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Lipid Profile and Obese Related Genes of Rats, Potential Therapeutic Effects of *Peganum harmala*/Zinc Oxide Nanoparticles

Mervat Abdelsattar[1], Youssef Elseady[2*], Walaa F. Awadin[3], Ahmed Hendawy[1], Abd EL-Aziz A. Diab[1]

[1]Department Physiology and Zoology, Faculty of Science, Zagazig University, Egypt.

[2]Department of Physiology, Faculty of Veterinary Medicine, Mansoura University, Mansoura 35516, Egypt.

[3]Department of Pathology, Faculty of Veterinary Medicine, Mansoura University, Mansoura 35516, Egypt.

***Correspondence**
Corresponding author: Youssef Elseady
E-mail address:elseady4370@yahoo.com

Abstract

The present study investigated the effects of methanolic extract of harmala nanoparticle (H/ZnONP) on the changes in serum lipid profiles, serum leptin levels and liver and kidney PPAR gene expression in high caloric diet (HCD) induced obese rats. After induction of obesity with HCD for one month to half numbers of rats. Non-obese group had three subgroups; G1: Control fed basal diets, G2: basal diets plus H/ZnONPs (200 mg/kg/day) and G3: basal diets plus H/ZnONPs (400 mg/kg/day). However, obese group was divided into three subgroups G4: HFD, G5: HFD+H/ZnONPs (200 mg/kg/day) and G6: HFD+ H/ZnONPs (400 mg/kg/day). After 4 weeks of treatment blood and tissue samples were collected and subjected to laboratory assay of lipid profile and leptin level in addition to expression of PPAR gene in liver and kidney. This study also investigated the possible protective effect of H/ZnONP 200 and 400 mg/kg BW on liver and kidney histology. The obtained results demonstrated that H/ZnONP treatment to obese rats significantly decreased serum cholesterols, triglyceride, and LDL level while relative expression of PPAR gene in liver and kidney was significantly increased. Based on the obtained results we can conclud that H/ZnONP supplementation has a potent anti-obesity effect in rats by improving lipid profile, enhance expression of PPAR gene in liver and kidney and improve liver and kidney histology particularly the high dose.

KEYWORDS
Obesity, Methanolic extract of *P. harmala* seed, ZnO nanoparticles

INTRODUCTION

Obesity is a chronic metabolic disease that occur due to excessive fat accumulation leading to energy imbalance that is associated with chronic disorders like diabetes mellitus Type II, cancer and heart diseases (Haslam and James, 2005).

The obesity complications usually occur since adipose tissue regarded as endocrine organ that secretes circulating hormones, such as adipokines, leptin and cytokines (tumor necrosis factor (TNF-α), adiponectin and interleukin 6 (IL-6) (Rega-Kaun *et al*., 2013).

Obesity is associated with a raised chance of insulin resistance and DM type II, as expanded FFA concentrations inhibits insulin signaling and GLUT-4 stimulated muscle glucose uptake driving to suppression of glycogen synthesis and glycolysis (Preis *et al*., 2010).

P. harmala is a member of the Zygophyllaceae family and is widely used in Middle Eastern and North African medicine including seeds and plant's alkaloids (Goel *et al*., 2009).

P. harmala extract has several therapeutic effects such as antitumor, anti-inflammatory, antioxidant, and blood glucose-lowering activities (Asghari and Lockwood, 2002; Giancarlo§ *et al*., 2006; Goel *et al*., 2009). These effects have mainly been attributed to the alkaloid components of the pH, including harmaline, harmine, and harmane (Singh *et al*., 2008). Harmine is a functioning component of *P. harmala* and known to have pharmacologic properties, primarily as a cancer prevention agent (Salahshoor *et al*., 2019). Furthermore, many studies (Singh *et al*., 2011; Anwer, 2012; Ozkol *et al*., 2012; Soliman and Fahmy, 2011) approved that improvement in the general lipid profile in animal models receiving *P. harmala* extract. Moreover, Vahidi-eyrisofla *et al*. (2015) cited that *P. harmala* improved serum lipid profile. These findings show that *P. harmala* increases the impact of cholesterol excretion.

Zinc oxide nanoparticles (ZnONPs) are of high attentiveness because they are produced by low cost, safety use in food preservation and can be formed efficiently. ZnONPs have extensive application in artificial flavoring (Berry and Curtis, 2003).

In spite of the fact that the NPs biosynthesis by different plant extracts is vague, it has been showed that the biomolecules in plant extract (protein, phenol, and flavonoids) play a part within the diminishment of metals particles and eclipsing the biosynthesized nanoparticles (Krishnaraj *et al*., 2010).

It was documented that the main methods to improve drugs safety and efficacy through using nano based delivery system to enhance therapeutic targeting (Kesharwani *et al*., 2018).

Nanoparticles have been developed as a drug delivery system of various chemotherapeutic drugs to enhance drug efficacy and safety (Kuppens *et al*., 2004).

P. harmala is generally and typically utilized for therapeutic purposes since antiquated times (Herraiz *et al*., 2010). It includes antibacterial, antifungal, antiviral, antidiabetic, insecticidal, hepatoprotective and cytotoxic (Asgarpanah and Ramezanloo, 2012). Many studies (Sethi and Vidal-Puig, 2007; Qazan, 2009; Singh *et*

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al., 2011; Takht Firoozeh *et al*., 2015), have approved the anti-lipidemic effect of harmal extract in rat. Moreover Berrougui *et al*. (2006) recommended the supplmentation of harmal extract to improve capacity of body to counteract lipid peroxidation .

Peroxisome proliferator-activated receptor (PPAR) is a master regulator of adipogenesis (Waki *et al*., 2007). Its expression increases the adipose tissue ability to accumulate fat (Ahmadian *et al*., 2013). So, we investigate potential therapeutic effect of harmal nanoparticles on obese rat.

The present study was carried out to investigate the therapeutic effect of *Peganum harmala* / zinc oxide nanoparticles (H/ZnONPs) on a high-fat diet (HFD) induced obesity.

MATERIALS AND METHODS

Ethical approval

This experimental study was performed with the confirmation of the local ethics committee on use and care for animal experiments at Zagazig University of Biology Department (permit number ZU-IACUC/1/F/81/2022).

Animals

Thirty-six adult male rats (Rattus norvigicus) weighting 200-250 g were used throughout the present study. They were obtained from the Animal House of Faculty of Veterinary Medicine, Mansoura University, Egypt. The animals were housed in standard conditions in metal cages and bedded with wood shavings and kept under standard laboratory conditions of aeration and room temperature at about 25°C. The animals were allowed to free access of standard diet and water ad libitum. The animals were accommodated to the laboratory conditions for four weeks before being experimented.

Obesity was induced by high fat diet containing 20% fat according to NRC (1995) and admitted for 4 weeks to half number of experimental rats.

Harmal /Zinc oxide nanoparticles preparation

P. harmala seeds were purchased from a local herb store with a fair degree of quality assurance. It was extracted and prepared with Zinc nanoparticle according to the methods Shin *et al*. (2007) and cited by Ismail *et al*. (2020).

Transmission electron microscopy (TEM) (JEM 1400 plus, JEOL Ltd., Japan) and scanning electron microscopy (SEM) (JCM 5700, JEOL Ltd., Japan) were used to determine the morphology, shape, and size of H/ZnO-NPs. The zeta potential (surface charge; mV) of the H/ZnO-NPs was determined using the zeta-potential analyzer ELSZ-2000, Otsuka Electronics, Japan, after proper dilutions of the sample.

Experimental design

A total number of 36 male rats were allocated into 2 main groups (18 rats each) as follows: Obese and non-obese with subsequent 3 subgroups. The rats were fed on basal diet and received the treatment according to the following protocol. Non-obese group had three subgroups; G1: control fed basal diets, G2: basal diets plus H/ZnONPs (200 mg/kg/day) (Takht Firoozeh *et al*., 2015), and G3: basal diets plus H/ZnONPs (400 mg/kg/day) (Takht Firoozeh *et al*., 2015). However, obese group divided into G4: HFD (Svegliati-Baroni *et al*., 2006), G5: HFD + H/ZnONPs (200 mg/kg/day) (Takht Firoozeh *et al*., 2015) and G6: HFD+ H/ZnONPs (400 mg/kg/day) (Takht Firoozeh *et al*., 2015).

Sampling

Animals were anesthetized after 4 weeks of experimental period, blood sample was collected from retro-orbital venous plexus in clean tube (Schermer, 1967) and left to coagulate to collect serum that kept frozen at -20°C until biochemical and hormonal assays. After 4 weeks of the experiment, tissue samples were collected from the liver and kidney, and kept frozen in triazole at -80°C until used for gene expression of PPAR-γ. Other tissue samples were taken from the liver and kidney and preserved in 10% formalin until routinely processed to prepare paraffin blocks. Tissue sections of 4 µm were cut and stained with hematoxylin-eosin (H&E) for histopathological observation.

Biochemical assay

Lipid profile

Determination of serum triglycerides (TG) concentration

Serum triglycerides (TG) were determined colorimetrically by using Spectrum kit (Egyptian Company for Biotechnology, Obour city, Cairo, Egypt), according to Fossati and Prencipe (1982).

Determination of serum total cholesterol (TC) concentration

Serum cholesterol was determined colorimetrically by using Spectrum kit (Egyptian Company for Biotechnology, Obour city, Cairo, Egypt), according to Varley and Richmond (1976).

Determination of high and low-density lipoprotein (HDL & LDL)

Serum HDL-cholesterol was determined according to Stein (1986) using Stanbio HDL cholesterol obtained from Stanbio Company. LDL was determined and calculated according to Friedewald *et al*. (1972).

Leptin hormone

Serum leptin levels were determined using (Rat) ELISA Kit: DRG® Leptin ELISA, according to the methods of Considine *et al*. (1996).

Gene expression analysis of PPAR-γ

Total RNAs of PPAR gene were extracted using RNA Mini Kit (RNeasy, 74104, Qiagen) according to the methods modify by Meadus (2003).

The primer sequence used for PCR analysis obtained from gene bank with accession number NG_028301.2 Forward sequence for PPAR was CGAGTGCCGAGTCTGTGGGGATAA, Reverse sequence for PPAR ATGGTGATTTGTCTGTTGTCTTTC. Forward sequence for GAPDH (Housekeeping gene) was GACATCAAGAAGGTGGTGAAGCAG, Reverse sequence for GAPDH was GACATCAAGAAGGTGGTGAAGCAG.

Histopathological examination

Small pieces of tissues (liver and kidney) were freshly collected directly after dissection and immediately transferred to 10% formalin solution for fixation. After 24 hours, the specimens were washed, dehydrated in ascending grades of alcohol, cleared in

xylol and embedded in paraffin. The paraffin blocks were cut into sections each 6 microns thick, using microtome. For staining, the paraffin sections were deparaffinized in xylene, then hydrated. Staining was done by use of Harris haematoxylin and eosin. After staining, the sections were dehydrated in alcohol, cleared in xylene and mounted with Canda balsam and examined by the a same pathologist (Bancroft and Gamble, 2008).

Semi-quantitative scoring of hepatic steatosis was evaluated using histological grading (from 0 to 3); 0= no steatosis, 1= mild steatosis (less than 33%), 2=moderate steatosis (more than 33% and less than 66%) and 3=severe steatosis (more than 66%).

Statistical Analysis

The data obtained from the animal experiments were expressed as mean and standard error (±SEM). The statistical differences among experimental groups were evaluated by one-way ANOVA and Tukey´s post hoc tests using the SPSS computer software program version 19. A difference of $p < 0.05$ in the mean values was considered significant (Yuan and Lin, 2006).

RESULTS

Characterization of H/ZnONPs using TEM imaging.

Figure 1A & B shows High-resolution TEM imaging for the structural morphology, shape, and size of the synthesized H/ZnONPs.

Lipid profile of control and different treated animal groups:

Effect of treatment of rats with H/ZnONPs on cholesterol levels (Table 1)

Cholesterol levels were significantly increased in obese rat than nonobese normal rat by a percent more than 50% when compared with the control group (G1). However, treatment of obese rats with H/ZnONPs nanoparticles minimized these increases but didn't return to normal level.

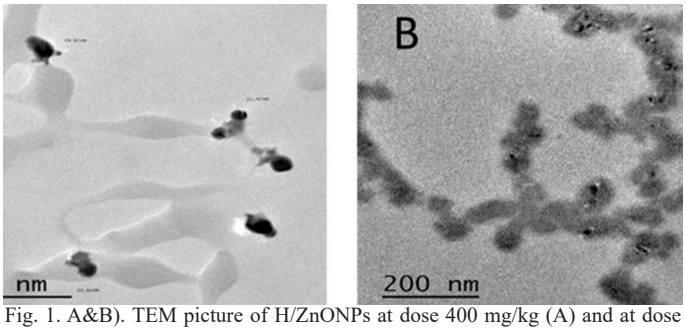

Fig. 1. A&B). TEM picture of H/ZnONPs at dose 400 mg/kg (A) and at dose of 200mg/kg (B)

Effect of H/ZnONPs treatment on TG levels (Table 1).

Obese rats in groups G4:G6 showed significant increases in serum TG levels when compared with nonobese groups by a percent started with 74% in control obese group (G4). Data of obese rats showed progressive decreases in the TG levels to reach to the minimal value in G6 that treated with 400 mg H/ZnONPs.

Effects of treatment of rats with H/ZnONPs on HDL-C (Table 1)

Obese rats in groups G4: G6 showed significant decreases when compared with nonobese groups by a percent started with13.2 percentage in control obese group (G4). The data of obese rat groups don't show significant variation among them as the result of H/ZnONPs treatment.

Effects of H/ZnONPs treatment of rats on LDL-C (Table 1)

Obese rats in groups G4 toG6 showed significant increases when compared with normal nonobese groups by a percent

Table 1. Lipid profile of control and different treated animal groups.

Parameters	Total Cholesterol	TG	HDL-C	LDL-C
Animal groups	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
G1	85.0±5.292	100.0±7.371	51.0±3.215	14.0±1.155
G2	79.0±2.082*	94.33±4.631*	50.33±1.453*	10.0±1.732*
G3	77.0±2.517*	83.67±4.055*	51.67±1.764*	8.667±1.202*
G4	147.8±5.186*	174.5±7.751*	44.25±3.497	68.75±2.428*
G5	129.0±4.021*, **	151.0±7.8*, **	44.25±2.72*, **	54.5±1.323*, **
G6	111.0±5.845*, **	130.5±5.951*, **	47.5±3.175*, **	37.5±1.555

G1: Nonobese (Control-negative group): standard diet. G2: Non obese + H/ ZnO nanoparticles (200 mg/kg/day). G3: Nonobese + H /ZnO nanoparticles (400 mg/kg/day).G4:Obese(Control-positive group): high-fat diet. G5: Obese+ H/ZnO nanoparticles (200 mg/kg/day). G6: Obese+ H/ ZnO nanoparticles (400 mg/kg/day).
*: Significant difference with normal -ve control (G1); **: Significant difference with obese +ve control (G4).

Table 2. Effect of H/ZnONPs on leptin and PPAR gene in experimental rat.

Animal groups	Parameters Leptin (ng/ml)	Hepatic PPAR (relative expression)	Nephritic PPAR relative expression
G1	3.287±0.111	1.033±0.1453	1.00±0.1155
G2	3.25±0.06351*	0.995±0.08231*	0.9684±0.1761*
G3	3.203±0.08212*	0.9757±0.09034*	0.9768±0.1468*
G4	4.173±0.1002*	0.0007843±0.0001484*	0.03299±0.01193*
G5	3.95±0.06868*, **	0.6403±0.2023*, **	0.7155±0.1739*, **
G6	3.788±0.05266*, **	0.6796±0.2042*, **	0.6401±0.2023*, **

G1: Nonobese (Control-negative group): standard diet. G2: Non obese + H/ ZnO nanoparticles (200 mg/kg/day). G3: Nonobese + H /ZnO nanoparticles (400 mg/kg/day).G4:Obese(Control-positive group): high-fat diet. G5: Obese+ H/ZnO nanoparticles (200 mg/kg/day). G6: Obese+ H/ ZnO nanoparticles (400 mg/kg/day).
*: Significant difference with normal -ve control (G1); **: Significant difference with obese +ve control (G4).

started with 391.0% in control obese group (G4). Data of obese rats showed progressive decreases in the LDL-C levels to reach to minimal value in G6 that treated with (400 mg/kg/day) H/ZnONPs.

PPARγ in liver and kidney tissue

Effects of treatment of rats with H/ZnONPs on Hepatic PPAR gene expression (Table 2).

The result appeared that obese rats in groups G4toG6 showed significant increases when compared with normal non-obese groups by a percent started with 99.9% in control obese group (G4). Data of normal rats showed progressive increases in the Hepatic PPAR expression to reach to maximum rate in G6 that treated with H/ZnONPs (400 mg/kg/day).

Effects of treatment of rats with H/ZnONPs nanoparticles on nephritic PPAR (Table 2)

The result appeared that obese rats in groups G4to G6 showed significant increases when compared with nonobese groups by a percent started with 96.7% in control obese group (G4). Data of normal rats showed progressive increases in the nephritic PPAR to reach to maximum value in G6 that treated with H/ZnONPs (400 mg/kg/day).

Effects of treatment of rats with H/ZnONPs on liver histopathology (Figures 2)

Histopathological assessment of H&E-stained liver sections from control groups G1-G3 showed normal hepatic architecture with no evidence of steatosis. In contrast, liver of HFD group G4 showed altered hepatic architecture with diffuse macro-vesicular intermingled with micro-vesicular steatosis in hepatocytes. Liver sections of HFD group G5 received H/ZnONPs (200 mg/kg/day) showed decreased hepatic steatosis in hepatocytes. Liver sections of HFD group G6 received H/ZnONPs (400 mg/kg/day) showed normal hepatic architecture.

Effects of treatment of rats with H/ZnONPs on kidney histopathology (Figures 3)

Histopathological assessment of H&E-stained kidney sections from control groups G1-G3 showed normal tubules and glomeruli. In contrast, kidney sections of HFD group G4 showed altered renal architecture, congested renal blood vessels and diffuse tubular hydropic degeneration with many necrotic and apoptotic renal epithelial cells, clumped glomerular tuft, dilated Bowman's space and thickened Bowman's capsule. Kidney sections of HFD group G5 received H/ZnONPs (200 mg/kg/day) showed multifocal areas of tubular ballooning degeneration with normalized picture of glomeruli. Kidney sections of HFD group G6 received H/ZnONPs (400 mg/kg/day) showed retained normal appearance of tubules and glomeruli.

DISCUSSION

Obesity is a significant metabolic risk factor for diabetes, dyslipidemia, hypertension, and cardiovascular complications (Poirier *et al*., 2006; Zhang *et al*., 2014). Researchers are drawn

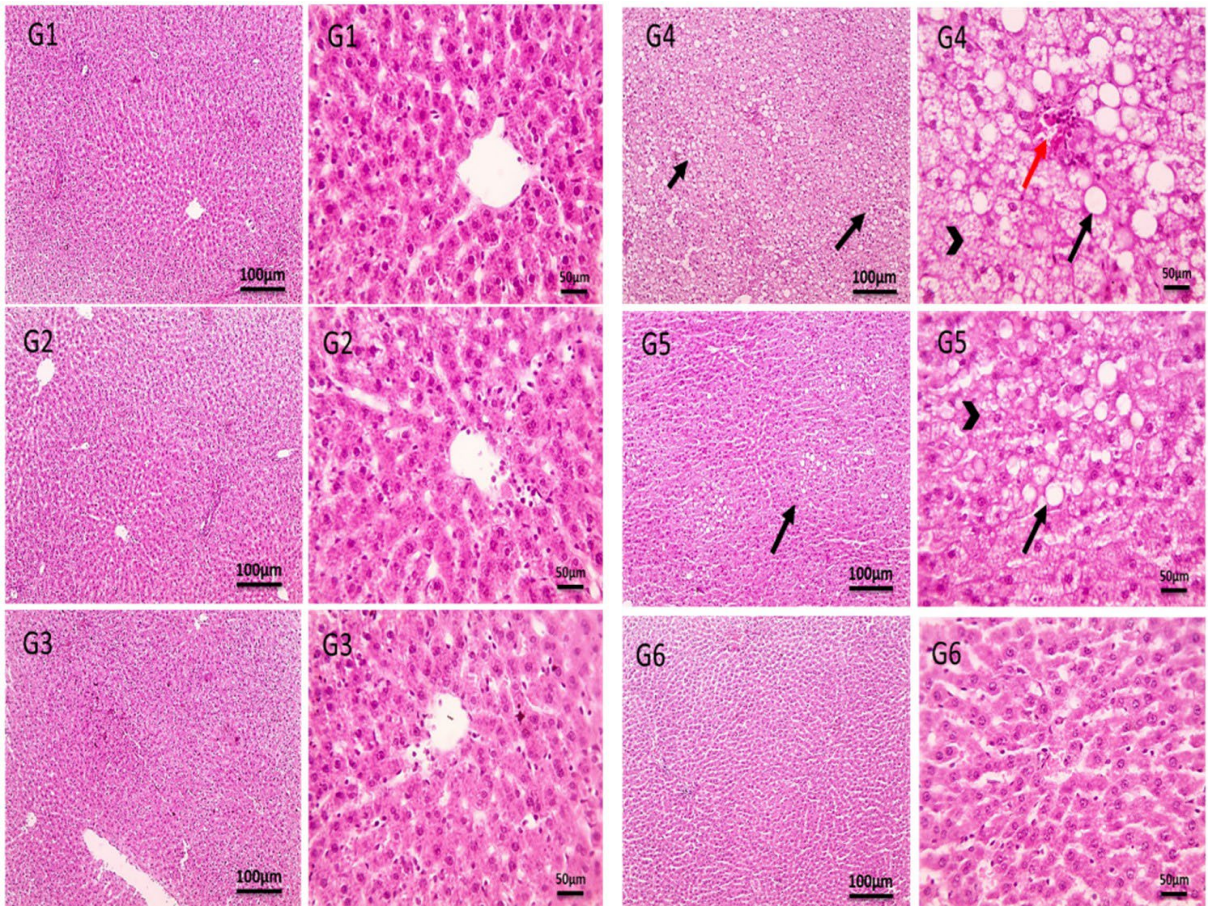

Fig. 2. Microscopic pictures of H&E stained liver sections from control and obese rats treated with H/ZO-NP. Control groups (G1-G3) show normally arranged hepatic cords around central veins with normal sinusoids with no evidence of steatosis (score = 0). While in obese rats' groups (4-6), group G4 showing altered hepatic architecture with diffuse macro-vesicular (black arrows) intermingled with micro-vesicular (black arrowheads) steatosis in hepatocytes around congested central veins (red arrows). Liver sections of HFD group G5 showed decreased (black arrows) intermingled with micro-vesicular (black arrowheads) steatosis in hepatocytes. Liver sections of HFD group G6 showed normal hepatic architecture. Low magnification X: 100 bar 100 and high magnification X: 400 bar 50.

to the fascinating field of nanotechnology and herbal medicine. According to Li *et al*. (2020), H/ZnONPs are effective in treating rat obesity. Here, we demonstrated how H/ZnONPs reduced lipid synthesis in obese model rats. According to earlier studies of He *et al*. (2003) and Magdy *et al*. (2020), harmine had anti-lipidemic effects in experimental obese rats.

The present study was an attempt to evaluate the protective effect of H/ZnO NPs on experimentally induced obesity in rats. The results showed that obesity was significantly increased lipid blood load as appeared in the serum level of TC, TG and LDL. In the H/ZnONP treated groups the serum levels of lipid parameters decreases significantly than control obese group. These results agree with Hayet *et al*. (2010) who found *P. harmala* seed extract caused a significant decrease in the total cholesterol levels, triglyceride and LDL, with a significant elevation in HDL level compared to untreated obese-diabetic rats. *P. harmala* is one of natural plant that is rich in β-carboline and quinazoline alkaloids that are enriched in many parts of the plant, including capsule, fruits and seeds (Herraiz *et al*., 2010).

As the serum levels of TG are directilly related to obesity (Mollashahi and Kazerani, 2020), the effects of H/ZnONP was evaluated in the present study and the data reported that harmal nanoparticles significantly lower the TG levels in the treated groups when compared with control obese one. These reduction in the serum levels of TC and TG in the treated groups my be attributed to harmine or 4- hydroxy pipecolic acid that present in seed extract as priviouslly cited by Singh *et al*. (2011). In regarding to the serum levels of HDL and LDL, the obtained data domenstrated that obese rat showed signifcant increases in serum level of LDL when compead with normal rats. In the same respect, obese rats treated with H/ZnONP showed significant decreses when compared with obese control one. These differences in the obtained results may be related to other compound in harmal seed as cited by Singh *et al*. (2011). The obtained data is in cosequence that reported by Li *et al*. (2020) who concluded that harmane that extracted from *P. harmala*, is an inhibitor for lipid accumulation. So they aproves that harmane down regulate expression of adipogenic and lipogenic factors. These previous results could support the present data regarding lipid profile. In the same respects, the present data get in consistant with Vahidi-eyrisofla *et al*. (2015) who found that, treated rats could have a benefit from using a methanolic extract of *P. harmala* to improve their serum lipid profile. These findings showed that *P. harmala* increases the impact of cholesterol excretion.

Leptin is a cytokine produced by white adipocytes and its levels is a key indicators for obesity (Kelesidis, 2010). It directly correlated to the fat stored in the body (Brennan and Mantzoros, 2006). This finding is consistent with the data obtained in this study, which indicated that serum leptin levels were higher in obese groups when compared with control one. Moreover, the results demonstrated that rat treated with H/ZnONP showed slight increases in leptin level . These finding could emphasize the hypolipidemic effects of H/ZnONP in treated groups.

Our results agree with the activity of enzymes involved in energy metabolism depends on zinc. It also influences the hormones leptin, insulin, and adiponectin, which control body fat (Marreiro *et al*., 2006).

PPAR is a members of nuclear receptor superfamily involved in adipocyte differentiation , maintenance and functions (Hernandez-Quiles *et al*., 2021).

It has been discovered and described in three isotypes α, δ and γ which have essential role in the expression of genes controlling storage and metabolism of lipids and glucose (Janani and Kumari 2015).

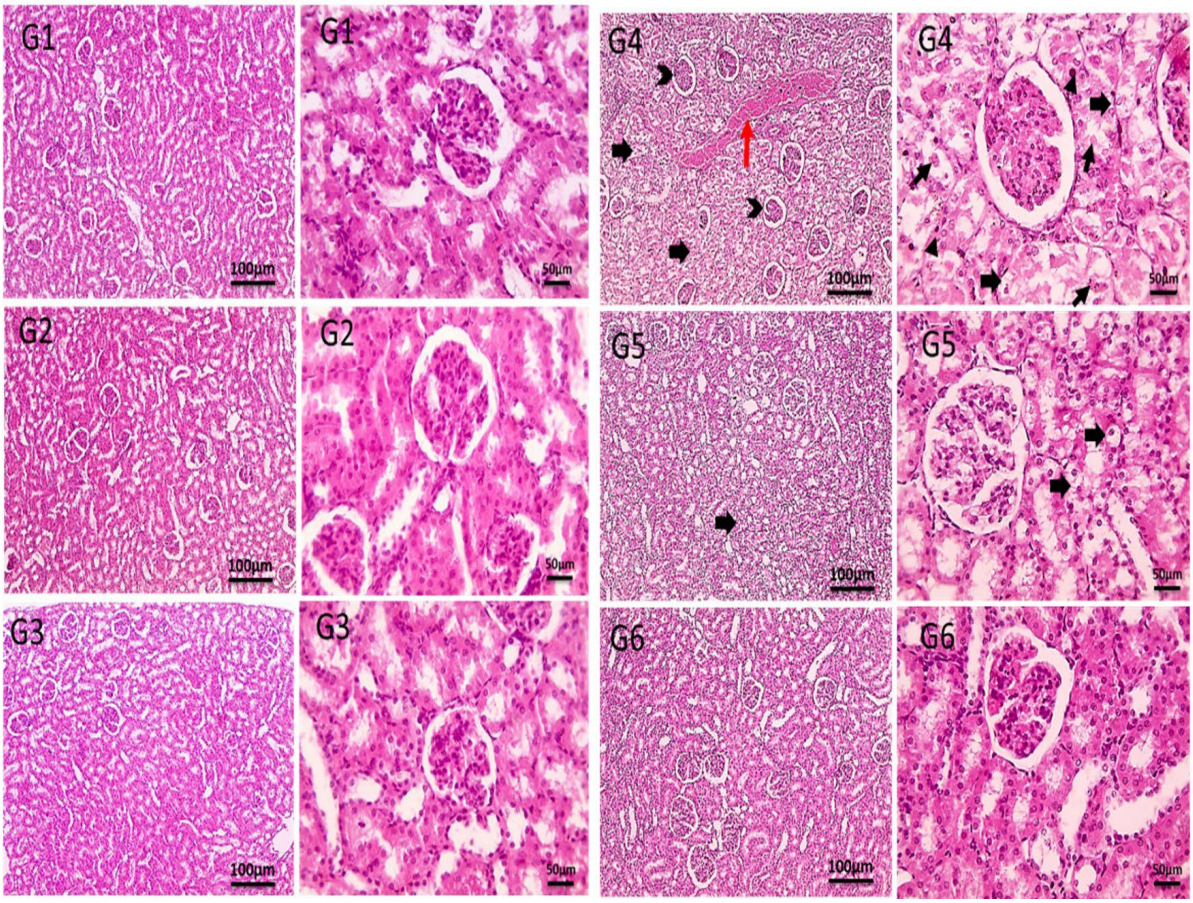

Figure 3. Microscopic pictures of H&E stained kidney sections from control groups G1-G3 showing normal tubules and glomeruli. While in HFD groups, G4 showing congested renal blood vessels (red arrows) and diffuse tubular hydropic degeneration (thick black arrows) with many necrotic (closed arrowheads) and apoptotic (thin black arrows) renal epithelial cells, clumped glomerular tuft, dilated Bowman's space and thickened Bowman's capsule (open arrowheads). Kidney sections of HFD group G5 received H/ZnONPs (200 mg/kg/day) showed multifocal areas of tubular ballooning degeneration (thick black arrows) with normalized picture of glomeruli. Kidney sections of HFD group G6 received H/ZnONPs (400 mg/kg/day) showed retained normal appearance of tubules and glomeruli. Low magnification X: 100 bar 100 and high magnification X: 400 bar 50.

Recent research described the molecular mechanism involved in PPAR γ activity in controlling metabolism and spot light on potential trail to uses this mechanisms to prevent and treat some metabolic diseases associated with fat metabolism like obesity and diabetes (Hernandez-Quiles *et al*., 2021).

In the present experiments, obesity increased the PPAR γ expression in both liver and kidney tissue significantly. Moreover, treatment by 200 and 400 mg/kg of H/ZnONP significantly upregulated PPAR gene expression in groups (G1, G2 and G3). and does not affect expression ratio in the obese groups compared with corresponding control one. This data were consistent with the previous obtained results of Tovar and Torres (2010) and Kumar *et al*. (2020) who approved that direct relationship found between PPAR gamma gene expression and fat accretion in adipose tissue. Moreover, Ahmadian *et al*. (2013) approved that fatty acid synthesis and glucose metabolism are coordinated by PPAR γ and upregulation of this gene promote adipogenesis and lipid uptake by fat cells and so induces obesity. Waki *et al*. (2007) have discovered that harmine facilitates adipogenesis invitro through selective upregulation of PPAR expression.

Harmine, is the active alkaloid extracted from *P. harmala* acts as a cell-type-specific regulator of PPAR inducing PPAR gene expression, that consider regulator of adipogenesis Waki *et al*. (2007). These concepts get in parallel with the data obtained in this study where PPAR gene was upregulated in the liver and kidney tissue in groups treated with H/ZnONP. In the same respect Magdy *et al*. (2020) found that diabetic rats treated with *P. harmala* showed upregulation in PPAR gene expression.

Our results agree with He *et al*. (2003) who reported that harmine is the major constituent of *P. harmala* and has been shown to upregulate the expression of PPARγ gene through the inhibition of Wnt protein signaling pathway. The PPARγ plays an important role in adipogenesis and regulates the metabolism of lipid in adipocyte. Our results showed a significant upregulation of PPARγ expression in *P. harmala* seed extract-treated rats when compared with groups (G1, G2 and G3). Our finding suggests that *P. harmala* induced PPAR gamma expression. This effect was unobserved in obese groups that may be masked by the over expression of PPARγ as the result of overloading of adipocyte by fat and over expression of this gene. This finding was previously described by Lehrke and Lazar (2005).

In the present study, the biochemical findings were supported by histopathological results. H/ZnONP (400 mg/kg) improved histology of liver and kidney, which may be attributed to its protective effects against hyperglycemia, hyperlipidemia.

CONCLUSION

High fat diet potentially increases the serum lipid overload in rat. Treatment of obese rats with H/ZnONP significantly alleviate hyperlipidemia, decrease obesity gene markers and improve histology of liver and kidney. This study offers scientific validation to the traditional use of harmal nanoparticles against several morbidities including hyperlipidemia. The precise molecular mechanisms behind these beneficial effects of H/ZnONP need to be further investigated.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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