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## Antidiabetic, Antihyperlipidemic and Antioxidant Effects of *Artemisia herba alba* Extract on Experimental Diabetes

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### ABSTRACT

*Artemisia herba alba* was widely used in traditional medicine for the treatment of diabetes. The objective of this study was to evaluate the antidiabetic, antihyperlipidemic and antioxidant effects of *Artemisia herba alba* extract on high fat diet and diabetic models. Wistar albinos male rats were divided into four groups, the first was fed with high fat diet, the second was mimetic diabetes type II with high fat diet combined with double low dose of streptozotocin, the third was a model of type I diabetes with high dose of streptozotocin and the fourth was a control group. The ethanolic extract of *Artemisia herba alba* was given orally (2 g kg<sup>-1</sup> b.wt.) and daily for a period of 8 weeks. Our results showed that *Artemisia herba alba* treatment reduces the blood glucose level significantly in type II diabetic group (17.50±2.34 g L<sup>-1</sup> vs., 10.93±3.19 g L<sup>-1</sup>). The plasma lipoproteins HDL, LDL-cholesterol and the triglyceride levels were altered by high fat diet and also by streptozotocin injection. These levels were also reverted back to near normalcy by treatment. Lipid peroxidation was decreased significantly by *Artemisia herba alba* supplementation in high fat diet and diabetic groups (p<0.05). Treatment with investigational drug increases antioxidant enzymes activities (superoxide dismutase and catalase in liver and kidneys) for type I and type II diabetic groups. In conclusion, this study suggests that the *Artemisia herba alba* has a beneficial effect in controlling diabetes by reducing lipid peroxidation and increasing antioxidant enzymes activities, which reduces the risk of developing diabetes complications.

**Key words:** Antidiabetic, antioxidant, antihyperlipidemic, *Artemisia herba alba*, diabetes

### INTRODUCTION

Diabetes is the most common metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, or its action (ADA., 2003). Its complications such as retinopathy and nephropathy are the major targets for medical intervention (Butt *et al.*, 2012; Vinod, 2012).

Metabolic disorders are significantly associated with obesity. Adipocytes are dynamic insulin-sensitive cells that

have endocrine properties and contribute to whole-body energy homeostasis (Kim *et al.*, 2007).

Type II diabetes is characterized by hyperglycemia with biochemical alterations of glucose and lipid peroxidation. Oxidative stress has been implicated in the pathogenesis of type II diabetes mellitus and its complications (Rahimi *et al.*, 2005).

There is an increasing interest in herbal medications especially for metabolic diseases; many researchers have

investigated antidiabetic and antilipidemic agents, including some plants and herbs (Surya *et al.*, 2014).

*Artemisia herba alba* which belong to Asteraceae family is commonly known by the arabic name “Shih”. It has been used in folk medicine by several cultures many years ago, in Iraq folk medicine, *Artemisia herba alba* was known as an anti-diabetic therapeutic agent (Wang and Ng, 1999). In North-Eastern Algeria it was used orally in the treatment of diabetes as described previously in Morocco (Tahraoui *et al.*, 2007; Boudjelal *et al.*, 2013).

The present study was carried out in order to evaluate the antidiabetic, antihyperlipidemic and antioxidant effect of an ethanolic extract of *Artemisia herba alba* in high fat diet and diabetic models.

## MATERIALS AND METHODS

**Plant material and preparation of the extract:** *Artemisia herba alba* was purchased from an herbalist in Tunis and it was collected from Southern Tunisia in May 2012. The plant material was dried at room temperature and stored in a dry place prior to use.

The dried aerial parts of plants were crushed to a fine powder. 10 g of plant material was soaked with 50 mL of 80% ethanol for twice 24 h, with occasional shaking. After filtration through Whatman No. 1 filter paper, the filtrate was evaporated under reduced pressure at 50°C and then freeze-dried (Hamza *et al.*, 2010). The yield of dried plant extract was 153 g kg<sup>-1</sup> of powdered material and was stored at room temperature in opaque bottles.

**Animals and dietary treatment:** Male Wistar rats weighing 210±10 g were procured from SIPHAT (Tunis, Tunisia). The animals were housed in standard polypropylene cages and maintained under controlled room temperature (22±2°C) with 12:12 h light and dark cycle. All the rats were provided with commercially available rat normal pellet diet (Almes, Mateur, Tunisia) and water *ad libitum*. The animals were kept for 2 weeks under standard conditions. All the experiments were conducted according to the Tunisian Ethical Committee for animals laboratory (approval number: FST/LNFP/Pro 152012). The normal diet provides 3143 kcal kg<sup>-1</sup> of food and contains 7.1% fat. The High Fat (HF) diet tallow diet provides 4493 kcal kg<sup>-1</sup> of food and contains 22% fat.

In this study the effects of *Artemisia herba alba* extract on four different lots were carried out. High fat diet was administered to the first group. In the second group, type I diabetes (DI) was induced by a single intraperitoneal injection of streptozotocin (STZ) 65 mg kg<sup>-1</sup> b.wt. (Sigma chemical company, France) dissolved in 0.4 mM citrate buffer (pH 4.5). On the third group, type II diabetes model (DII) was developed by combination of high fat diet for two weeks followed by two low-doses STZ injection (30 mg kg<sup>-1</sup> b.wt.) with an interval of one week. Three days after administration of STZ, the tail vein blood glucose level was measured in all animals. Blood glucose levels of 250 mg dL<sup>-1</sup> and above were considered

diabetic. The fourth group was a control one (C). Each of these batches (HF, DI, DII and C) was divided in two groups with seven rats per groups: Treated with the *Artemisia herba alba* extract and untreated rats. Extract was administered intragastrically to the animal at the dose of 2 g kg<sup>-1</sup> b.wt. as an aqueous suspension for 8 weeks.

**Blood samples and tissues preparation:** After two months of treatment, the animals were sacrificed by decapitation and the blood was collected in tubes containing EDTA. The plasma was immediately separated by low-speed centrifugation (for 1500 g for 15 min, 4°C). Liver, heart and kidneys were removed immediately, rinsed with cold saline solution and weighed. All the samples were stored at -80°C until use.

**Biochemical analysis:** Glucose, Total Cholesterol (TC), Triglyceride (TG) and High-Density Lipoproteins (HDL) contents in plasma were determined with The SYNCHRON LX<sup>®</sup> System, UniCel<sup>®</sup> Dx<sup>®</sup>C 600/800 System. Glucose concentration was measured by an oxygen rate method employing a Beckman Coulter Oxygen electrode. The TC, TG and HDL were determined by a timed endpoint enzymatic method. The Low-Density Lipoproteins (LDL) and the Very Low-Density Lipoproteins (VLDL) were calculated by the formula of Friedewald *et al.* (1972).

**Determination of lipid peroxidation:** The lipid peroxidation level was measured as malondialdehyde (MDA) which is the end product of lipid peroxidation reacting with thiobarbituric acid (TBA) as a TBA Reactive Substance (TBARS) to produce a red colored complex with a peak absorbance at 532 nm (Jurczuk *et al.*, 2004). The MDA activity was expressed as nmoles per milligram of protein.

Proteins concentrations were determined according to the method of (Bradford, 1976) by using bovine serum albumin as a standard.

**Antioxidant enzymes activity:** The activity of superoxide dismutase (SOD) was measured according to the epinephrine method, based on the capacity of SOD to inhibit autoxidation of adrenaline to adrenochrome (Misra and Fridovich, 1972). Catalase activity was determined by measuring the decomposition rate of H<sub>2</sub>O<sub>2</sub> at 240 nm (Jurczuk *et al.*, 2004). Enzyme activity in tissue was expressed as units per milligram of protein.

**Mineral trace:** Iron (Fe), calcium (Ca) and phosphor (P) were measured in serum using commercial kits from Biomagreb, Tunis, Tunisia.

**Statistical analysis:** Data is presented as Means±Standard Deviation (SD) for seven rats per group. The differences were examined by the one way analysis of variance (ANOVA) followed by the Test of Mann-Whitney using the SPSS 15 program (SPSS Inc., Chicago, IL, USA). The differences were considered significant at p<0.05.

## RESULTS

**Body weights:** The mean body weights are illustrated in Fig. 1. At the end of experiment, body weights were significantly higher in the High Fat diet (HF) rats compared to control diet group ( $p < 0.05$ ) (Fig. 1a). In the DII and DI groups a significant increase of body weights was observed between *Artemisia herba alba* treated and untreated rats ( $p < 0.05$ ) (Fig. 1b).

**Liver, kidneys and heart weights:** The Table 1 summarized the mean liver, kidneys and heart weights. It was observed that high fat diet increases organs weights. There was a significant difference in the heart and kidneys weights between the HF untreated and control groups ( $p < 0.005$ ). As demonstrated in the Table 1, however for the heart and kidney there was no significant difference.

In DI group, we have noted a significant loss of organ weights compared to the control group. However, the *Artemisia herba alba* treatment increases significantly the weights of heart (+15%), kidney (+14%) and liver (+21%).

For DII group, there was no significant difference in organ weights between treated and untreated rats and also with the control group.

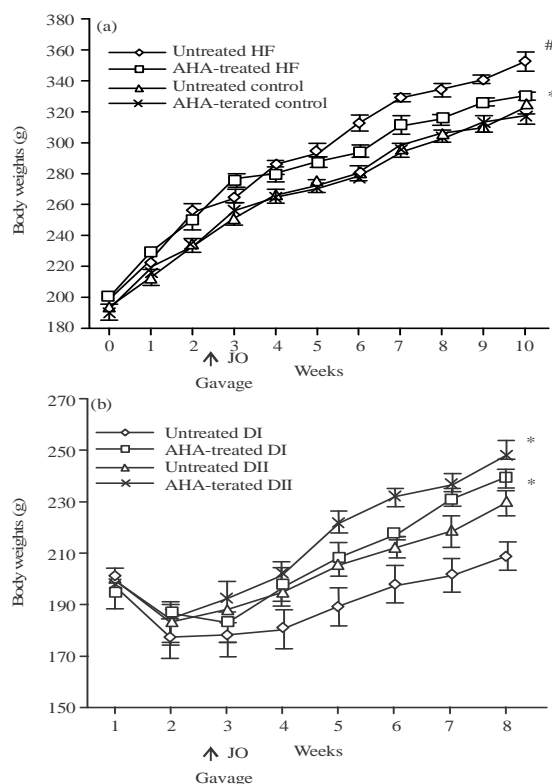


Fig. 1(a-b): Effect of *Artemisia herba alba* treatment on body weights in (a) High fat diet rats and (b) Diabetic rats. HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba*, \* $p < 0.05$ , AHA-treated vs untreated group # $p < 0.05$ , AHA-untreated group vs control

**Levels of plasma glucose:** The mean fasting blood glucose level of the HF untreated group was not significantly higher than that of the rats treated with *Artemisia herba alba* and also control group (Fig. 2).

The blood glucose concentration was significantly higher in the DI and DII groups compared to the control group ( $p = 0.003$  and  $p = 0.002$ ). As shown in the Fig. 1, the administration of *Artemisia herba alba* to diabetic rats decreases the blood glucose levels. In DI group, the glycemia value was higher in untreated than in treated groups but the difference was not statistically significant ( $20.18 \pm 5.44$  g L<sup>-1</sup> vs  $15.31 \pm 5.41$  g L<sup>-1</sup>). However for type II diabetic, treatment with *Artemisia herba alba* decreases significantly the glycemia levels ( $17.50 \pm 2.34$  g L<sup>-1</sup> vs  $10.93 \pm 3.79$  g L<sup>-1</sup>,  $p < 0.05$ ).

**Lipids concentrations:** The plasma cholesterol concentrations were significantly higher in HF groups compared to control group ( $p = 0.003$ ). The supplementation of *Artemisia herba alba* decreases significantly the LDL cholesterol in HF groups by 26.7%. No significant difference in LDL and cholesterol levels was found between treated and untreated DI and DII groups (Table 2).

Table 1: Liver, kidneys and heart weights in treated and untreated different groups

Treatments	Liver	Kidneys	Heart
Weights (mg)			
<b>Untreated groups</b>			
HF	8.33±0.73 <sup>#</sup>	1.99±0.33 <sup>#</sup>	0.87±0.06 <sup>#</sup>
DI	4.87±0.61 <sup>##</sup>	1.52±0.11 <sup>##</sup>	0.54±0.04 <sup>##</sup>
DII	7.71±0.96	1.78±0.21	0.72±0.10
C	7.88±1.18	1.59±0.17	0.78±0.36
<b>AHA-Treated groups</b>			
HF	7.18±0.65*	1.79±0.36	0.79±0.06
DI	5.91±0.67*	1.74±0.17*	0.62±0.72*
DII	7.27±0.63	1.68±0.19	0.68±0.08
C	7.98±0.67	1.69±0.13	0.81±0.06

HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba*. Values are Means±SD,  $p < 0.05$ , AHA-treated vs untreated group, \* $p < 0.05$ , # $p < 0.01$ , AHA-untreated group vs control

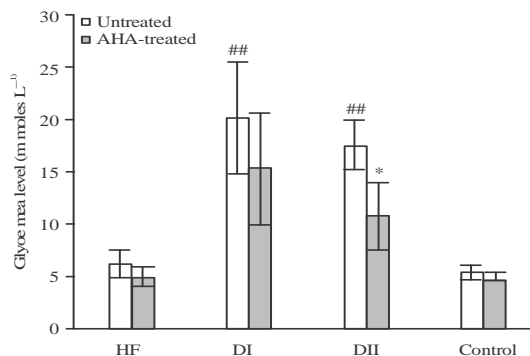


Fig. 2: Levels of blood glucose in treated with *Artemisia herba alba* and untreated groups, HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba*, data are expressed as Means±SD. \* $p < 0.05$ , AHA-treated vs untreated DI group, # $p < 0.01$ , AHA-untreated group vs control

Table 2: Total cholesterol, triglyceride, HDL and LDL concentrations in treated with *Artemisia herba alba* and untreated different groups

Parameters	Total cholesterol	Triglyceride	HDL-cholesterol	LDL-cholesterol
----- (mmol L <sup>-1</sup> ) -----				
<b>Untreated groups</b>				
HF	2.00±0.08 <sup>##</sup>	0.97±0.12	0.60±0.07 <sup>##</sup>	0.96±0.08 <sup>##</sup>
DI	1.50±0.33 <sup>#</sup>	0.62±0.28 <sup>#</sup>	0.66±0.23	0.55±0.37
DII	1.73±0.30 <sup>##</sup>	1.22±0.41	0.76±0.08 <sup>##</sup>	0.42±0.27
C	1.29±0.20	0.96±0.21	0.49±0.10	0.37±0.21
<b>AHA-Treated groups</b>				
HF	1.83±0.08 <sup>**</sup>	0.92±0.13	0.61±0.05	0.80±0.13 <sup>*</sup>
DI	1.27±0.50	0.42±0.24	0.61±0.24	0.47±0.24
DII	1.47±0.31	0.84±0.22	0.67±0.19	0.42±0.21
C	1.15±0.16	1.00±0.19	0.41±0.10	0.28±0.09

HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba*, HDL: High density lipoprotein, LDL: Low density lipoprotein. Values are Means±SD of 7 rats per group, data are expressed as Means±SD, \*p<0.05, \*\*p<0.01, AHA-treated vs untreated group, #p<0.05, ##p<0.01, AHA-untreated group vs control

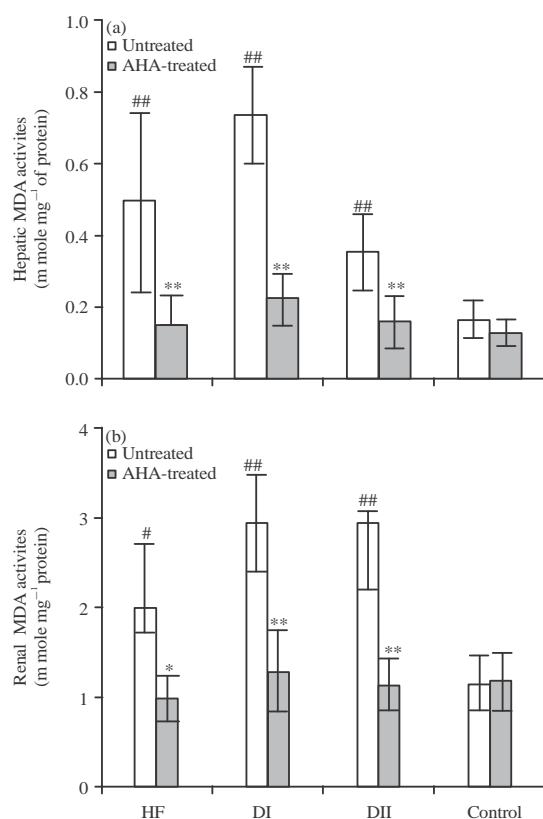


Fig. 3(a-b): Malondialdehyde activities in (a) Liver and (b) Kidneys in *Artemisia herba alba* treated and untreated groups, HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba* data are expressed as Means±SD. \*p<0.05, \*\*p<0.01, AHA-treated vs untreated group #p<0.05, ##p<0.01, AHA-untreated group vs control

**Lipid peroxidation:** *Artemisia herba alba* treatment decreased significantly MDA activities in liver and kidneys of high fat diet group compared to the untreated group ( $p = 0.01$ ) (Fig. 3). Diabetes caused progressive accumulation of lipid peroxidation in liver and kidneys in both DI and DII groups. The administration *Artemisia herba alba* extract decreased significantly this peroxidation by 30% in the liver of DI rats

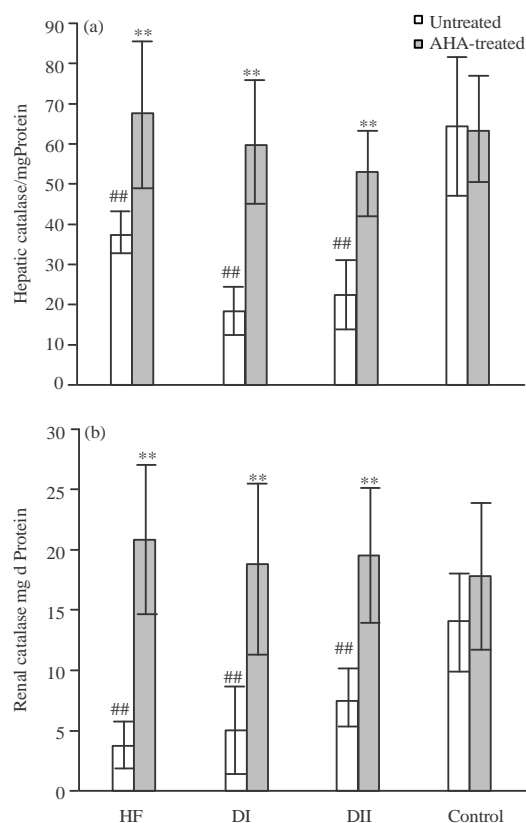


Fig. 4(a-b): Catalase activities in (a) Liver and (b) Kidneys in *Artemisia herba alba* treated and untreated groups, HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba*, data are expressed as Means±SD. \*\*p<0.01, AHA-treated vs untreated group ##p<0.01, AHA-untreated group vs control

and by 45% for the DII rats. The same result was observed in the kidneys with a decrease of 38% for the DI group and 45% for the DII (Fig. 4).

**Antioxidant enzymes activities:** Tissue antioxidant enzymes activities of treated with *Artemisia herba alba* and untreated rats are presented in Fig. 5. In HF, DI and DII groups we have observed that the treatment increase significantly the SOD and

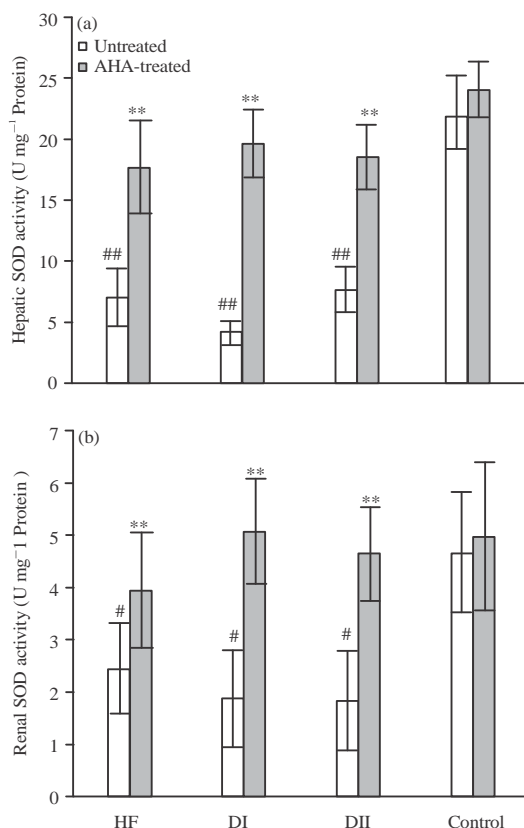


Fig. 5(a-b): Superoxide dismutase activities in (a) Liver and (b) Kidneys in *Artemisia herba alba* treated and untreated groups, HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, AHA: *Artemisia herba alba* data are expressed as Means $\pm$ SD, \*\* $p < 0.01$  AHA-treated vs untreated group # $p < 0.05$ , # $p < 0.01$ , AHA-untreated group vs control

Table 3: Magnesium, calcium, iron and phosphor our levels in blood in *Artemisia herba alba* treated and untreated different groups

Treatments	Calcium (Ca)	Phosphor (P)	Iron (Fe)
	----- (mmol L <sup>-1</sup> ) -----		
<b>Untreated groups</b>			
HF	2.46 $\pm$ 0.39	1.70 $\pm$ 0.62	22.77 $\pm$ 7.70
DI	2.25 $\pm$ 0.26 <sup>#</sup>	1.10 $\pm$ 0.42 <sup>#</sup>	39.80 $\pm$ 6.93 <sup>#</sup>
DII	2.20 $\pm$ 0.19 <sup>#</sup>	1.23 $\pm$ 0.30 <sup>#</sup>	29.63 $\pm$ 2.35 <sup>#</sup>
C	2.61 $\pm$ 0.50	2.11 $\pm$ 0.30	17.55 $\pm$ 5.38
<b>AHA-Treated groups</b>			
HF	2.54 $\pm$ 0.49	1.80 $\pm$ 0.39	12.77 $\pm$ 3.50*
DI	2.79 $\pm$ 0.26*	1.70 $\pm$ 0.44	23.35 $\pm$ 8.30*
DII	2.55 $\pm$ 0.28*	1.34 $\pm$ 0.32	20.01 $\pm$ 3.99*
C	2.75 $\pm$ 0.41	1.75 $\pm$ 0.31	15.48 $\pm$ 7.02

HF: High fat diet, DI: Type I diabetic, DII: Type II diabetic, HA: *Artemisia herba alba*, values are Means $\pm$ SD of 7 rats per group data are expressed as Means $\pm$ SD, \* $p < 0.05$ , AHA-treated vs untreated group # $p < 0.05$ , AHA-untreated group vs control

catalase enzyme in liver ( $p < 0.05$ ). In kidneys the same results were observed in DI and DII groups for the catalase enzyme but not for the SOD.

**Calcium, iron and phosphor levels in plasma:** There was a significant difference only for iron between the *Artemisia herba alba* treated and untreated high fat diet groups ( $p = 0.025$ ) (Table 3). The induction of diabetes caused a significant decrease in Ca and P and significant increase in iron levels in plasma compared to control groups. However, under these conditions, the administration of *Artemisia herba alba* extract attenuated these changes.

For the diabetic type I group, there was a significant difference in the Ca, P and Fe between the treated with *Artemisia herba alba* and untreated group. There was a significant difference only in the Ca and Fe between the treated and untreated group, for the diabetic type II.

## DISCUSSION

*Artemisia herba alba* was known traditionally to have a variety of biological effects including hypoglycemic, hypolipidemic, antiinflammatory, antifungal and antimicrobial activities (Al-Shamaony *et al.*, 1994; Mohamed *et al.*, 2010; Messaoudene *et al.*, 2011). For the hypolipidemic and antioxidant effects, scientific data on its efficacy are scarce.

The first purpose of this study was to design obese and diabetic animals models that would imitate the physiopathology characteristic of human syndrome. Our results showed that HF diet groups which consumed high saturated fat (tallow) have demonstrated a disturbance in lipid profile and an increase of organs and body weights in comparison to normal rats. As reported by others, consumption of high fat tallow diet induced early and persistent leptin resistance compared to the unsaturated fat diets (Flanagan *et al.*, 2008). Most experimental studies reported that a high fat diet increases body fat accumulation and induces obesity in rodents (Kim *et al.*, 2000).

In the present study, the diabetic type II group was developed with high fat diet combined to double low doses of STZ and produce hyperglycemia around the 17.5 mmol L<sup>-1</sup>, which is not very elevated compared to that of the high dose of STZ type I diabetic model that have glycemia around the 20.19 mmol L<sup>-1</sup>. Our data showed that heart, kidneys, liver and body weights were significantly decreased by high dose of STZ. This effect may be due to lack of insulin which leads to the degradation of lipids and structural proteins which are known by their contribution to body weight (ADA., 2003).

However organs and body weights of the low double dose of STZ combined with high fat diet group doesn't differ significantly compared to those of the control group.

Many studies have reported that the rats fed with high fat diet develop insulin resistance but not frank hyperglycemia or diabetes (Tanaka *et al.*, 2007; Flanagan *et al.*, 2008). It is suggested that the high fat diet might be a better way to initiate the insulin resistance which is one of the important features of type II diabetes (Kim *et al.*, 2000). At the same time, STZ is widely used to reproducibly induce both insulin-dependent and



non insulin dependent type II diabetes presently by inducing beta cell death through alkylation of DNA (Szkudelski, 2001). Although high dose of STZ severely impairs insulin secretion mimicking type I diabetes, low dose of STZ has been known to induce a mild impairment of insulin secretion which is similar to the feature of the later stage of type II diabetes (Skovso, 2014; Srinivasan *et al.*, 2005). High fat diet combined with double low doses of STZ was proved to be a better way for developing a stable animal model of type II diabetes, which presented a typical characteristic of this diabetes as insulin resistance, hyperglycemia and blood lipid disorder (Zhang *et al.*, 2008; Skovso, 2014). Metabolic syndrome is strongly linked to the development of coronary heart diseases and stroke mainly through an increased risk of insulin resistance and other abnormalities including atherogenic dyslipidemia and high blood pressure (Steinberg *et al.*, 1996). All this reports confirm that we have accomplished our goal with economical and successful method.

The second attempt of this study was to evaluate the antidiabetic, antihyperlipidemic and antioxidant activities of *Artemisia herba alba*. Treatment with ethanolic extract of *Artemisia herba alba* reduces significantly blood glucose level in type II diabetic rats but not in type I diabetic animals. It has been reported that type II diabetes was more reasonable to be treated by therapeutic compound than type I. Therapeutically, it is difficult to reduce elevated blood glucose level only with insulin administration (Zhang *et al.*, 2008). In a previous work, Hamza *et al.* (2011) have reported that ethanolic extract of *Artemisia herba alba* reduced significantly the glycemia in high fat diet induced diabetic mice (Hamza *et al.*, 2010, 2011). Other reports demonstrated that aqueous extract of *Artemisia herba alba* is an hypoglycemic agent in diabetic rat (Marrif *et al.*, 1995; Hamza *et al.*, 2010). Al-Shamaony *et al.* (1994) gave a clear view that *Artemisia herba alba* extract prevented a significant elevation in the glycosylated hemoglobin in both diabetic rats and rabbits, fed daily for four weeks with *Artemisia herba alba* aqueous extract. Furthermore, Mexican species of artemisia have been reported to possess hypoglycemic and hyperlipidemic effects (Ahmad *et al.*, 2014).

The mechanisms of antidiabetic effect of *Artemisia herba alba* involved multiple factors. It may be resulting from the influence of bioactive constituents. Numerous studies have reported that some flavonoids have been a direct effect on glucose metabolizing enzymes and expression of the glucose transporter GLUT4 (Daisy *et al.*, 2010).

The presence of aromatic hydroxyl groups in many flavonoids is associated with its antioxidant properties, particularly its free radical scavenging effects. These properties have been shown to protect pancreatic islet cells from oxidative stress as well as to help in the regeneration of Beta cells as shown with epicatechin and quercetin found in green tea (Coskun *et al.*, 2005).

Management of diabetes can also be achieved by reducing post-prandial hyperglycemia by delaying the activities of the enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase. These enzymes are responsible for the digestion of carbohydrates and absorption of glucose in the digestive tract, respectively (Bhandari *et al.*, 2008; Gulati *et al.*, 2012). The antioxidant and  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory activities of plants and foods have been associated with their anti-diabetic activity (Gulati *et al.*, 2012).

Therefore, plant based  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitors are likely to be useful in regulating blood-glucose level (Gao *et al.*, 2013). Hypoglycemic effect of *Artemisia herba alba* may be due to  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory potential.

We found that treatment with *Artemisia herba alba* reduced significantly the cholesterol concentration in high fat diet. This result was confirmed by other studies which have found that administration of aqueous extract of *Artemisia herba alba* to alloxan induced diabetic rats or rabbits decreased serum lipid levels by increasing the utilization of glucose, thereby depressing the mobilization of fat (Mansi *et al.*, 2007; Hamza *et al.*, 2010).

Clinical and experimental studies have proven that consumption of high cholesterol diet is one of the major contributors of cardiovascular disease (CVD) due to the development of atherosclerosis, hyperlipidemia as well as abnormal lipid metabolism (Keevil *et al.*, 2007).

Natural products possessing hypocholesterolemic and hypolipidemic properties are commonly used as functional foods in recent decades to prevent the development of CVD (Wu *et al.*, 2013; Oloyede *et al.*, 2015).

In our investigation, treatment with *Artemisia herba alba* reduces significantly the MDA concentrations in liver and kidneys of the high fat diet type I diabetic and also type II diabetic groups.

In diabetes, changes in the antioxidant parameters status have been reported in various tissues (Rahimi *et al.*, 2005). Mechanisms that contribute to increase oxidative stress in diabetes included non-enzymatic glycosylation, autooxidative glycosylation and metabolic stress (Limaye *et al.*, 2003; Gandhi *et al.*, 2014). The increase of lipid peroxidation products, in tissue of STZ-induced diabetic rats has been previously reported and it is well known that hyperglycaemia increases lipid peroxidation, which may contribute to long-term tissue damage (Rahimi *et al.*, 2005).

In high fat diet, our result demonstrated that treatment with *Artemisia herba alba* extract increases significantly the SOD in liver and kidneys. In liver, also the treatment increases significantly the catalase enzyme. Furthermore, the treated diabetic rats showed a significantly increase in catalase and SOD enzyme in liver and kidneys. Our findings confirm other investigations that reported a significant increase of antioxidant enzymes activities in tissues of diabetic rats treated with extracts from several plants (Hsieh *et al.*, 2014).

Our results showed that hyperglycemic is accompanied with the breakdown of SOD and catalase activities in hepatic

and renal tissues. Hypoglycemia destroys non enzymatic antioxidant defenses by allowing reactive oxygen species to damage cells and tissues. The STZ cytotoxicity is mainly due to DNA alkylation which results in cellular necrosis. The STZ applied also systemically damages to organs expressing GLUT2, such as kidneys and liver (Lenzen, 2008).

Our results are confirmed by Abid *et al.* (2007) that compared the antioxidant effects of *Artemisia herba alba* decoction with a green or black tea decoction. The conclusion of this study showed that *Artemisia*, as well as green tea decoctions, increased the total antioxidant status, whole blood glutathion peroxidase activity, zinc, copper(Cu) and iron (Fe) status.

The hyperglycemia induces a loss of the antioxidant enzyme cofactors; calcium and phosphor, these metal are essential for insulin secretion and production. Oral administrations of *Artemisia herba alba* extract enhanced these changes. The increase of calcium leads to membrane depolarization, activation of voltage gated  $Ca^{2+}$  channels, a rise in cytoplasmic  $Ca^{2+}$  concentration and there by insulin release (Rivoira *et al.*, 2015).

Our finding display that *Artemisia herba alba* treatment decreases iron levels in plasma, this may protect tissues against damage caused by an excess of free radicals and ion-dependent metal lipid peroxidation. In this case, it has been demonstrated that most of the lipid peroxidation observed in vivo is involved with iron. Iron participates in the Fenton reaction, generating hydroxyl radicals that are particularly reactive with lipids (Abid *et al.*, 2007).

Khlifi *et al.* (2013) studied the antioxidant activity of *Artemisia herba alba*; they observed that levels of phenolic contents in plant extracts correlated well with their antioxidant activity diphenyl-1-picrylhydrazyl (DPPH) and 3-ethylbenzthiazoline-6-sulphonic acid (ABTS). They also reported good correlations between DPPH, ABTS and 2, 2-azobis (2-amidinopropane) dihydrochloride (AAPH) assays with the anthocyanins content levels. Furthermore, phenolic content correlates with antioxidant activity of extracts, confirming that these entities are likely to contribute to the radical-scavenging activity of plant extracts (Farzaneh and Carvalho, 2015). The flavonoids detected in *Artemisia herba alba* show also a structural diversity starting from common flavonoids (flavones glycosides and favonols) to the methylated flavonoids which is very unusual (Saleh *et al.*, 1987).

They also reported that the content of tannins and flavonoids in the extracts correlates with their anti-inflammatory activity (Khlifi *et al.*, 2013).

The phytochemical analysis of *Artemisia herba alba* extract indicated that the sesquiterpene lactones are the important being metabolites and they are also responsible for the importance of these plants in medicine and pharmacy (Hamza *et al.*, 2010).

## CONCLUSION

In conclusion our study demonstrates that ethanolic extract of *Artemisia herba alba* improves oxidative stress in

diabetic rat; reduces lipid peroxidation and increase antioxidant enzyme activities. Moreover, it also decreases hyperglycemia and dyslipidemia. Further study will investigate the mechanism of extracts actions and identify the required biological active ingredients.

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