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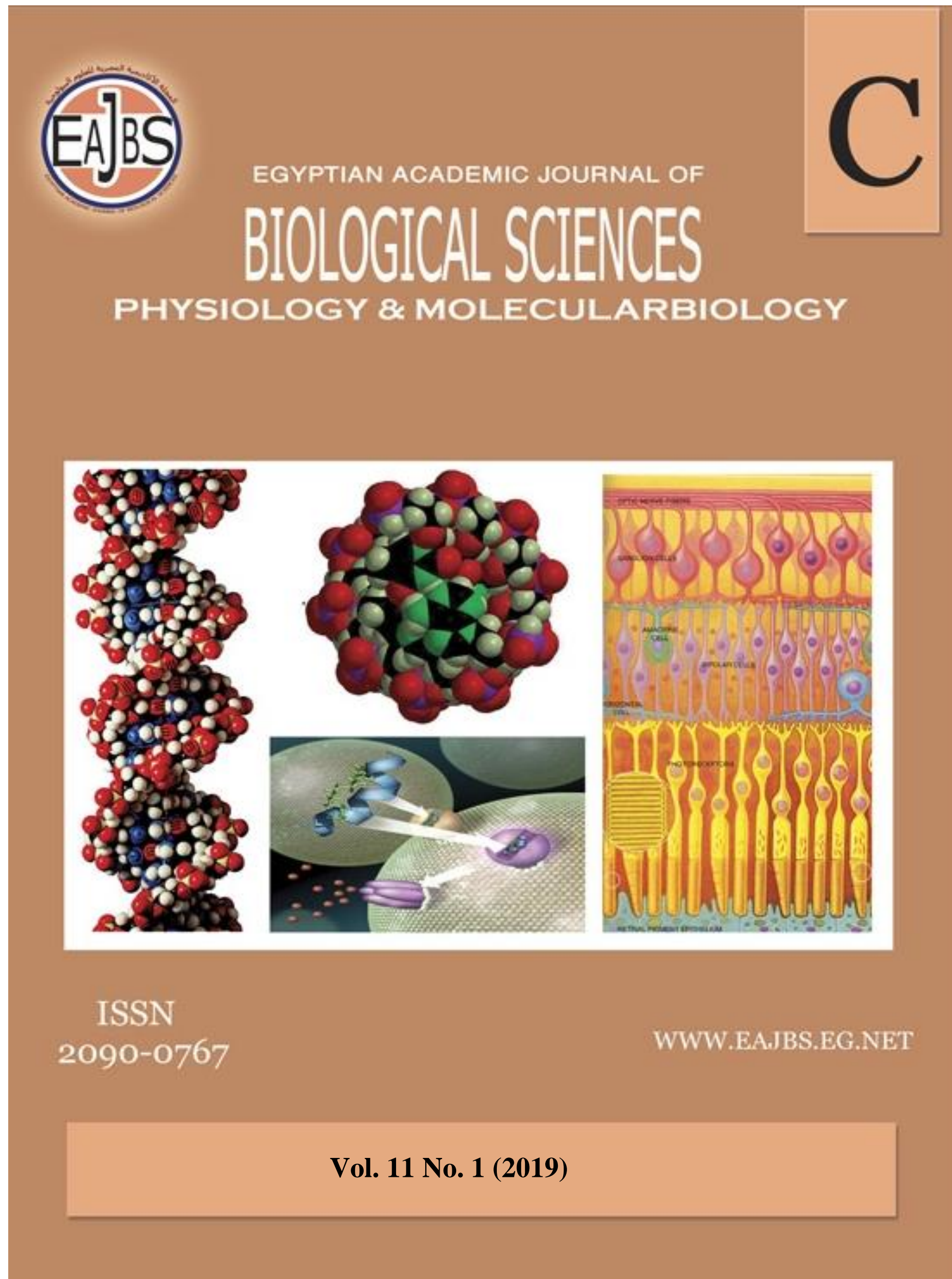

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Obesity Modulating Efficiency **of *Moringa oleifera* Extract on Obese Modeled Rats**

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ABSTRACT

Obesity is a chronic metabolic disorder that is raised by multiple biological and environmental factors. The objective of this study was to determine the thermogenesis potential of Egyptian *Moringa oleifera* against obesity disorder. Adult male Wistar albino rats (150-170g) were randomly divided into four groups (10 animals each) as follows: group (1) healthy rats fed standard diet and served as control, group (2) animals orally *Moringa oleifera* extract-standard diet (20%), group (3) obese rats fed high-fat diet and group (4) obese animals administrated *Moringa oleifera extract*-high-fat diet (20%). After six weeks of feeding, the results revealed that feeding of obese animals on moringa (20%) mixed diet succeeded to decline the body weight as well as obesity-induced disorders; this was evidenced by the significant reduction of body weight gain and BMI values as well as levels of serum ALAT, ASAT, urea, creatinine, total cholesterol, triglycerides, LDL, LDH, CK, PON1, TNF-α and glucose. Also, cardio-hepatic MDA and nitric oxide levels ware decreased coupled with marked elevation in the levels of serum HDL and irisin as well as cardio-hepatic GSH, SOD and CAT. Moreover, the histopathological findings showed a marked regeneration. In conclusion, *Moringa oleifera*, as a food supplement, could play a beneficial role in management of obesity and its disorders; this could be exhibited through its bioactive components with thermogenesis mechanism and/or other multiple pathways.

INTRODUCTION

Nowadays obesity has emerged as a major health problem and risk factor for various disorders worldwide. Obesity is defined as a disease process characterized by excessive body fat accumulation with multiple organ-specific consequences. The prevalence of obesity is increasing to epidemic proportions globally (Ogden *et al.,* 2012).

Obesity is associated with a multitude of adverse health effects. Central or visceral fat in obesity pours out free fatty acids and increases insulin resistance.

The adipose cells secrete multiple hormones, known as 'adipokines,' and arkers of inflammation. Obesity is associated with a higher risk of diabetes, hypertriglyceridemia, decreased high-density lipoprotein (HDL) cholesterol, hypertension, stroke, proteinuria, gallstones, fatty change in the liver, nonalcoholic steatohepatitis, pancreatitis, venous thrombosis, hypoventilation syndrome, and osteoarthritis (Kumari *et al.,* 2010; Shen *et al.,* 2010). Other conditions for which obesity poses an increased risk include sleep apnea, asthma, stress incontinence, depression, and several types of cancer (Gaby, 2011).

Obesity has an immense impact globally in terms of human suffering and economic burden, resulting from the chronic disease and disability associated with obesity. The conventional treatment for obesity includes decreasing caloric intake and increasing physical activity, that is, 'diet and exercise.' Medications have also been utilized. However, the long-term success rate of most weight loss programs is very low (Gaby, 2011).

In many cultures of the world, herbal remedies are increasingly being employed in an attempt to achieve the same purpose. In India, for instance, the leaf of *Moringa oleifera* Lam is claimed to possess a cholesterol-reducing effect, and is used to treat patients with heart disease and obesity; for this reason, it was decided to resolve this claim by investigating the effects of the crude extract of leaves of *Moringa oleifera* Lam on the serum, liver and kidney cholesterol; as well as the effect on serum total protein and albumin was also examined in the same animal model. (Ghasi *et al.* 2000).

Moringa oleifera (Moringaceae) has been recognized as it is containing a great number of bioactive compounds. The most used parts of the plant are the leaves, which are rich in vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins and saponins. The high number of bioactive compounds might explain the pharmacological properties of Moringa. Many studies, in vitro and in vivo, have confirmed these pharmacological properties. The roots, bark, gum, leaf, fruit (pods), flowers, seed, and seed oil of *MO* are reported to have various biological activities, including protection against gastric ulcers, antidiabetic, hypotensive and anti-inflammatory effects. It has also been shown to improve hepatic and renal functions and the regulation of thyroid hormone status. *MO* also protect against oxidative stress, inflammation, hepatic fibrosis, liver damage, hypercholesterolemia, bacterial activity, cancer and liver injury (Vergara-Jimenez et al., 2017)**.**

Moringa oleifera, an important multipurpose crop, is rich in various phytochemicals: flavonoids, antioxidants, vitamins, minerals and carotenes. Biochemical pathway analysis revealed that 28 identified metabolites were interconnected with 36 different pathways as well as related to different fatty acids and secondary metabolites synthesis biochemical pathways. It is well known that different tissues of *Moringa oleifera* have nutritional, medicinal and therapeutic values; therefore, Mahmud *et al.* (2014) provided a publicly available Moringa metabolite database; also it was appreciated for nutritive and health-promoting value, as well as improving mineral nutrition, arbuscular mycorrhizal fungi that can affect plants' synthesis of compounds those are bioactive against chronic diseases in humans.

The antioxidant capacity and antimicrobial activity of the essential oil of *Moringa oleifera* grown in Mozambique was investigated. The antimicrobial activity of the essential oil was assayed against two gram-positive strains (*Bacillus cereus, Staphylococcus aureus*), two gram-

negative strains (*Escherichia coli, Pseudomonas aeruginosa*), and five fungal strains of agro-food interest (*Penicillium aurantiogriseum, Penicillium expansum, Penicillium citrinum, Penicillium digitatum, and Aspergillus nigerspp*.). B. *cereus and P. aeruginosa,* as well as the fungal strains were sensitive to the essential oil (Marrufo et al 2013). The main objective of this study was to assess the ameliorating and thermogenesis efficiency of Moringa aqueous extract of dry leaves on obese modeled rats in a trial for managing massive body weight gain and protecting against its complication.

MATERIALS AND METHODS

Herb Extraction:

This study dealt with the aqueous extract of the herb rather than that of organic solvents; this due to the possible effects of the organic solvents on the conformation and configuration structure of the extract components. *Moringa oleifera Lam* (Moringaceae) is purchased from the stores of Abd El-Rahman Harraz (Bab El-Khalk zone, Cairo, Egypt), and was identified by special botanists**,** botany department, faculty of science Al Azhar university and was found to carry taxonomic serial number (TSN 503874).

Moringa Aqueous Extract Preparation:

Moringa aqueous extracts (MAE) was carried out according to the method of Berkovich *et al.* (2013); after grinding of *Moringa oleifera* dry leaves, a specimen of the powdered leaves was soaked with distilled water (1.25, W:W) in a glass conical flask for three hours, then immerse the container in a boiling water bath for 40 min. After filtration, the solid residues were subjected to the same process once again, and then the two water fractions were combined and re-filtered through Whatman No.1 filter paper (Whatman International Ltd, Maidstone, England). The filtrate was subjected to lypholyzation process through freeze drier (Snijders Scientific-tilburg, Holland) under pressure, 0.1 to 0.5 mbar and temperature -35 to -41°C conditions. The dry extract was stored at 4°C until used.

Determination of Total Extract Yield:

The combined extracts were transferred to a quick fit round bottom flask with a known weight (W1), then freeze-dried and weighed again (W2). Finally, the yield was calculated from the following formula:

Extract yield (g/ g crude herb) = (W2 −W1)/W3

Where, W1 is the weight of clear and dry quick fit flask in grams, W2 is the weight of the flask after lypholization in grams, and W3 is the weight of the crude powdered herb in grams.

Determination of Total Phenolics Content:

The content of total phenolic compounds in the aqueous extract was analyzed spectrophotometrically using modified Folin–Ciocalteu colorimetric method of Jayaprakasha and Jaganmohan (2000). In brief, 5 mg of the extract was dissolved in a 10 ml mixture of acetone and water (6:4 v/v). - Samples (0.2 ml) mixed with 1.0 ml of 10-folds diluted Folin-Ciocalteu reagent and 0.8 ml of sodium carbonate solution (7.5%). After 30 min at room temperature, the absorbance was measured at 765 nm using UV – 160 1PC UV-visible spectrophotometer (Shimadzu, Japan).Total phenolic content as catechin equivalents (CE) was monitored from standard curve.

Radical Scavenging Activity (RSA):

The capacity of antioxidants in the extracts to quench DPPH radical was determined using the method of Nogala-Kalucka *et al*. (2005). In this method, dissolve a certain weight of the extract in methanol (MeOH) to obtain a concentration of 200 ppm. A volume of 200µl from this solution was made up to 4 ml by MeOH. Add 1 ml of DPPH (6.09×10^{-5} mol/l) solution (in MeOH), and after 10 minutes the absorbances of both tested and control

sample [1 ml of DPPH solution (6.09 x 10^{-5} mol/l) and 4 ml MeOH] were measured at 516 nm using spectrophotometer (UV-Visible, Shimadzu, Japan) using. . The radical scavenging activity of the extract was calculated according to the following equation:

RSA% = [absorbance of control sample - absorbance of tested sample]/absorbance of control sample) x 100

Animals and Induction of Obesity:

Adult male Wistar albino rats (their weights were 150-170g) were obtained from Animal Colony, National Research Centre, Cairo, Egypt. The animals were housed in suitable plastic cages for one week for acclimation before the experimental study. Excess tap water and standard rodent food pellets [20.3% protein (20% casein and 0.3% DL-Methionine), 5% fat (corn oil), 5% fibers, 3.7% salt mixture and 1% vitamin mixture; obtained from Meladco company for animals and rodents food pellets, El-Obour City, Cairo, Egypt] were always available. All animals received human care in compliance with the standard insitiuations criteria as cited by animal ethical committee number FWA00014747, National Research Centre. After the animals being acclimatized, a number of rats were fed on a high (46%) fat diet [25.5 % corn oil and 20.5% beef tallow or lard), 24% carbohydrates (6% corn starch and 18% sucrose), 20.3% proteins (20 casein and 0.3% DL-Methionine), 5% Fiber, 3.7% salt mixture, and 1% vitamin mixture] for 16 weeks according to Noeman *et al.* (2011). The weight and nose-anus length of each rat of both control and obese groups were measured at the start of the experiment and after seven weeks. BMI was determined by dividing the weight (g) by the square of the nose-anus length (cm^2). Animals with BMI greater than 0.68 g/cm^2 were considered obese as previously described by Novelli *et al.* (2007). Rats that recorded BMI values below that level were excluded from the study. However, all rats of the obese group attained the target BMI and were all included.

Experimental Design:

After induction of obesity, both normal and obese rats were randomly divided into four groups (10 animals each); group 1 acted as control group and included healthy rats fed standard diet, group 2 included normal rats administrated with Moringa aqueous extract (1000 mg/kg b.w) and fed a standard diet, group 3 included untreated obese rats fed a high-fat diet, and group 4 included obese rats administrated with Moringa aqueous extract (1000 mg/kg b.w) and fed the same high-fat diet.

BMI and Body Weight Gain:

After induction of obesity, body weights, nose-anus length, weight gain and BMI of both obese and normal rat groups were recorded at start and end of the experiment. Both BMI value and body weight gain were calculated according to the formulae.

$$BMI = \frac{weight\ (g)}{nose - anus\ length\ (cm^2)}$$

$$\text{Body weight gain (\%)} = \frac{W2-W1}{W1} * 100$$

W_1 is the animals' weight at the start.

W_2 is the animals' weight at the end of the experiment.

Blood and Tissue Sampling:

At the end of the study period (six weeks) and after recording the end weight and length of the animals, they were fasted overnight. Following diethyl ether anesthesia and using heparinized capillary tubes, blood specimens were withdrawn from the retro-orbital plexus into vacutainer collecting tubes and left 20 minutes to

clot, then centrifuged at 3000 rpm for 10 minutes using cooling centrifuge (IEC centra-4R, International Equipment Co., USA). The sera were separated, divided into aliquots and stored at -80°C until biochemical measurements were carried out as soon as possible. After blood collection, the animals were rapidly sacrificed and a part of liver and whole heart of each animal was dissected out, washed with saline, dried, rolled in a piece of aluminum foil and stored at -80°C until homogenization and biochemical determinations; another part of each liver was preserved in a formalin-saline solution (10%); immediately processed, sectioned, stained and prepared for microscopic examination for histological changes.

Biochemical Determinations:

The activity of serum aminotransferases (ALAT and ASAT) was determined according to the kinetic method described by Schumann and Klauke (2003) and using instruction manual of reagent kits purchased from Human Gesell Schaft fur Biochemical und Diagnostic mbH, Germany. Serum GGT activity was measured according to the kinetic method described by IFCC (1983) using reagent kits purchased from BioSystems S.A. Costa Brava 30, Barcelona, Spain. Serum ALP activity was assayed according to the method of Moss and Henderson (1999) using the reagent kits purchased from DiaSys Diagnostic systems GmbH Germany. Serum total proteins and albumin concentrations were evaluated according to the photometric systems of Johnson *et al.* (1999) using reagent kits purchased from DiaSys Diagnostic systems GmbH Germany. Serum total cholesterol, triglycerides, LDL and HDL levels were determined according to the methods of Artiss and Zak (1997), Cole *et al.* (1997), Wieland and Seidel (1983) and Lopes-Virella *et al.* (1977) respectively, using reagent kits purchased from DiaSys Diagnostic System GmbH, Germany. Serum CK and LDH activities were determined according to the methods described by IFCC (1983) and Van der heiden (1994), respectively using reagent kits purchased from Spectrum Diagnostic System MDSS GmbH, Egypt. Serum glucose level was determined, at time of sampling, according to the method described by Young (2001) using reagent kits obtained from Co., Dokki, Giza, Egypt. Urea and creatinine levels were assessed according to the methods described by Young (2001) using reagent kits purchased from Diamond Diagnostic, MDCS GmbH Schiffgraben, Hannover, Germany.

Paraoxonase-1 (PON-1) Activity*:*

Serum PON1 activity was determined according to the kinetic spectrophotometric chemical method described by Eckerson *et al.* (1983) using a substrate buffered mixture [Paraoxon (1.0 mo L^{-1}), $CaCl_2$ (1.0 mmol L^{-1}), Glycin Buffer (50 mmol L^{-1})]. Under the above system, PONase can hydrolyze paraoxon (Sigma) to ρ-nitrophenol and diethylphosphate. The rate of paraoxon hydrolysis can be measured spectrophotometrically at 405 nm and 37 ºC by monitoring the increase of absorbance at zero time and each two minutes interval for 10 minutes. All samples were run in duplicate; the average value was used for activity calculation using a molar extinction coefficient of 18, 300 M^{-1} cm^{-1} for p-nitrophenol. Results are expressed as U/L for PON1 activity (nanomole paraoxon hydrolyzed per minute).

Leptin, Irisin and TNFα Levels:

Serum Leptin concentration was performed using ELISA (Dynatech Microplate Reader Model MR 5000, 478 Bay Street, Suite A213 Midland, ON, Canada) and instruction manual of rats' reagent kit (SG-20057) purchased from SinoGeneClon Biotech Co., Ltd, No.9 BoYuan Road,YuHang District 311112, Hang Zhou, China. Serum irisin and TNFα concentrations were performed using ELISA (Dynatech Microplate Reader Model MR 5000,

478 Bay Street, Suite A213 Midland, ON, Canada) and instruction manual of human reagent kits (No. SG-10179 and SG-10127, respectively) purchased from SinoGeneClon Biotech Co., Ltd, No.9 BoYuan Road,YuHang District 311112, Hang Zhou, China.

GSH, SOD, CAT, and NO :

Liver and heart GSH, SOD, CAT and NO levels were determined according to the methods of Beutler *et al.* (1963), Aebi (1984), Nishikimi *et al.* (1972) and Montgomery *et al.* (1961) respectively, using reagent kits obtained from Biodiagnostic Co., Dokki, Giza, Egypt.

Lipid Peroxidation (MDA):

Lipid peroxidation end product, malondialdehyde (MDA), level of both liver and heart homogenates was estimated chemically according to the method described by Ruiz-Larnea *et al.* (1994) on the base of MDA reaction with thiobarbituric acid (TBA) which forms a pink complex that can be measured photometrically. In this method 0.5 ml liver homogenate supernatant [1g Liver or heart tissue was homogenized in 10 ml phosphate buffer pH 7.4 and cool centrifuged at 5000 rpm for 10 minutes] was added to 4.5 ml working reagent [0.8 g TBA was dissolved in 100 ml perchloric acid (10%) and mixed with trichloroacetic acid (20%) in volume ratio 1 to 3, respectively]. In a boiling and shaking water bath, the sample-reagent mixture was left for 20 minutes, then carried out to cool at room temperature, and centrifuged for 5 minutes at 3000 rpm. The absorbance of the clear pink supernatant was measured photometrically at 535 nm against reagent blank (0.5 ml distilled water + 4.5 ml working reagent). The lipid peroxidation level was calculated in nM MDA/gram liver tissue according to the following formula:

$$MDA\ (nmol\ g^{-1}) = [\{A_{535} \times 10^9 / (1.56 \times 10^5) \times 10^3\}\ x\ AD] \times 10^{-1}$$

Where, $1.56x10^5\ M^{-1}L^{-1}cm^{-1}$ = extinction coefficient of MDA, AD is assay dilution

Histopathology:

The liver of different groups was sectioned into 5um thick paraffin sections, stained with hematoxylin and eosin (Drury and Wallington, 1980) and investigated by light microscope.

Statistical Analysis:

Comparisons between means were carried out using one-way ANOVA test followed by post hoc test (Duncan) at $p \leq 0.05$ (Steel & Torrie, 1960). This analysis was computed using SAS program software; copyright (c) 1998 by SAS Institute Inc., Cary, NC, USA.

RESULTS

The yield amount, total phenolic content and radical scavenging activity of the powdered leaves of *Moringa oleifera* are shown in Figure 1.

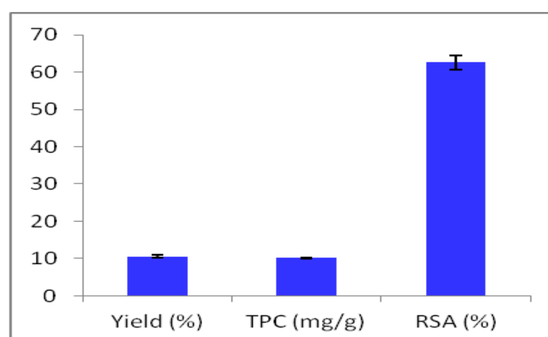

Fig. 1: Yield, total phenolic content (TP) and radical scavenging activity (RSA) of three replicates of dry powdered leaves of *Moringa oleifera*.

The data revealed that obese rats recorded a significant elevation in body mass index (BMI) and body weight gain (BWG) when it was compared with control group. Fortunately, administration of obese rats with MAE resulted in a significant reduction in

both BMI and BWG close to that of healthy control (Figures 2&3).

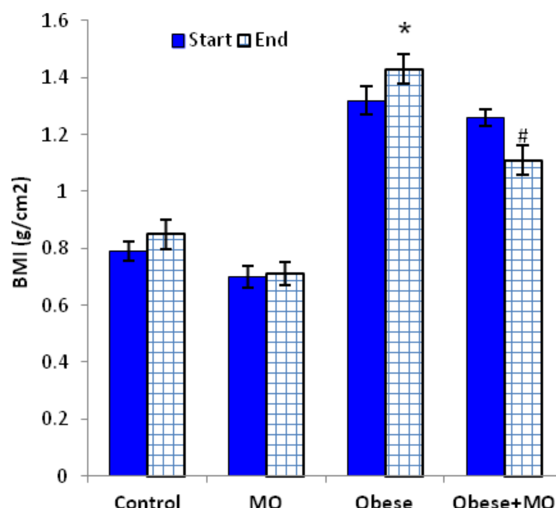

Fig. 2. Body mass index (BMI) of obese and MAE-traded animals' groups in compare to control animals' group. Data were treated with ANOVA followed by post hoc (Duncan) test at level p≤0.05. (*) is significance from control group and (#) is significance from obese group.

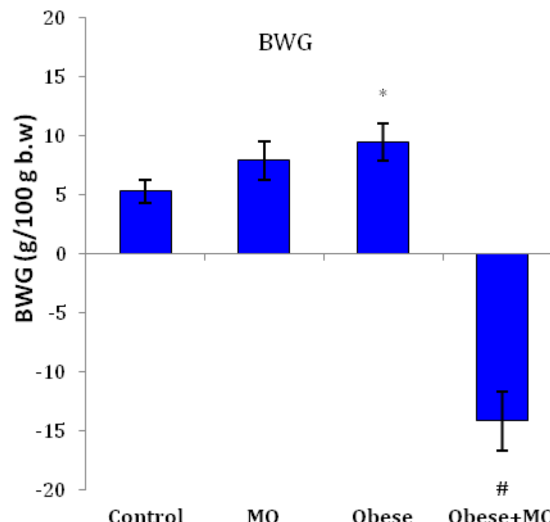

Fig. 3. Body weight gain (BWG) of obese and MAE-traded animals' groups in compare to control animals' group. Data were treated with ANOVA followed by post hoc (Duncan) test at level *p*≤0.05. (*) is significance from control group and (#) is significance from obese group.

Oral treatment of healthy animals with MAE neither deteriorate the activities of serum ALAT, ASAT, GGT and ALP nor the levels of total proteins, albumin, globulin, creatinine and urea. In contrast, obese animals' group recorded a significant increase in the activity of ALAT, ASAT, GGT and ALP, but neither deteriorate protein profile (total protein and albumin) nor kidney function (urea and creatinine), when both groups were compared with the healthy group. Favorably, treatment of the obese-rats group with MAE resulted in significant improvements in the activity of ALAT, ASAT, GGT and ALP in compare to obesity-rats' group (Table 1).

Table 1: Activity of serum ALAT, ASAT, GGT and ALP and levels of total proteins, albumin, globulin, creatinine and urea of control, obese and MAE-treated animals groups.

	Control	MAE	Obese	Obese + MAE
ALAT(U/L)	27.3 ± 2.4^{DC}	24.4 ± 1.2^{D}	52.5 ± 3.3^{A}	34.3 ± 0.84^{B}
ASAT(U/L)	46.7 ± 3.1^{C}	48.5 ± 2.7^{C}	143.5 ± 9.9^{A}	101.9 ± 12.4^{B}
GGT(U/L)	5.4 ± 0.41^{AB}	4.9 ± 0.28^{B}	6.4 ± 0.38^{A}	5.7 ± 0.33^{AB}
ALP(U/L)	196.4 ± 8.6^{B}	181.8 ± 9.5^{B}	288 ± 30.4^{A}	211.6 ± 7.4^{B}
Alb (g/dl)	4.6 ± 0.31^{AC}	4.5 ± 0.33^{BC}	4.4 ± 0.18^{C}	5.5 ± 0.29^{A}
T.P (g/dl)	6.9 ± 0.31^{A}	6.5 ± 0.17^{A}	$6.3\pm\pm0.17^{A}$	7 ± 0.18^{A}
Creat(mg/dl)	0.88 ± 0.04^{A}	0.87 ± 0.06^{A}	0.9 ± 0.03^{A}	0.91 ± 0.05^{A}
Urea(mg/dl)	44.3 ± 2.4^{A}	49.4 ± 3^{A}	40.7 ± 5.2^{A}	35.9 ± 4.1^{A}

Data are expressed as mean ± standard error of mean. All data were subjected to one-way ANOVA followed by post hoc test (Duncan) at *p*≤0.05. Within the same row, means with different superscript letters are significantly different. (MEA) is Moringa aqueous extract.

Regard to Table (2) and comparing with the normal control group, administration of rats with MO didn't disturb the level glucose or lipid profile or CK activity, but significantly reduced LDH activity. Counteract, obese rats group revealed a significant elevation in serum glucose, total cholesterol, triglycerides and LDL-c levels as well as CK and LDH activity matched with a significant reduction in HDL-c level. In comparison with obese group, treatment of obese rats with MAE resulted in significant improve-ements in serum levels of glucose, total cholesterol, triglycerides and LDL-c, and activity of serum CK and LDH

levels coupled with a marked raise in HDL-c.

Table 2: Serum glucose, total cholesterol, triglycerides, HDL, LDL, LDH and CK levels of control, obese and MAE-treated animals groups.

	Control	MAE	Obese	Obese + MAE
Glucose (mg/dl)	71.1±2.4^{C}	73.6±4.1^{BC}	106.6±6.6^{A}	88.2±4.9^{BC}
Cho (mg/dl)	84.8±6.1^{D}	77.2±2.5^{D}	178.2±6.7^{A}	140.4±10.4^{B}
Trig (mg/dl)	74.7±3.2^{CD}	72.2±3.7^{CD}	160.7±10.8^{A}	123.6±5.8^{B}
HDL (mg/dl)	43.7±2.1^{A}	45.9±2.1^{A}	31.8±2.2^{B}	38.3±3.2^{AB}
LDL (mg/dl)	40.9 ± 5.2^{D}	31.2±1.7^{D}	137.8±7.2^{A}	93.2±3.7^{B}
CK (U/L)	110.8±2.7^{AB}	97.9±1.6^{ABC}	43±5.7^{D}	137.5±32.8^{A}
LDH (U/L)	1596±56.3^{D}	1669±84.4^{CD}	2799±130.8^{A}	2167±39.7^{B}

Data are expressed as mean ± standard error of mean. All data were subjected to one-way ANOVA followed by post hoc test (Duncan) at $p \leq 0.05$. Within the same row, means with different superscript letters are significantly different. (MEA) is Moringa aqueous extract.

Similarly, MAE never disturbs the serum irisin, TNFα, leptin and PON1 levels; while obese group showed a significant reduction in serum irisin as well as serum PON1 activity coupled with a significant elevation in serum TNFα and leptin levels when both rats groups were compared with control group. In additional the obese group, favorably treatment of obese animals with MAE significantly down-regulated the serum TNFα and leptin levels, and up-regulated serum irisin level and PON1 activity (Table 3).

Table 3: Serum irisin and TNFα levels, and activity of PON1 of control, obese and MAE-treated animals groups.

	Control	MAE	Obese	Obese + MAE
Irisin (µg/mL)	4.2 ± 0.13^{A}	4 ±0.22^{A}	2.4±0.22^{B}	3.9 ± 0.23^{A}
PON1 (IU/l)	331.3±8.3^{BC}	312.6±8.4^{BC}	526.1± 29^{A}	411.3±39.9^{B}
TNFα (ng/ml)	36.5±3.8^{C}	37.4± 2^{C}	79.4± 3^{A}	57.7 ± 2.5^{B}
Leptin (ng/ml)	76±4.4^{C}	71±2.7^{C}	170±4.7^{A}	86±3.4^{B}

Data are expressed as mean ± standard error of mean. All data were subjected to one-way ANOVA followed by post hoc test (Duncan) at $p \leq 0.05$. Within the same row, means with different superscript letters are significantly different. (MEA) is Moringa aqueous extract.

Comparing with normal rats, rats MAE neither adverse the livers' nor the hearts' oxidative stress voltage (NO and MDA) and the antioxidant battery (GSH, SOD and CAT), while obese rats group recorded a significant reduction in the values of the antioxidant battery (GSH, SOD and CAT) lined with a significant increase in the oxidative stress voltage (NO and MDA). In addition, MAE with high-fat diet resulted in a significant decrease in MDA and NO levels, matched with a significant increase in the values of the antioxidant battery (GSH as well as activity of SOD and CAT) in both liver and heart tissues when compared to the obese rats group Tables (4&5).

Table 4: Levels of NO, MDA and GSH and activity of SOD and CAT of liver tissue of control, obese and MAE-treated animals groups.

	Control	MAE	Obese	Obese + MAE
NO (µmo1/g tissue)	63.8±2.2^{D}	65.3±3.7^{D}	141.3± 5^{A}	90.6±3.2^{B}
MDA (nmol/g tissue)	169.8±11.4^{C}	162.2±8.5^{C}	401.1±15.2^{A}	220.6±5.8^{B}
GSH (mmol/g tissue)	71.5±3.9^{A}	74 ± 2.9^{A}	48.6±2.5^{C}	61.2±3.3^{B}
SOD (IU/g tissue)	37459±2034^{A}	40830±2217^{A}	25901±964,7^{B}	29010±1080^{B}
CAT (IU/g tissue)	73.6±1.1^{A}	75.1±0.6^{A}	53.1±2.8^{C}	64.5± 2^{B}

Data are expressed as mean ± standard error of mean. All data were subjected to one-way ANOVA followed by post hoc test (Duncan) at $p \leq 0.05$. Within the same row, means with different superscript letters are significantly different. (MEA) is Moringa aqueous extract.

Table 5: Levels of NO, MDA and GSH, and activity of SOD and CAT of heart tissue of control, obese and obese-treated animals groups.

	Control	MAE	Obese	Obese + MAE
NO (µmo1/g tissue)	22.9±3.3^{AB}	19 ± 0.54^{B}	27.9±1.8^{A}	21.1±1.7^{B}
MDA (nmol/g tissue)	78.3±4.5^{C}	70.8± 5^{C}	118.4±4.3^{A}	102.5±1.5^{B}
GSH (mmol/g tissue)	28.1±1.4^{A}	25.8± 1^{AB}	17.4±0.49^{C}	23.9±0.6^{B}
SOD (IU/g tissue)	1405±60.1^{A}	1408±74.1^{A}	1407±48.6^{A}	1417±33^{A}
CAT (IU/g tissue)	10.1±0.08^{A}	10.3±0.05^{A}	7.6 ± 0.3^{C}	8.7± 0.27^{B}

Data are expressed as mean ± standard error of mean. All data were subjected to one-way ANOVA followed by post hoc test (Duncan) at $p \leq 0.05$. Within the same row, means with different superscript letters are significantly different. (MEA) is Moringa aqueous extract.

Histopathological Results Of Liver:

The microscopic examinations of the liver sections of the control, obese and obese-treated animals groups are illustrated in the Figures (4-9).

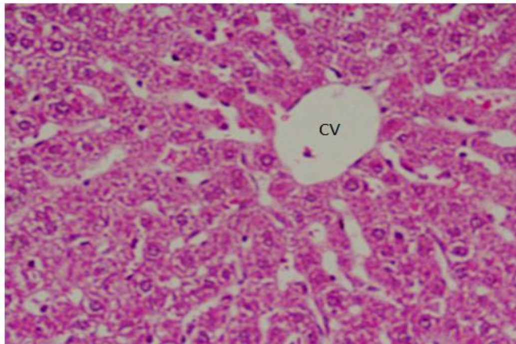

Fig. 4: Section of the liver of control rats showing normal histological structure of hepatic lobules and central vein (cv). (Hx& Ex400)

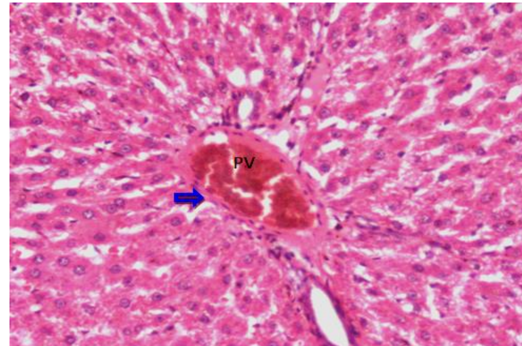

Fig. 5: Section of the liver of rats treated with moringa showing dilated and congested portal (blue arrow PV) . (Hx & Ex400)

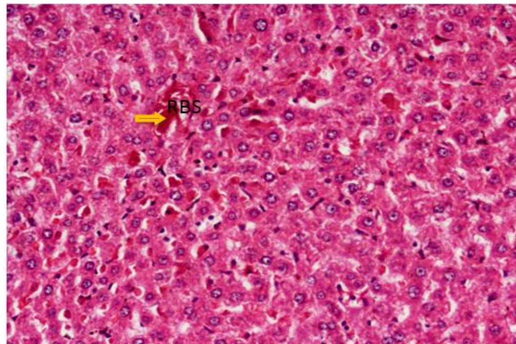

Fig. 6: Another filed of the liver of rats treated with moringa showing red blood cells in blood sinusoids (orange arrow RBC). (Hx&Ex200)

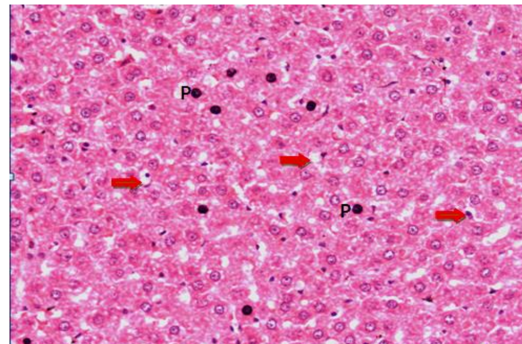

Fig. 7: Section of liver of obese rats showing micro vesicular (red arrow) steatosis and sings of degeneration in the form of pyknosis (P). (Hx&Ex200).

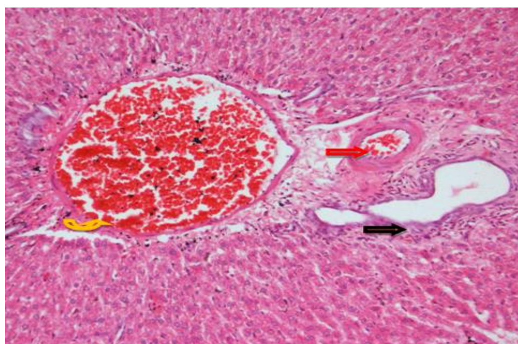

Fig. 8: Another filed of liver of obese rats showing dilated, congested in portal vein (orange arrow), fibrosis in portal area, dilated bile duct (red arrow) and cellular infiltration around (black arrow), (Hx&Ex100)

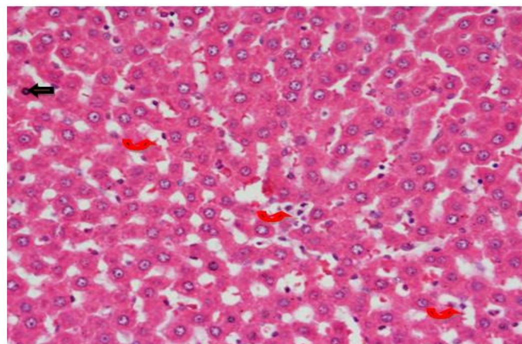

Fig. 9: Section of liver of obese rat treated with moringa showing most hepatocyte cells appeared normal although dilated blood sinusoids and few inflammatory cells was seen (red arrow). (Hx&Ex400)

DISCUSSION

Nowadays Obesity has emerged as a major health problem and risk factor for various disorders worldwide (Roh and Jung 2012). Overweight and obesity are defined as abnormal or excessive fat accumulation triggered by disproportion in energy intake and expenditure (Spiegelman and Flier 2001& Panico and Iannuzzi 2004). Obesity is a major risk factor for augmented morbidity and mortality and is associated with various medical ailments (Wang and Lobstein 2006). High fat diet-induced obesity has been considered as the most popular model among researchers due to its high similarity of mimicking the usual route of obesity episodes in human (Buettner *et al.* 2007) and so why it is considered as a reliable tool for studying obesity as they will readily gain weight when fed high-fat diets (Gajda 2009). Visceral adiposity is regarded as the direct link between obesity and several metabolic diseases, including risk of incidence of type 2 diabetes, atherosclerosis and hypertension, which are totally clustered under the clinical signs of the metabolic syndrome. This study confirmed the effectiveness of aqueous extract of *M. oleifera* in improving obesity and dyslipidemia occurred in obese rats after long-term treatment with MAE. (Ahmed *et al.* 2014)

Moringa oleifera, an important multipurpose crop, is rich in various phytochemicals such as flavonoids, antioxidants, vitamins, minerals and carotenes. Biochemical pathway analysis revealed that 28 identified metabolites were interconnected with 36 different pathways as well as related to different fatty acids and secondary metabolites synthesis biochemical pathways (Mahmud *et al*. 2014).

Mostly, there is no suitable drug for treating diet-caused obesity; in regard of that, herbs are implicated as potential protective agents; therefore, the present study attempted to investigate the obesity controlling or thermoregulatory potential of *Moringa oleifera* in an obese-rat model.

Herein, this study showed that administration of normal rats with MAE never disturb either hepatic or kidney functions; this was monitored from the comparable values of ALAT, ASAT, GGT and ALP activities or total proteins, albumin, globulin, creatinine and urea levels as well as liver histological structures. This finding reflects the safe effect of MAE and is concomitant with Awodele *et al.* (2012).

Results of this study declared that MAE has a hepato-nephro-protective therapeutic effect on obese rats; this was monitored from marked improvement in ALAT, ASAT, GGT and ALP activities or total proteins, albumin, globulin, as well as urea and creatinine levels in serum; this result goes in parallel with that of Yang *et al.* (2011) and Fakurazi *et al.* (2012) who attributed that to the antioxidant potential of MAE included phytochemicals. Also, Buraimoh (2011) and Halaby et al. (2013) stated that this effect might be due to the potent antioxidant property of MAE contents (vitamins, a-tocopherol, ascorbic acid and 3-carotene, as well as glutathione) that act against oxidative stress, indicates its protective role against liver damage. This protective action may be also due to improvement of hepatic steatosis and fat accumulation in the liver (Hamaguchi *et al.,* 2005 and Hanley *et al.,* 2005).

Fortunately, The present study recorded that treatment of obese rats with MAE significantly reduced the percentage of body weight gain and consequently BMI value as well as serum glucose, total cholesterol, triglycerides and LDL-cholesterol (those were elevated as a consequence of obesity) coupled with significant improvement in HDL (which was decreased due to obesity) showing apparent anti-obesity potential. This

finding is in agreement with Mehta *et al.* (2003), Jain *et al.* (2010) and Bais *et al.* (2014). This improvement could be attributed to one or more mechanisms; MAE may reduce fat accumulation and free fatty acid, and/or it may increase energy expenditure-related fatty liver degradation and decreased fatty acid synthesis and fat intake in the liver. Also, the melatonin, an ingredients found in MAE, have a variety of important functions including direct free radical scavenging and anti-inflammatory properties. Other bioactive constituents are found in MAE such as dopamine, dopa, coumarins, alkaloids and saponins, polyphenols, flavonoids and anthocyanin may influence glucose metabolism by several mechanisms such as inhibition of carbohydrate digestion and glucose absorption in the intestine, stimulation of insulin secretion from the pancreatic ß-cell, modulation of glucose release from liver, activation of insulin receptors and glucose uptake in the insulin-sensitive tissues, and modulation of hepatic glucose output. In addition, Moringa was found containing polyphenols that able to inhibit digestive enzymes such as salivary amylase, intestinal sucrase and a-glucosidase, consequently, reduce digestibility action and promotes pancreatic β-cells. It was suggested that *Moringa oleifera* also showed anti- dyslipidemia effects in human patients with hyperlipidemia (Nambiar et al., 2010). It also improved the lipid profile in human with type 2 diabetes besides its beneficial effects on blood glucose (Kumari, 2010).

Moringa oleifera significantly improved the lipid profile as it reduced total cholesterol, triglycerides and LDL-c besides the up-regulation of HDL-c; this finding was in accordance with Rojas and Gomes (2013), Mehta *et al.* (2003), Jain *et al.* (2010), Bais *et al.* (2014) and Toma *et al.* (2015), who showed that *moringa oleifera* decreased cholesterol, triglycerides, VLDL, LDL, and increased HDL in hypercholestermic rats; reflecting its efficiency for reducing the risk of cardiovascular disease. Obesity is a dominant risk factor of atherosclerosis as it can increase the cholesterol content of platelets, polymorphonuclear leukocytes and endothelial cells, so that endothelial and smooth muscle cells, neutrophils and platelets may be sources of free radicals and oxygen free radicals that have been implicated in the pathogenesis of hypercholesterolemic atherosclerosis and antioxidants suppress its development.

Jaiswal *et al.* (2013) found that *M. oleifera* aqueous extract significantly increased the efficiency of several antioxidant agents such as glutathione reduced, superoxide dismutase, catalase, and reduced the oxidative agents such as MDA and NO in hepato-cardio tissues; these findings are in line with the results of our present study. Additionally, *M. oleifera* aqueous extract has contained the major groups of phytochemicals that contribute to the total antioxidant capacity of plant foods, mostly as polyphenols, flavonoids, carotenoids and antioxidant vitamins such as vitamins C and E (Lako *et al.,* 2007). Quercetin and kaempferol are the predominant flavonoids in *M. oleifera*. These compounds may act synergistically increasing the levels of antioxidant activity within these plant products and thereby, creating their desired therapeutic benefits (Manguro and Lemmen, 2007; Amaglo *et al*., 2010; Kasolo *et al.,* 2010); this could interpret the potential of MAE to restore SOD and CAT activities as well as GSH, MDA and NO levels in hepato-cardio tissues. Moringa has been suggested as a contains, vitamins and carotenoids and these compounds mainly contribute to the antioxidant properties as well as other biological activities. In addition, it was evidenced that β-Carotene exist in MAE is efficiently converted into vitamin A in the body and has shown significant

hepatoprotective effects. The main antioxidant activity that has been associated with the phenolic content ability is to scavenge free radical formation. The ability of a certain phenolic compound to bind to minerals may be beneficial in some cases, since copper and iron can be initiators of hydroxyl radical (Verma *et al.* 2009), that findings confirm the high RSA of MAE herein our study.

Previously, it was stated that Moeinga inhibited production of macrophage inflammatory cytokine (TNF-α), which was induced by lipopolysaccharide (Kooltheat et al., 2014), predicting its anti-inflammatory as reported by Waterman et al. (2014) who evidenced that Moeinga decreased the gene expression and production of inflammatory markers. Our results showed that MAE has anti-inflammatory, thermogenic and anti-atherosclerotic behaviors as it markedly reduced the inflammatory cytokine (TNF-α), elevated the thermogenic myokine (irisin) and raised the activity of the anti-atherosclerotic enzyme (PON1) in orally administration MAE with obese rats. This result is in agreement with Mahajan et al. (2007) and Rajanandh et al. (2012) also. Mahajan et al. (2007) reported that obesity leads to increased levels of monocytes that secrete increased amounts of TNF-α through up-regulation of P_{38} MAPK, protein kinase (PKC-α and PKC-β), protein kinase (PKC-α and PKC-β), and nuclear factor (NF)-κB.

Irisin is secreted by muscle tissue during exercising (Boström *et al.* 2012), and shows wide spread in body tissues. It has been shown that irisin exists not only in muscles but also in white fat tissue, liver, adult and fetal testes as well as in epididymis tissue (Aydin *et al.* 2014). The irisin level increased 3-4 folds, and brown fat cell development accompanied with the decrease in white fat tissue (Boström *et al.* 2012). Thus, irisin is defined as an anti-obesity myokin. Huh *et al.,* 2012 stated that mechanisms underlying irisin combined with the increase of brown fat, may unravel the basis of physical exercise concluded a decrement in serum irisin level in obese animals, and he suggested that benefits on different conditions. Irisin seems to induce a brown-like phenotype in some white adipocytes.

PON1 is an antioxidant enzyme that inhibits oxidative modification of LDL and contributes to most of the antioxidative activity that has been attributed to HDL. PON1 can destroy active lipids in mildly oxidized LDL. (Aviram *et al.* 1999) Most serum PON1 is bound to the surface of HDL. The activity of PON1 (an anti-atherosclerotic marker) was significantly lower in obese subjects than in controls. Several studies have suggested that there is an association between increased oxidative stress and BMI in obese animals (Keaney *et al.* 2003). Rector *et al.* (2007) described lower serum PON1 activity with increased body weight. Sorenson *et al.* (1999) demonstrated that PON1 is a lipid-dependent enzyme; in fact, the confirmation of PON1 within the hydrophobic environment of HDL is crucial for its activity. Phospholipids, especially those with long fatty acid chains, stabilize PON1 enzyme and are required to bind PON1 to lipoprotein surface. The restored PON1 activity after treatment of obese rats with MAE could be attributed to the antioxidative and atherosclerotic properties of the bioactive compounds exist in Moringa as it significantly increased the efficiency of several antioxidant agents such as glutathione reduced, superoxide dismutase, catalase, and reduced the oxidative agents such as MDA and NO (Jaiswal *et al.*, 2013).

CONCLUSION

Moringa oleifera has many bioactive compounds with multiple pharmacological and medical properties; it can markedly down-regulate BMI, atherosclerotic markers

as well some well-known cardiovascular risk factors, and preferably up-regulates PON1 activity and irisin level. It can presumably be considered, as a supplement, for future long-term studies on prevention and treatment of obesity, dyslipidemia and atherosclerotic disorders.

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ARABIC SUMMERY

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٢- المركز القومى للبحوث – الشعبة الطبيه- قسم الباثولوجى.
٣- المركز القومى للبحوث – الشعبة الطبيه- قسم الفسيولوجيا الطبيه.

تعتبر السمنة من الامراض المزمنة وتحدث نتيجه عوامل بيولوجية وبيئية متعددة، وكان الهدف من هذه الدراسة هو العمل على تقليل السمنه بواسطه مستخلص نبات المورنجا. ففى هذة الدراسه تم تقسيم الجرذان اليافعه (تتراوح اوزانها من ١٥٠-١٧٠ جم) عشوائياً إلى أربع مجموعات (١٠ حيوانات لكل منهما) على النحو التالي: مجموعة (١) جرذان سليمة تغذيت على نظام غذائي طبيعى وتعمل كمجموعة ضابطه (٢) حيوانات تم تجريعها على مستخلص المورنجا المائى جرعه (١٠٠٠مجم/كجم من وزن الجرذ) ، مجموعة (٣) االجرذان المستحدث بها السمية تغذت على نظام غذائي غني بالدهو، ومجموعة (٤) الجرذان المستحدث بها السمية وتغذت على النظام الغذائي الغنى بالدهون وتم تجريعها بالمستخلص المائى لنبات المورنجا. بعد ستة أسابيع من التجريع ، أظهرت النتائج أن معاملة الحيوانات السمينة بمستخلص المورنجا نجحت في إنقاص وزن الجسم وكذلك تعديل ومنع الاضطرابات المصاحبة للسمنة ؛ وقد وضح ذلك من خلال الانخفاض الكبير في معدل زيادة وزن الجسم و كذلك قيم مؤشر كتلة الجسم ، وكذلك مستويات مصل الدم من انزيمات الكبد، اليوريا، الكرياتينين، الكوليسترول الكلي، الدهون الثلاثية ، ومنخفضه الكثافه ، وانزيمات القلب ، وانزيم الباركزونيز ، وعامل النخرالورمى- نوع الفا ، والسكر. أيضا ، انخفض مستوى كل من NO و MDA بانسجة القلب والكبد مقترنة بارتفاع ملحوظ في مستويات HDL و irisin بمصل الدم ، فضلا عن ارتفاع مستوى GSH ، SOD و CAT بانسجة القلب والكبد. علاوة على ذلك ، أظهرت النتائج الهستوباثولوجية وجود تحسن ملحوظ. الخلاصه ، يمكن أن تستخدم المورنجا كمكمل غذائي ، لانها تلعب دوراً مفيدا في علاج السمنة واضطراباتها. ويمكن عرض ذلك من خلال مكوناتها النشطة بيولوجيًا باستخدام آلية توليد الحرارة ومسارات ايضية متعددة أخرى.