 3. Effects of selenium nanoparticles (SeNPs) and zinc oxide nanoparticles (ZnONPs) on lipid profile level in rats fed a high fat diet (HFD).

| Groups Parameters | Control Normal diet | High fat diet (HFD) | HFD + SeNPs | HFD + ZnONP |
|-----------------------|----------------------------|----------------------------|-----------------------------|----------------------------|
| Cholesterol (mg/dl) | 80.8 ± 1.64 ^c | 126.6 ± 4.48 ^a | 85.4 ± 3.57 ^c | 102.26 ± 9.03 ^b |
| Triglycerides (mg/dl) | 70.21 ± 8.54 ^d | 218.6 ± 22.3 ^a | 120.03 ± 11.21 ^c | 182.1 ± 12.31 ^b |
| Total lipid (mg/dl) | 369.21 ± 32.9 ^c | 825.93 ± 73.7 ^a | 401.15 ± 44.2 ^c | 521.4 ± 55.8 ^b |
| HDL (mg/dl) | 52.51 ± 3.5 ^a | 34.81 ± 1.79 ^c | 45.05 ± 2.58 ^b | 48.52 ± 4.43 ^{ab} |
| LDL (mg/dl) | 14.28 ± 0.99 ^b | 48.12 ± 4.72 ^a | 16.37 ± 1.48 ^b | 17.38 ± 3.60 ^b |

Values are presented as Mean ± SD (n=6). Different letters indicate significant difference (P<0.05).

Table 4. Effects of selenium nanoparticles (SeNPs) and zinc oxide nanoparticles (ZnONPs) on the level of malondialdehyde (MDA) and antioxidant biomarkers glutathione (GSH) level and catalase (CAT) activity in rats fed a high diet (HFD).

| Groups Parameters | Control Normal diet | High fat diet (HFD) | HFD + SeNPs | HFD + ZnONP |
|----------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| MDA (nmol/ml) | 52.45 ± 3.19 ^c | 85.7 ± 18.6 ^c | 46.45 ± 2.89 ^c | 66.25 ± 10.9 ^b |
| GSH (mg/dl) | 56.35 ± 5.3 ^a | 22.68 ± 1.6 ^c | 58.09 ± 7.07 ^a | 39.09 ± 9.11 ^b |
| CAT (µ/ml) | 0.68 ± 0.07 ^a | 0.058 ± 0.04 ^d | 0.51 ± 0.05 ^b | 0.39 ± 0.09 ^c |

Values are presented as Mean ± SD (n=6). Different letters indicate significant difference (P<0.05).

Table 5. Effects of selenium nanoparticles (SeNPs) and zinc oxide nanoparticles (ZnONPs) on liver enzymes (ALT, AST and ALP) as well as creatinine and uric acid levels in rats fed a high fat diet (HFD).

| Groups Parameters | Control Normal diet | High fat diet(HFD) | HFD + SeNPs | HFD + ZnONP |
|----------------------|----------------------------|-----------------------------|----------------------------|----------------------------|
| ALT (u/l) | 47.34 ± 4.8 ^c | 96.32 ± 13.4 ^a | 45.6 ± 6.2 ^c | 69.2 ± 10.8 ^b |
| AST (u/l) | 51.57 ± 6.9 ^c | 118.92 ± 11.39 ^a | 72.4 ± 4.2 ^b | 101.8 ± 7.5 ^a |
| ALP (u/l) | 216.54 ± 35.4 ^c | 693.95 ± 71.8 ^a | 471.12 ± 50.5 ^b | 421.52 ± 75.4 ^b |
| Total protein (g/dl) | 8.09 ± 0.36 ^c | 6.54 ± 0.38 ^d | 9.37 ± 1.13 ^b | 10.63 ± 1.13 ^a |
| Albumin (g/dl) | 3.77 ± 0.17 ^b | 3.09 ± 0.05 ^c | 5.82 ± 0.58 ^a | 5.57 ± 0.64 ^a |
| Creatinine (mg/dl) | 0.67 ± 0.05 ^d | 1.06 ± 0.03 ^a | 0.83 ± 0.09 ^c | 0.94 ± 0.04 ^b |
| Uric acid (mg/dl) | 5.77 ± 0.85 ^c | 9.71 ± 1.13 ^a | 6.97 ± 0.91 ^{bc} | 8.04 ± 1.2 ^b |

Values are presented as Mean ± SD (n=6). Different letters indicate significant difference (P<0.05).

with total lipids ($r = 0.705$, $p < 0.01$), Total cholesterol ($r = 0.704$, $p < 0.01$), Triglycerides ($r = 0.689$, $p < 0.01$) and LDL ($r = 0.707199$), and a negative correlation between body

weight HDL-C value ($r = -0.421$, $p < 0.01$), Figure 1. Also, Figure 1. Showed significantly positive correlation between body weight and leptin hormone ($r = 0.703$, $p < 0.01$) and

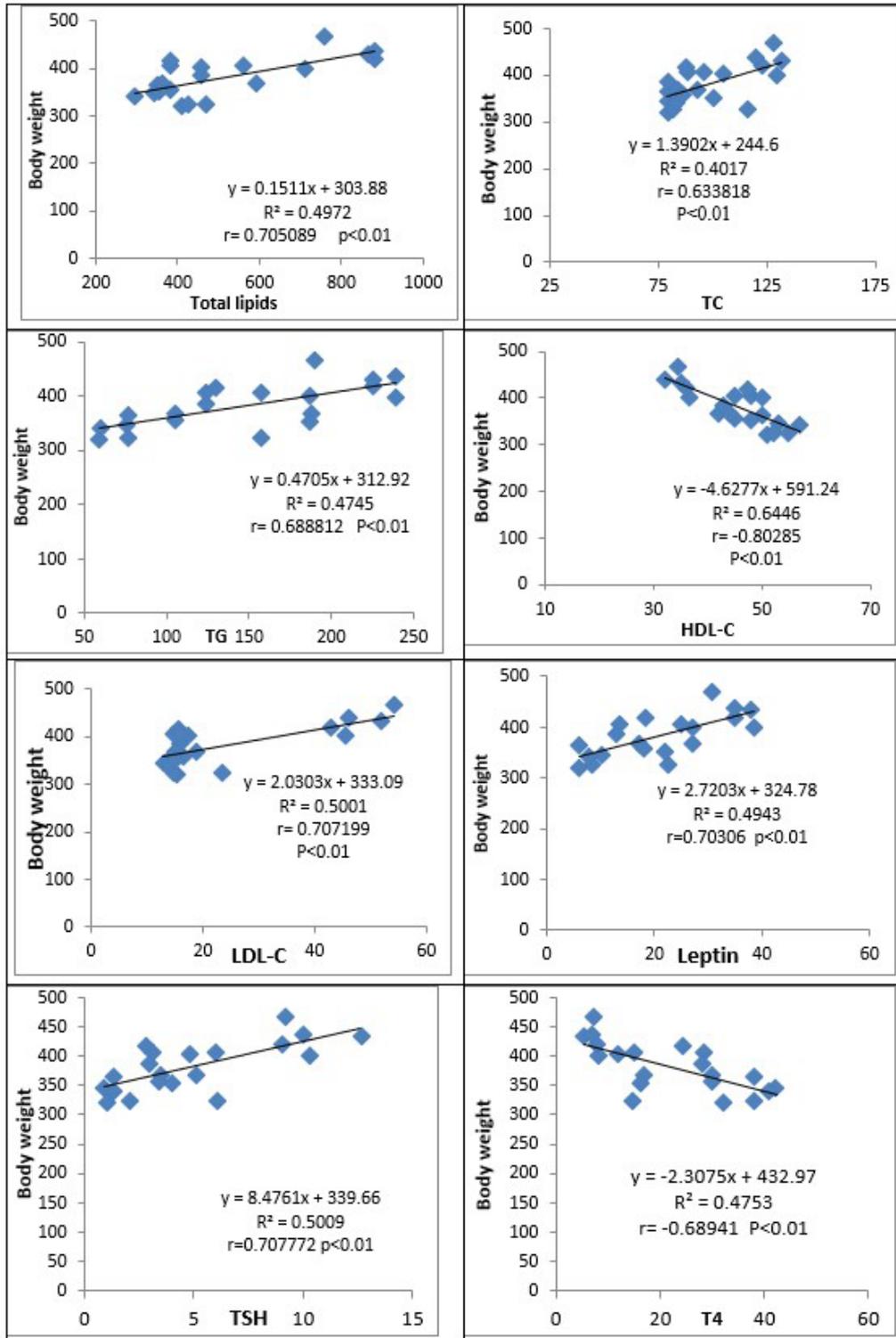


Figure 1. Illustrated correlation coefficient between body weight and total lipids, TC, TG, HDL-C, LDL-C, Leptin, TSH and T4 in all tested groups.

TSH ($r = 0.707$, $p < 0.01$) and negative correlation with T_4 ($r = -0.689$, $p < 0.01$).

4. Discussion

Obesity and related syndromes are a worldwide health problem represents the greatest risk to human health. High fat diet is the main cause for body weight gain and obesity (Othman et al., 2019). In the present study, rats fed a high fat diet (HFD) for 10 weeks exhibited high body weight gain. This obese model is closely related to many models in previous studies (Chung et al., 2018). Obesity is accompanied with increased oxidative stress, as there is an increase in free radical production in adipose tissue and liver of mice fed on HFD (Bensenor et al., 2012; Rahman et al., 2017). So, to relieve obesity and related effects, a proposed promising strategy is the use of antioxidant nanoparticles in treatment obese rats.

Several studies have demonstrated enhanced bioavailability of nanoparticles (De et al., 2008; Nazarizadeh and Asri-Rezaie, 2016). As the chemical & physical properties of nanoparticles such as shape, size determine their absorption, cellular uptake, bio distribution and clearance. Thus, the present study determined the therapeutic effects of SeNPs and ZnONPs in treating obese rats fed on HFD.

SeNPs is an antioxidant; micronutrient present in many foodstuffs enough amounts of selenium exhibited a protective effect against various diseases (Flores-Mateo et al., 2006). Selenium decreases body weight significantly and ratio of adipose tissue to body weight decreased in rats treated with Se 200 μ g/kg body weight (Wang et al., 2016). Berger et al. (1992) demonstrated effect of zinc deficiency in obese patients and its association with renal, cardiovascular diseases, diabetes and metabolic syndrome has been approved (Gupta, 2017).

Treatment with SeNPs as well as ZnONPs reduced body gain by inhibiting the increase in lipid fractions, cholesterol total lipids and triglycerides and increasing HDL-level (Table 3). This anti-hyperlipidemic effect may be due to regulation of hepatic cholesterol metabolism and decreasing oxidative stress.

Obesity is associated with increased leptin level. The present results revealed that HFD increased serum leptin level. It is well-known that physiological leptin signaling is important in maintaining body weight. Leptin resistance is a characteristic for HFD-induced obesity, the mechanism that leads to leptin resistance including inflammatory processes and oxidative stress with an increase NADPH-oxidase activation which increased the ROS production (Wannamethee et al., 2007; Huang et al., 2015). SeNPs and ZnONPs supplementations could therefore induce beneficial effects in reducing peripheral and central leptin resistance through their antioxidant activity. Previous studies revealed that, selenium M an endoplasmic reticulum-resident selenoprotein with antioxidant properties was highly expressed in hypothalamic area involved in energy metabolism and its removal resulted in elevated serum leptin levels increased adiposity and hypothalamic leptin resistance (Pitts et al., 2013).

The current experiment showed low T_4 level and increased TSH level in rats fed HFD, indicated hypothyroxinemia. Zhang et al. (2018) reported that increased intake of HFD and increased serum lipid fractions caused a decrease in thyroid T_3 & T_4 hormones and increased TSH level, that can be ameliorated by dietary modification (Shao et al., 2014). Nano selenium and nano zinc oxide succeeded in restoring thyroid integrity by lowering oxidative stress as they increase GSH, GPX activities and reduce MDA level. Also nanoparticles effect can be applied through affecting hypothalamic pituitary thyroid axis and therefore affect the level of thyroid hormones displayed in the study.

Development of oxidative stress in HFD rats with consequent reduction in the antioxidant defense systems were observed as a significant increase in the oxidative stress marker (MDA) and decrease in the antioxidant markers including GSH & CAT. Meanwhile, treatment with SeNPs and ZnONPs elevated GSH level & CAT activity significantly and reduced MDA activity.

From the point of view, SeNPs treated group has more adjustable antioxidant activity than ZnONPs group. This relate to SeNPs potential to keep the glutathione in the reduced form, which can remove the free radicals. Also, selenium functions in the active site of many antioxidant enzymes such as thioredoxin reductase and glutathione. ZnONPs may either increase the production of GSH or reduce oxidative stress contributing to less degradation of GSH or have both effects (Ukperoro et al., 2010). Also, the antioxidant effect of zinc has been approved by inhibiting $OH\cdot$ formation in antagonist transition metal catalyzed reaction (Jomova and Valko, 2011).

The present results demonstrated a significant increase in serum liver enzymes (ALT, AST,ALP),serum creatinine and uric acid in HFD rats group . These hepatic and renal pathological changes can be attributed to the increase of MDA, a lipid peroxidation marker that can play a crucial role in cellular membrane damage through free radical chain reaction mechanism (Wong-Ekkabut et al., 2007). Treatment with SeNPs and ZnONPs improved liver and kidney functions toward control levels, but the best ameliorative effect appears in SeNPs treated group . These alleviating effects of nanoparticles may be due to radical scavenging ability of SeNPs and ZnONPs in protecting the integrity and functions of tissue (Majeed et al., 2018) and restoration of endothelial dysfunction and vascular disorders through regulating antioxidant enzymes (Oztürk et al., 2015; Usrey et al., 2020) also, decreasing MDA and free radial levels (Dawei et al., 2009). Tinggi (2008), reported that selenium has been used as a substitute for sulfur in protein synthesis, and the resultant selenoproteins show better biological activity which may be the cause for the increased total protein in SeNPs treated group.

5. Conclusion

From the present study, it could be concluded that, SeNPs and ZnOPs are strong antioxidants, showed lower oxidative stress, good hypolipidemic effects indicating lower obesity state accompanied with improvements in liver,

kidney functions and thyroid hormones. The underlying mechanism of both SeNPs and ZnOPs may be attributed to their antioxidant effects. The strongest ameliorative effect in decreasing oxidative stress and concomitantly obesity and its syndromes have been shown by SeNPs, as it is incorporated as selenocysteine (SEC) in many antioxidant enzymes as glutathione peroxidase, thioredoxin reductase and selenoprotein, where it acts as the redox center of all these enzymes. So, SeNPs can be used as a healthy supplementary to relieve obesity and its complications. Also, ZnONPs is a good antioxidant.

Acknowledgements

This study was supported by Biological Applications Department, Nuclear Research Centre, Atomic Energy Authority, Egypt.

References

- AGARWAL, H., NAKARA, A. and SHANMUGAM, V.K., 2019. Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: a review. *Biomedicine and Pharmacotherapy*, vol. 109, pp. 2561-2572. <http://dx.doi.org/10.1016/j.biopha.2018.11.116>. PMID:30551516.
- ARTHUR, J.R., MCKENZIE, R.C. and BECKETT, G.J., 2003. Selenium in the immune system. *The Journal of Nutrition*, vol. 133, no. 5, suppl. 1, pp. 1457S-1459S. <http://dx.doi.org/10.1093/jn/133.5.1457S>. PMID:12730442.
- BASHANDY, S.A.E., ALAAMER, A., MOUSSA, S.A.A. and OMARA, E.A., 2018. Role of zinc oxide nanoparticles in alleviating hepatic fibrosis and nephrotoxicity induced by thioacetamide in rats. *Canadian Journal of Physiology and Pharmacology*, vol. 96, no. 4, pp. 337-344. <http://dx.doi.org/10.1139/cjpp-2017-0247>. PMID:28813612.
- BEAL, T., MASSIOT, E., ARSENAULT, J.E., SMITH, M.R. and HIJMANS, R.J., 2017. Global trends in dietary micronutrient supplies and estimated prevalence of inadequate intakes. *PLoS One*, vol. 12, no. 4, p. e0175554. <http://dx.doi.org/10.1371/journal.pone.0175554>. PMID:28399168.
- BENSENOR, I.M., OLMOS, R.D. and LOTUFO, P.A., 2012. Hypothyroidism in the elderly: diagnosis and management. *Clinical Interventions in Aging*, vol. 7, pp. 97-111. <http://dx.doi.org/10.2147/CIA.S23966>. PMID:22573936.
- BERGER, M.M., CAVADINI, C., BART, A., MANSOURIAN, R., GUINCHARD, S., BARTHOLDI, I., VANDERVALE, A., KRUPP, S., CHIOLÉRO, R., FREEMAN, J. and DIRREN, H., 1992. Cutaneous copper and zinc losses in burns. *Burns*, vol. 18, no. 5, pp. 373-380. [http://dx.doi.org/10.1016/0305-4179\(92\)90035-S](http://dx.doi.org/10.1016/0305-4179(92)90035-S). PMID:1445626.
- BERNARDIS, L.L., 1970. Prediction of carcass fat, water and lean body mass from Lee's nutritive ratio in rats with hypothalamic obesity. *Experientia*, vol. 26, no. 7, pp. 789-790. <http://dx.doi.org/10.1007/BF02232553>. PMID:4914444.
- BEUTLER, E., DURON, O. and KELLY, B.M., 1963. Improved method for the determination of blood glutathione. *The Journal of Laboratory and Clinical Medicine*, vol. 61, pp. 882-888. PMID:13967893.
- CARRASCO-RANDO, M., ATIENZA-MANUEL, A., MARTÍN, P., BURKE, R. and RUIZ-CÓMEZ, M., 2016. Fear-of-intimacy-mediated zinc transport controls the function of zinc-finger transcription factors involved in myogenesis. *Development*, vol. 143, no. 11, pp. 1948-1957. <http://dx.doi.org/10.1242/dev.131953>. PMID:27068109.
- CHASAPIS, C.T., LOUTSIDOU, A.C., SPILIOPOULOU, C.A. and STEFANIDOU, M.E., 2012. Zinc and human health: an update. *Archives of Toxicology*, vol. 86, no. 4, pp. 521-534. <http://dx.doi.org/10.1007/s00204-011-0775-1>. PMID:22071549.
- CHUNG, A.P.Y.S., GURTU, S., CHAKRAVARTHI, S., MOORTHY, M. and PALANISAMY, U.D., 2018. Geraniin protects high-fat diet-induced oxidative stress in Sprague Dawley rats. *Frontiers in Nutrition*, vol. 5, p. 17. <http://dx.doi.org/10.3389/fnut.2018.00017>. PMID:29616223.
- DAWEI, A.I., ZHISHENG, W. and ANGUO, Z., 2009. Protective effects of nano-ZnO on the primary culture mice intestinal epithelial cells in vitro against oxidative injury. *Journal of Animal and Veterinary Advances*, vol. 8, no. 10, pp. 1964-1967.
- DE, M., GHOSH, P.S. and ROTELLO, V.M., 2008. Applications of nanoparticles in biology. *Advanced Materials*, vol. 20, no. 22, pp. 4225-4241. <http://dx.doi.org/10.1002/adma.200703183>.
- DONMA, M.M. and DONMA, O., 2016. Promising link between selenium and peroxisome proliferator activated receptor gamma in the treatment protocols of obesity as well as depression. *Medical Hypotheses*, vol. 89, pp. 79-83. <http://dx.doi.org/10.1016/j.mehy.2016.02.008>. PMID:26968915.
- EL-SHIEKH, R.A., AL-MAHDY, D.A., MOUNEIR, S.M., HIFNAWY, M.S. and ABDEL-SATTAR, E.A., 2019. Anti-obesity effect of argel (Solenostemma argel) on obese rats fed a high fat diet. *Journal of Ethnopharmacology*, vol. 238, p. 111893. <http://dx.doi.org/10.1016/j.jep.2019.111893>. PMID:30999011.
- EMARA, S.S., EL-ZAHER, H.M., MICHAEL, M.I. and EID, S.Y., 2019. Comparative effects of nano-selenium and sodium selenite supplementation on blood biochemical changes in relation to growth performance of growing New Zealand white rabbits. *Arab Journal of Nuclear Sciences and Applications*, vol. 52, no. 4, pp. 1-14. <http://dx.doi.org/10.21608/ajnsa.2019.5423.1124>.
- FLORES-MATEO, G., NAVAS-ACIEN, A., PASTOR-BARRIUSO, R. and GUALLAR, E., 2006. Selenium and coronary heart disease: a meta-analysis. *The American Journal of Clinical Nutrition*, vol. 84, no. 4, pp. 762-773. <http://dx.doi.org/10.1093/ajcn/84.4.762>. PMID:17023702.
- FRIEDEWALD, W.T., LEVY, R.I. and FREDRICKSON, D.S., 1972. Estimation of concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clinical Chemistry*, vol. 18, no. 6, pp. 499-502. <http://dx.doi.org/10.1093/clinchem/18.6.499>. PMID:4337382.
- FURUKAWA, S., FUJITA, T., SHIMABUKURO, M., IWAKI, M., YAMADA, Y., NAKAJIMA, Y., NAKAYAMA, O., MAKISHIMA, M., MATSUDA, M. and SHIMOMURA, I., 2004. Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of Clinical Investigation*, vol. 114, no. 12, pp. 1752-1761. <http://dx.doi.org/10.1172/JCI21625>. PMID:15599400.
- GITTNER, L.S., KILBOURNE, B.J., VADAPALLI, R., KHAN, H.M.K. and LANGSTON, M.A., 2017. A multifactorial obesity model developed from nationwide public health exposome data and modern computational analyses. *Obesity Research & Clinical Practice*, vol. 11, no. 5, pp. 522-533. <http://dx.doi.org/10.1016/j.orcp.2017.05.001>. PMID:28528799.
- GUPTA, A., 2017. *Nutritional anemia in preschool children*. Singapore: Springer. Role of zinc, copper and selenium in nutritional anemia, pp. 185-199. http://dx.doi.org/10.1007/978-981-10-5178-4_10.
- HUANG, C.J., MCALLISTER, M.J., SLUSHER, A.L., WEBB, H.E., MOCK, J.T. and ACEVEDO, E.O., 2015. Obesity-related oxidative stress: the impact of physical activity and diet manipulation. *Sports*

- Medicine - Open*, vol. 1, no. 1, p. 32. <http://dx.doi.org/10.1186/s40798-015-0031-y>. PMID:26435910.
- JOMOVA, K. and VALKO, M., 2011. Advances in metal-induced oxidative stress and human disease. *Toxicology*, vol. 283, no. 2-3, pp. 65-87. <http://dx.doi.org/10.1016/j.tox.2011.03.001>. PMID:21414382.
- KIELISZEK, M. and BŁAŻEJAK, S., 2016. Current knowledge on the importance of selenium in food for living organisms: a review. *Molecules*, vol. 21, no. 5, p. 609. <http://dx.doi.org/10.3390/molecules21050609>. PMID:27171069.
- LEON-CABRERA, S., SOLÍS-LOZANO, L., SUÁREZ-ÁLVAREZ, K., GONZÁLEZ-CHÁVEZ, A., BÉJAR, Y.L., ROBLES-DÍAZ, G. and ESCOBEDO, G., 2013. Hyperleptinemia is associated with parameters of low-grade systemic inflammation and metabolic dysfunction in obese human beings. *Frontiers in Integrative Neuroscience*, vol. 7, p. 62. <http://dx.doi.org/10.3389/fnint.2013.00062>. PMID:23986664.
- LUCAS, J.M., 2010. Microarrays: molecular allergology and nanotechnology for personalised medicine (II). *Allergologia et Immunopathologia*, vol. 38, no. 4, pp. 217-223. <http://dx.doi.org/10.1016/j.aller.2010.04.003>. PMID:20537785.
- LUCK, H., 1974. Catalase. In: H.U. Bergmeyer, ed., *Method of enzymatic analysis*. New York: Academic Press, vol. 2, pp. 885-890.
- MAJEED, W., ZAFAR, M., BHATTI, A. and JOHN, P., 2018. Therapeutic potential of selenium nanoparticles. *Journal of Nanomedicine & Nanotechnology*, vol. 9, no. 1, p. 1000487. <http://dx.doi.org/10.4172/2157-7439.1000487>.
- MIRONAVA, T., HADJIARGYROU, M., SIMON, M., JURUKOVSKI, V. and RAFAILOVICH, M.H., 2010. Gold nanoparticles cellular toxicity and recovery: effect of size, concentration and exposure time. *Nanotoxicology*, vol. 4, no. 1, pp. 120-137. <http://dx.doi.org/10.3109/17435390903471463>. PMID:20795906.
- NAZARIZADEH, A. and ASRI-REZAIE, S., 2016. Comparative study of antidiabetic activity and oxidative stress induced by zinc oxide nanoparticles and zinc sulfate in diabetic rats. *AAPS PharmSciTech*, vol. 17, no. 4, pp. 834-843. <http://dx.doi.org/10.1208/s12249-015-0405-y>. PMID:26349687.
- OHKAWA, H., OHISHI, N. and YAGI, K., 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical Biochemistry*, vol. 95, no. 2, pp. 351-358. [http://dx.doi.org/10.1016/0003-2697\(79\)90738-3](http://dx.doi.org/10.1016/0003-2697(79)90738-3). PMID:36810.
- ORTEGA, M., RODRÍGUEZ-RODRÍGUEZ, E., APARICIO, A., JIMÉNEZ-ORTEGA, A.J., PALMEROS, C., PEREA, J.M., NAVIA, B. and LÓPEZ-SOBALER, A.M., 2012. Young children with excess of weight show an impaired selenium status. *International Journal for Vitamin and Nutrition Research*, vol. 82, no. 2, pp. 121-129. <http://dx.doi.org/10.1024/0300-9831/a000101>. PMID:23065837.
- OTHMAN, A.I., AMER, M.A., BASOS, A.S. and EL-MISSIRY, M.A., 2019. Moringa oleifera leaf extract ameliorated high-fat diet-induced obesity, oxidative stress and disrupted metabolic hormones. *Clinical Phytoscience*, vol. 5, no. 1, p. 48. <http://dx.doi.org/10.1186/s40816-019-0140-0>.
- OZTÜRK, Z., GURPINAR, T., VURAL, K., BOYACIOĞLU, S., KORKMAZ, M. and VAR, A., 2015. Effects of selenium on endothelial dysfunction and metabolic profile in low dose streptozotocin induced diabetic rats fed a high fat diet. *Biotechnic & Histochemistry*, vol. 90, no. 7, pp. 506-515. <http://dx.doi.org/10.3109/10520295.2015.1042050>. PMID:25978137.
- PITTS, M.W., REEVES, M.A., HASHIMOTO, A.C., OGAWA, A., KREMER, P., SEALE, L.A. and BERRY, M.J., 2013. Deletion of selenoprotein M leads to obesity without cognitive deficits. *The Journal of Biological Chemistry*, vol. 288, no. 36, pp. 26121-26134. <http://dx.doi.org/10.1074/jbc.M113.471235>. PMID:23880772.
- POWELL, S.R., 2000. The antioxidant properties of zinc. *The Journal of Nutrition*, vol. 130, no. 5, pp. 1447S-1454S. <http://dx.doi.org/10.1093/jn/130.5.1447S>. PMID:10801958.
- RAHMAN, H.A., SAHIB, N.G., SAARI, N., ABAS, F., ISMAIL, A., MUMTAZ, M.W. and HAMID, A.A., 2017. Antiobesity effect of ethanolic extract from *Cosmos caudatus* Kunth leaf in lean rats fed a high fat diet. *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, p. 122. <http://dx.doi.org/10.1186/s12906-017-1640-4>. PMID:28228098.
- SÁINZ, N., BARRENETXE, J., MORENO-ALIAGA, M.J. and MARTÍNEZ, J.A., 2015. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. *Metabolism: Clinical and Experimental*, vol. 64, no. 1, pp. 35-46. <http://dx.doi.org/10.1016/j.metabol.2014.10.015>. PMID:25497342.
- SÁNCHEZ, A., ROJAS, P., BASFI-FER, K., CARRASCO, F., INOSTROZA, J., CODOCEO, J., VALENCIA, A., PAPAPIETRO, K., CSENDES, A. and RUZ, M., 2016. Micronutrient deficiencies in morbidly obese women prior to bariatric surgery. *Obesity Surgery*, vol. 26, no. 2, pp. 361-368. <http://dx.doi.org/10.1007/s11695-015-1773-9>. PMID:26108638.
- SHAO, S.-S., ZHAO, Y.-F., SONG, Y.-F., XU, C., YANG, J.-M., XUAN, S.-M., YAN, H.-L., YU, C.-X., ZHAO, M., XU, J. and ZHAO, J.-J., 2014. Dietary high-fat lard intake induces thyroid dysfunction and abnormal morphology in rats. *Acta Pharmacologica Sinica*, vol. 35, no. 11, pp. 1411-1420. <http://dx.doi.org/10.1038/aps.2014.82>. PMID:25263336.
- SRIVASTAVA, P., BRAGANCA, J.M. and KOWSHIK, M., 2014. In vivo synthesis of selenium nanoparticles by *Halococcus salifodinae* BK18 and their anti-proliferative properties against HeLa cell line. *Biotechnology Progress*, vol. 30, no. 6, pp. 1480-1487. <http://dx.doi.org/10.1002/btpr.1992>. PMID:25219897.
- STRANGES, S., SIERI, S., VINCETI, M., GRIONI, S., GUALLAR, E., LACLAUSTRA, M., MUTI, P., BERRINO, F. and KROGH, V., 2010. A prospective study of dietary selenium intake and risk of type 2 diabetes. *BMC Public Health*, vol. 10, p. 564. <http://dx.doi.org/10.1186/1471-2458-10-564>. PMID:20858268.
- TAPIERO, H. and TEW, K.D., 2003. Trace elements in human physiology and pathology: zinc and metallothioneins. *Biomedicine and Pharmacotherapy*, vol. 57, no. 9, pp. 399-411. [http://dx.doi.org/10.1016/S0753-3322\(03\)00081-7](http://dx.doi.org/10.1016/S0753-3322(03)00081-7). PMID:14652165.
- THANOPOULOU, A.C., KARAMANOS, B.G., ANGELICO, F.V., ASSAAD-KHALIL, S.H., BARBATO, A.F., BEN, M.P., DJORDJEVIC, P.B., DIMITRIJEVIC-SRECKOVIC, V.S., GALLOTTI, C.A., KATSILAMBROS, N.L., MIGDALIS, I.N., MRABET, M.M., PETKOVA, M.K., ROUSSI, D.P. and TENCONI, M.-T.P., 2003. Dietary fat intake as risk factor for the development of diabetes: multinational, multicenter study of the Mediterranean Group for the Study of Diabetes (MGSD). *Diabetes Care*, vol. 26, no. 2, pp. 302-307. <http://dx.doi.org/10.2337/diacare.26.2.302>. PMID:12547853.
- TINGGI, U., 2008. Selenium its role as antioxidant in human health. *Environmental Health and Preventive Medicine*, vol. 13, no. 2, pp. 102-108. <http://dx.doi.org/10.1007/s12199-007-0019-4>. PMID:19568888.
- TORRES, S.K., CAMPOS, V.L., LEÓN, C.G., RODRÍGUEZ-LLAMAZARES, S.M., ROJAS, S.M., GONZÁLEZ, M., SMITH, C. and MONDACA, M.A., 2012. Biosynthesis of selenium nanoparticles by *Pantoea agglomerans* and their antioxidant activity. *Journal of Nanoparticle Research*, vol. 14, no. 11, p. 1236. <http://dx.doi.org/10.1007/s11051-012-1236-3>.
- UKPERORO, J.U., OFFIAH, N., IDRIS, T. and AWOGOKE, D., 2010. Antioxidant effect of zinc, selenium and their combination on the liver and kidney of alloxan-induced diabetes in rats.

- Mediterranean Journal of Nutrition and Metabolism*, vol. 3, no. 1, pp. 25-30. <http://dx.doi.org/10.3233/s12349-009-0069-9>.
- USREY, E.-Z., GHANIM, N.F.-A., MEHANY, H.M., ZOMARRA, M.A.E.-A. and AMER, M.A.A., 2020. Biochemical and histopathological studies on the role of selenium nanoparticles and selenium oxide against chemically induced diabetes in male rats. *Archives of Nutrition and Public Health*, vol. 2, no. 2. Online.
- VIAL, G., DUBOCHAUD, H., COUTURIER, K., COTTET-ROUSSELLE, C., TALEUX, N., ATHIAS, A., GALINIER, A., CASTEILLA, L. and LEVERVE, X.M., 2011. Effects of a high-fat diet on energy metabolism and ROS production in rat liver. *Journal of Hepatology*, vol. 54, no. 2, pp. 348-356. <http://dx.doi.org/10.1016/j.jhep.2010.06.044>. PMID:21109325.
- WANG, Y., GAO, X., PEDRAM, P., SHAHIDI, M., DU, J., YI, Y., GULLIVER, W., ZHANG, H. and SUN, G., 2016. Significant beneficial association of high dietary selenium intake with reduced body fat in the coding study. *Nutrients*, vol. 8, no. 1, p. 24. <http://dx.doi.org/10.3390/nu8010024>. PMID:26742059.
- WANNAMETHEE, S.G., TCHERNOVA, J., WHINCUP, P., LOWE, G.D.O., KELLY, A., RUMLEY, A., WALLACE, A.M. and SATTAR, N., 2007. Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease. *Atherosclerosis*, vol. 191, no. 2, pp. 418-426. <http://dx.doi.org/10.1016/j.atherosclerosis.2006.04.012>. PMID:16712853.
- WONG-EKKABUT, J., XU, Z., TRIAMPO, W., TANG, I.-M., TIELEMAN, D.P. and MONTICELLI, L., 2007. Effect of lipid peroxidation on the properties of lipid bilayers: a molecular dynamics study. *Biophysical Journal*, vol. 93, no. 12, pp. 4225-4236. <http://dx.doi.org/10.1529/biophysj.107.112565>. PMID:17766354.
- XIE, Y., HE, Y., IRWIN, P.L., JIN, T. and SHI, X., 2011. Antibacterial activity and mechanism of action of zinc oxide nanoparticles against *Campylobacter jejuni*. *Applied and Environmental Microbiology*, vol. 77, no. 7, pp. 2325-2331. <http://dx.doi.org/10.1128/AEM.02149-10>. PMID:21296935.
- ZHANG, X., CHEN, W., SHAO, S., XU, G., SONG, Y., XU, C., GAO, L., HU, C. and ZHAO, J., 2018. A high-fat diet rich in saturated and mono-unsaturated fatty acids induces disturbance of thyroid lipid profile and Hypothyroxinemia in male rats. *Molecular Nutrition & Food Research*, vol. 62, no. 6, p. e1700599. <http://dx.doi.org/10.1002/mnfr.201700599>. PMID:29363248.