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# EFFECTS OF THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS ALPHA AGONIST AND CINNAMON OIL ON OBESITY INDUCED BY HIGH-FRUCTOSE DIET

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## ABSTRACT

In this research, we investigated the effect of *cinnamon* oil and peroxisome proliferator-activated receptor alpha (PPARα) agonist (fenofibrate) on increase of obesity in rats induced by high-fructose diet (HFD). Animals received 23% (w/v) of fructose in water per day for 12 weeks. To determine the role of *cinnamon* oil on obesity, male *wistar* rats were randomized into four groups (6 rats per group): (i) control (standard diet), (ii) high fructose diet (HFD), (iii) HFD with fenofibrate at dose 100 mg/kg for 30 days and (iv) HFD with *cinnamon* oil at dose of 50 mg/kg for 30 days. The outcomes measured were body weight, body fat, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, oral glucose tolerance test and weight organs. The values of glucose in blood, glucose intolerance, plasma total cholesterol, triglycerides, cholesterol (LDL) were significantly increased after 12 weeks of high fructose feeding; however, *cinnamon* oil and fenofibrate diet restricted the elevation of these parameters in comparison with the HFD fed to control group. In contrast, cholesterol (HDL) was slightly decreased in the HFD group and was increased in the groups treated by *cinnamon* oil and PPARα agonist. These results suggest that *cinnamon* oil had a regulative role of glucose intolerance, hyperglycemia, hypertriglyceridemia and

hypercholesterolemia in high fructose-induced obesity rats, indicating a lower risk of obesity and its complications.

**KEYWORDS:** Obesity, fructose, *cinnamon* oil, and peroxisome proliferator activated receptor, *wistar* rat.

## INTRODUCTION

In recent years, obesity has become a serious problem and the number of people suffering from it has dramatically increased. It is often associated with large cormobid disorders such as pro-inflammatory problems.[1, 2] Hypertension, hyperglycemia, type 2 diabetes and dyslipidemia.[3,4] As we noted, obesity is a complex disease with multi-factorial causes among which are genetic and environmental ones. Some researchers have shown that the consumption of soft drinks in particular carbonated beverages has increased markedly with raise in the prevalence of obesity in the united state (U.S) and worldwide.[5] Most soft drinks are sweetened with sugars containing a high proportion of fructose.[6] The metabolism of fructose is done by the liver. The portal vein delivers absorbed fructose to the liver and then this fructose are phosphorylated by the enzyme fructokinase to fructose -1-phosphate, which can be converted to glycerol -3- phosphate for the synthesis of glycerol.[7] or metabolized to acetyl CoA, and incorporated into fatty acids. The result will be a rapid stimulation of lipogenesis and an increase of triglycerides.[8] Causing a risk of weight gain.[9] Which is associated with a reduction in insulin sensitivity.[10] Furthermore, fructose does not stimulate pancreatic ß cells to release insulin against the effect of glucose. This causes a reduction in the delivery of insulin into the central nervous system (CNS) and could affect weight gain. [11,12] Under experimental conditions, human consumption of beverages containing fructose, rather than glucose, led to the increase of visceral adipose tissue.[13] With impairments in leptin and ghrelin production resulting in hyperphagia and obesity.[11] Evidence from animal studies showed a weight gain in fructose-fed rats compared to naturally-fed rats.[14] Other studies found that rats receiving high fructose diet develop insulin resistance, hyperinsulinemia, obesity and hypertension.[15] Obesity prevails in both human genders and all age groups, so the general public has a concern about its control and treatment. Increasing attention has been focused on the role of peroxisome proliferators-activated receptors (PPARs) agonists in recent years. (PPARs) agonists are ligands of nuclear receptor proteins that function as transcription factors regulating the expression of genes. Three isoforms, encoded by separate genes, are identified: PPAR alpha, PPAR gamma and PPAR sigma/beta.

The PPARs regulate target gene expression by binding to specific peroxisome proliferators response elements (PPREs) in enhancer sites of regulated genes. Each receptor binds to its PPRE as a heterodimer with a retinoid X receptor (RXR). Upon binding an agonist, the conformation of a nuclear receptor is modified and stabilized such as a binding cleft and the recruitment of transcriptional co-activators occurs. The PPARs activation results in an increase in gene transcription.[16] The central role of PPARs agonists as transcriptional mediators is the regulation of important metabolic processes that influence lipid metabolism, glucose homeostasis, tissue remodeling, tumorigenesis, atherosclerosis and inflammatory processes of higher organisms.[17, 18, 19, 20] PPARs agonists, in particular PPAR α agonists, are playing essential roles in the regulation of cellular differentiation, development, and metabolism (carbohydrate, lipid, protein). In this study, we will focus on PPAR α agonist as potential therapeutic targets for the treatment of obesity and its related disorders. The clinical importance of PPARα agonist originates with fibrate class which is lipid-lowering drugs.[21] PPARα is most highly expressed in the liver where it regulates fatty acid beta oxidation.[22] The knowledge of traditional medicines has allowed us to identify foods, food supplements, herbs and spices which are believed to treat obesity effects. One of the widely used flavoring and medicinal spices is *cinnamomun cassia*. The latter is the outer skin of an ever green tall tree belonging to the family Lauraceae, which contains large amounts of bioactive molecules including essential oils (cinnamic aldehyde and cinnamyl aldehyde), tannin, mucus, and carbohydrates. Apart from its use as a spice, it is known to possess a wide range of pharmacological effects such as anti-bacterial.[23] Anti-fungul.[24] Anti-inflammatory.[25] Anti-oxidant.[26] And anti-diabetic effects.[27] A recent study showed that *cinnamon* lowers blood glucose, total cholesterol, and triglyceride levels in diabetic mice.[28] As far as we know, the effect of *cinnamon* oil on obesity has not been studied yet. There are some studies about the relationship between fructose consumption and the risk of obesity, but they are limited due to the newness of the subject. Therefore, the aim of the present work was to evaluate the further role of *cinnamon* oil in ameliorating the lipid profile and to compare it with the effect of PPAR alpha agonist (fenofibrate) in obese rats induced by high fructose-diet.

## MATERIALS AND METHODS

### Animals and study Protocol

The study was performed on male adults *Wistar* rats, weighing approximately 160±5g. The animals are used in this study with respect to the principles governing research on animals defined by the Organisation for Economic Cooperation and Development (OECD).[29] And

the Canadian Council on Animal Care (CCAC). The rats were grouped and placed into scientific cages located in the animals room, which was maintained at a temperature of 22˚C to 24˚C and a humidity between 60% and 70%, with a 12-h light/12-h dark cycle, and where the animals had free access to water and food (standard diet) consisted of (13% protein, 2% fat, 9% minerals and vitamin A, D, E). The fructose was obtained from the *Nature's Flavors* Company (Orange, CA, USA) and was prepared in beverage solution to (23% w/v). The rats were weighted at the beginning of the study and then once a week.

They were then divided into the following groups which contain six rats (n=6 per group).

**Group I:** control rats which received only standard diet.

**Group II:** they received standard diet with 23% of high fructose diet (HFD).

**Group III:** they received 23% of (HFD) and were treated with fenofibrate (F6020, *Sigma-Aldrich*) orally in a dose of 100 mg/kg/body weight/day for 30 days.

Group IV: they received 23% of (HFD) and were treated with cinammon oil orally in a dose 50 mg/Kg/body weight/day for 30 days.

**Preparation of cinnamon oil**

*Cinnamon* was procured from local market and *Cinnamon* oil (CO) was extracted by hydrodistillation in a Clevenger-type apparatus at 100 ℃ for 5h and finally the oil was isolated and kept in a dark glass in the refrigerator until required for further use. The plant is identified by Botany Laboratory and Plant Protection, Faculty of Sciences, Ibn Tofail University, Morocco.

**Intraperitoneal glucose tolerance test**

In the last day of the experiment, the animals were kept fasting for 12 h and then anesthetized with chloral (0, 5 ml/100g the body weight, i.p). A blood sample was checked at time (t=0) from the tail vein. Thereafter, 2 g/kg glucose was injected intraperitoneally and after 0, 60, 90 and 120 minutes, blood samples were checked by the glucose meter (ACCU-CHEK Active, Germany) to determine the glucose concentration.

**Serum analysis**

At the end of the experiment, the rats were euthanized by rapid decapitation, the trunk blood was collected and the plasma lipid profile was determined by measuring the content of triglycerides, total cholesterol, HDL-c and LDL-c using reagent kits as indicated by the manufacturer’s instructions (*BioSystems S.A, Spain*).

**Isolation of visceral adipose tissue**

Visceral adipose tissue was excised immediately after the decapitation; the unilateral body fat pads from abdominal region were collected and weighted individually from each group, and their organs weight (liver, spleen and kidney) was recorded.

**Statistical analysis**

All data are expressed in mean ± standard errors (S.E.M.). To determine the differences between experimented groups, a statistical analysis was performed by analysis of variance (ANOVA) followed by a post-hoc tests. The differences were considered significant when $p < 0.05$, very significant when $p < 0.01$ and highly significant when $p < 0.001$.

**RESULTS**

To determine the role of *cinnamon* oil and PPARα agonist (fenofibrate) in the treatment of obesity, we randomized the *wistar* rats into four groups (6 rat/ group). The control group and the second group were fed on a high-fructose diet (HFD) while the two others were fed on the HFD associated with different treatments such as fenofibrate and *cinnamon* oil. Except for the control group, all rats received HFD for 12 weeks. The outcomes measured were body weight, body fat, fasting blood glucose, total cholesterol, HDL-c, LDL-c, triglycerides, oral glucose tolerance test and organs weight (Table.1).

**Table 1: The effects of *cinnamon* oil and fenofibrate on body weight, organs weight and biochemical parameters induced by 23% of fructose drinking solution for 12 weeks.**

| Groups | Control | HFD | HFD+Fenofibrate | HFD+Cinnamon oil |
|---|---|---|---|---|
| Body weight initial (g) | 160,5±4,89 | 163,17±4,71 | 161,33±4,37 | 164±2,08 |
| Body weight final (g) | 324,5±5,79 *** | 512,5±11,14 | 386,58±3,15*** | 264,75±16,55*** |
| Cumulative weight change (%) | 202,18*** | 314,09 | 239,62*** | 161,43*** |
| Liver weight absolute (g) | 11,62±0,84*** | 17,59±0,56 | 10,56±0,43*** | 10,18±0,67*** |
| Liver weight relative (%) | 3,58±0,26 | 3,43±0,07 | 2,73±0,04*** | 3,84±0,07* |
| Spleen weight absolute | 0,78±0,009 | 1,27±0,018 | 0,99±0,032 | 0,76±0,012 |
| Spleen weight relative (%) | 0,24±0,01 | 0,24±0,02 | 0,25±0,01 | 0,29±0,1 |
| Kidney weight absolute (g) | 0,94±0,035* | 1,28±0,128 | 0,85±0,034** | 0,95±0,042* |
| Kidney weight relative (%) | 0,29±0,014 | 0,24±0,024 | 0,21±0,008 | 0,36±0,015** |

The results of this chart above are expressed by the mean ± standard error (SEM), ($n$ = 6 per group). The control, the high fructose diet (HFD) group and the different treatments like fenofibrate, *cinnamon* oil respectively represent the different doses of 100 mg/kg and 50 mg/kg,.

* Compared with HFD group: *p < 0.05, **p<0, 01, ***p<0,001.

**Effects of fructose on body weight**

As shown in figure 1, all groups of HFD rats gained significantly more body weight during the 12 weeks of study than the control group, (HFD: n=6, p<0,001). This increase in body weight was due to hyperphagia in HFD rats. The control group grew normally with a final weight that was 202, 18% of the initial baseline body weight, whereas it was 314, 09% in the HFD group. But the rats treated with *cinnamon* oil and the fenofibrate showed a significantly decrease body weight with (p<0,001) compared to HFD group.

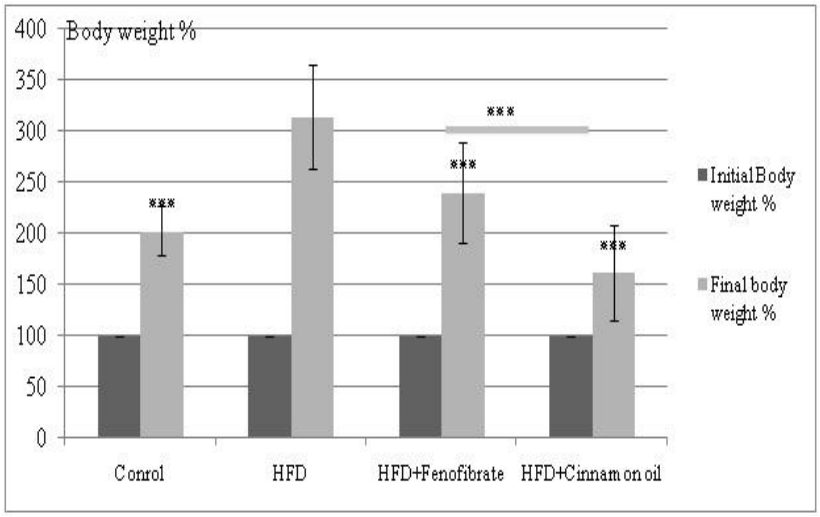


**Figure 1: the cumulative change in body weight in male rats during 12 weeks as percent of initial weight (%)**

* Compared with HFD group: *p < 0.05, **p<0, 01, ***p<0,001.

**Serum parameters**

High fructose diet caused a significant increase in serum triglycerides, total cholesterol, serum LDL-c, ratio total cholesterol /HDL-c, and ratio LDL-c/HDL-c compared to water-drinking rats as well as a significant decrease in serum HDL cholesterol. Moreover, it was observed that *cinnamon* oil have the same effect of fenofibrate to reduce the circulation of lipid profile compared to groups drinking HFD (Fig. 2).

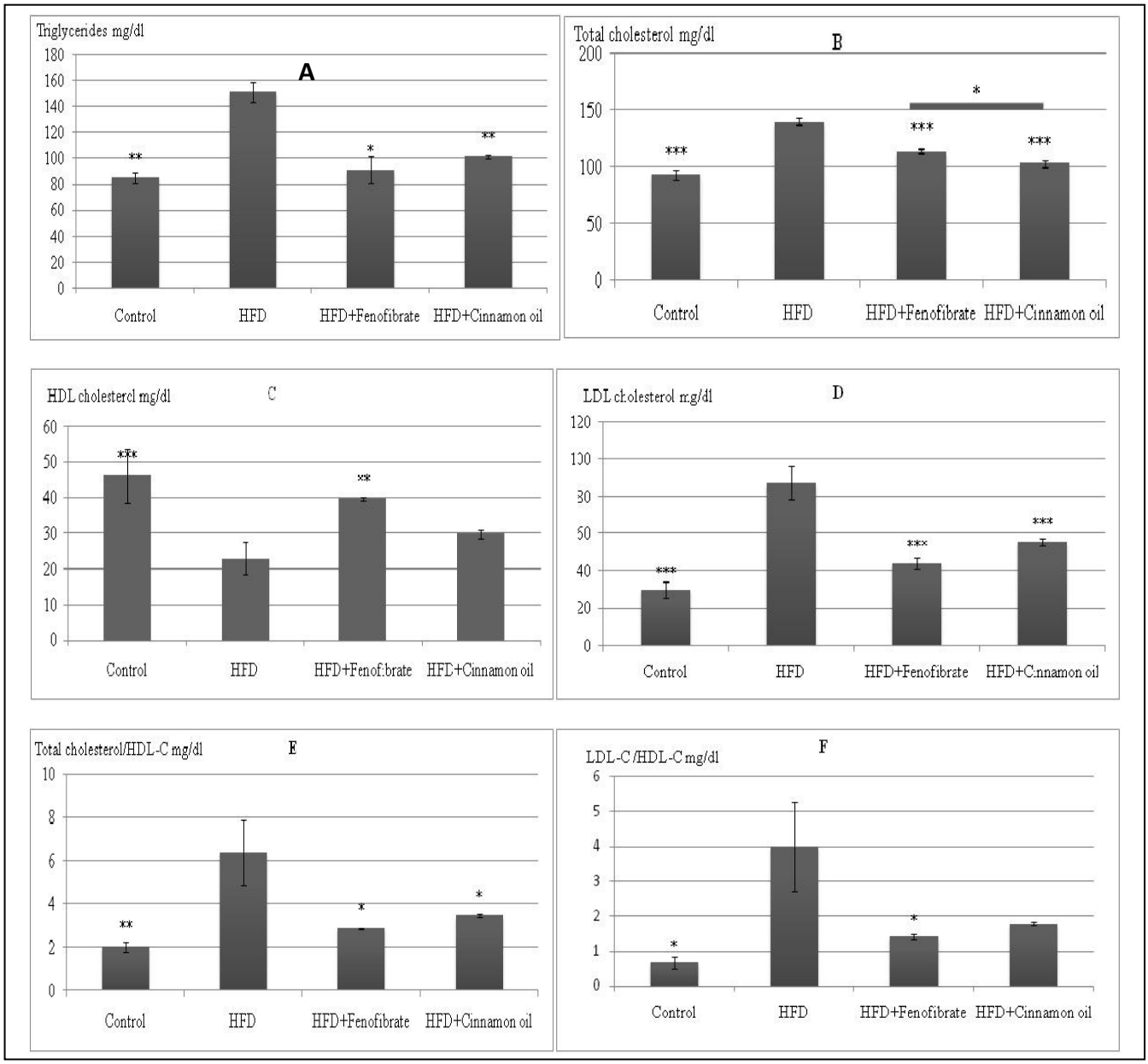


**Figure 2: Plasma levels of triglycerides (A), total cholesterol (B), HDL-cholesterol (C), LDL-cholesterol (D), ratio total cholesterol /HDL-cholesterol (E), and ratio LDL cholesterol /HDL cholesterol (F) in rats drinking solution containing 23% fructose for 12 weeks. Controls received tap water. The different treatments (fenofibrate and *cinnamon* oil) respectively represent the different doses of 100 mg/kg and 50 mg/kg.**

* Compared with HFD group: *p < 0.05, **p<0, 01, ***p<0,001 (one-way ANOVA followed by a post-hoc).

**Effect of HFD on tolerance of glucose**

Blood glucose levels of the HFD group were not significantly different from the control group at time (t= 0**).** The HFD group had a significantly higher level of glucose than the

control group at t=120 min after the subcutaneous injection of glucose, but the treatment of HFD rat with fenofibrate and *cinnamon* oil induced a significant improvement in serum glucose at the same time. The average level of glucose in blood for all groups is presented in (Fig. 3).

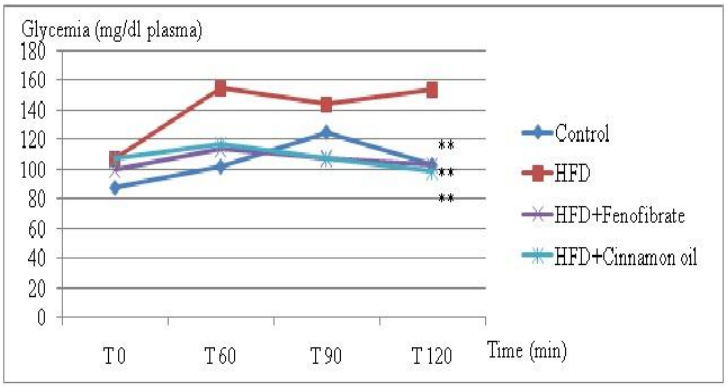


**Figure 3: shows the variation of glucose tolerance test in terms of time in rats that drink the fructose and the different treatments in the other groups. Shown are the means ± SEM (*n* = 6 per group).**

* Compared with HFD group: *p < 0.05, **p<0, 01, ***p<0,001

**Effect of fructose on body fat**

Obesity is characterized by an increase in body fat. We observed a significant fat deposit per gram of body weight in the group consuming HFD which is more than rats offered water to drink. This effect was higher in the abdominal region**.** The current study showed that all rats treated with fenofibrate and *cinnamon* oil have associated with significant decrease in body fat compared of rats with HFD group (Fig. 4).

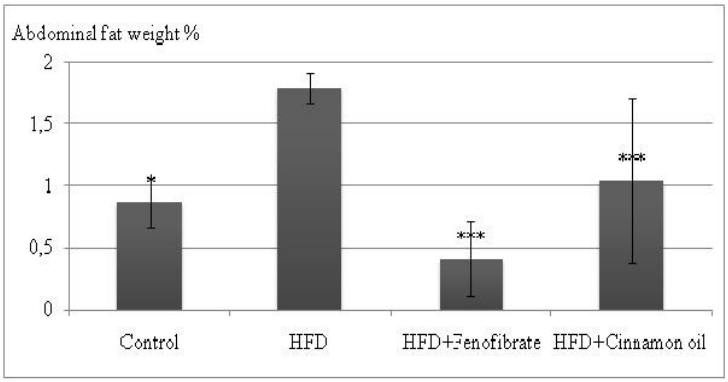


**Figure 4: Fat pads weight (%) change in male rats received HFD with food during 12 weeks and different treatments with the *cinnamon* oil and the fenofibrate, which are shown as the means ± SEM (*n* = 6 per group).**

* Compared with HFD group: *p < 0.05, **p<0, 01, ***p<0,001.

**Effect of fructose supplementation on organs weight**

In the end of our research we recorded the weight of some organs influenced by fructose in all animal groups (table.1). We noticed a significant increase in the liver weight of the HFD group compared with the control group (p=0,000). However, it was observed that the relative liver weight decreased significantly in the groups treated with fenofibrate and *cinnamon* oil but did not differ from control group. This effect is not recorded in the kidney, adrenal gland and spleen whose differences remained non-significant between all groups.

## DISCUSSION

Dietary factors that have an effect on obesity are not only diet composition but also a source of energy whose excess will definitely lead to fatal consequences. The experiment in both animals and humans supports the effects of dietary fat in development of overweight conditions and obesity.[9] Dietary fat is dense in energy in macronutrients and is less satiating than carbohydrates and proteins, so it could lead to over consumption.[30] Also, different studies have shown that dietary carbohydrates and sugars increase the risk of weight gain.[9] Here in our study, we focus on dietary carbohydrates. Fructose is a carbohydrate used by scientists to be a tool to generate the diabetes and/or obesity in animal models in the context of certain research. More recently, human and animals studies are investigating the potential role of fructose in the etiology of obesity and metabolic diseases. Some scientists suggested that because of the quick metabolic changes.

A recent study showed that a 21% (w/v) concentration of fructose in diet conferred a significant increase in blood glucose and triglycerides after eight weeks on the diet regimen in male albino *wistar* rats.[31] However, another study have showed that feeding a high fructose diet in drinking water (53% *w/v*) for 10 weeks haven't induced an hypertriglyceridemia, hyperinsulinemia or diabetes mellitus type II in male *sprague dawly* rats.[32] It may be due to the differences in the characteristics of the rats species used in various studies. Therefore, in our research we tried to evaluate the effect of fructose in a dose of (23% *w/v*) in the development of the risk of obesity in male *wistar* rats. There are a number of studies which demonstrated the association between high fructose diet and increase of weight gain, body fat, plasma glucose, cholesterol and triglycerides in animal models. In the present study, we found that an access of HFD (23%) in rats led to an increase in body weight for 12 weeks compared to controls (p<0,001) (fig.1). This increase might be due to an effect of fructose which stimulates the hyperphagia and more calories intake,

inhibits ghrelin factors effective in the central nervous system's satiety center and did not influence the insulin and leptin secretion.[12] In a related study which reported that 50 day access to 32% fructose caused an excess of nutrition, weight gain and high fat deposition in rats.[33] Similar results have confirmed that the rats with high fructose corn syrup (HFCS) gained more body weight compared to control group after 8 weeks of access.[34] A more recent study have demonstrated that mice with access to a 15% fructose solution gained significantly more weight and had higher rates of body fat than mice with access to a 10% sucrose solution.[35] In our study, the body weight is associated with significant increase in body fat in rats consuming fructose solution in comparison with control group. Furthermore, this increase was observed notably heavier in abdominal region (fig. 4). This is a support demonstrating that these changes in body fat are a key indicator of obesity.[36] Excess fat in the abdomen is considered as the most predictor of risk factors to impaired health and diminished longevity.[37] Which meaning that the likelihood for developing diseases is higher for those with abdominal obesity.

We evaluated the weight of some organs of all the animals under experiment and observed in HFD group an increase in liver weight which was significantly different from control group ($p<0,001$). This is resulted in a hepatic storage of lipids by indicating that fructose treatment increases lipogenesis. Hella jurgens identified that fructose produced a hepatic lipid accumulation with a characteristic of pericentral pattern.[35] Clinical studies have linked the intake of excessive fructose with the development of nonalcoholic fatty liver disease in humans, and have correlated the amount of fructose ingested with the risk for progression to cirrhosis.[38,39] Also, the administration of fructose increases kidney weight, it is known to induce renal hypertrophy and tubulointerstitial disease in rats.[40] This is not observed in our study. Obesity is characterized, not just by increase in body weight and body fat, but also by changes in the plasma of some lipids such as triglycerides, total cholesterol, cholesterol (LDL), and glycemia. The results of the present study showed an increase of triglycerides, LDL cholesterol, total cholesterol, ratio total cholesterol/HDL-cholesterol, ratio LDL cholesterol /HDL cholesterol in the rats fed HFD compared to control group (Fig. 2). Similar studies showed that the consumption of the fructose in adult rats has diminished the glucose tolerance and insulin sentivity, as well as, it have elevated triglycerides, cholesterol and body fat.[11,41] When a diet containing 17% fructose was given to healthy men and women, a highly significant increase of 32% in plasma triacylglycerol concentrations was observed in men but

not in women.[42] Moreover, fructose intake has been linked to the increased incidence of obesity and diabetes.[43]

Our study showed that rats receiving 23% fructose for 12 weeks have an impaired glucose tolerance, as demonstrated by the higher glycemia values achieved after i.p. glucose administration as compared to controls at (t=120min) (Fig. 3). Other study found that 10% (w/v) of fructose solution given for 12 weeks period increases blood glucose and triglycerides level in male *wistar* rats.[44] Contrarily to findings in previous study, when *rats* and *hamster* consumed fructose, they did not cause a significant impairment in glucose tolerance (IGT).[45]

The central role of PPARs agonists - as transcriptional mediators in the regulation of important metabolic processes that influence the lipid metabolism, glucose homeostasis, cell differentiation, obesity, cancer, and the vasculature - has been reviewed in great detail.[17-19]
After the treatment with fenofibrate, we found that serum cholesterol, LDL cholesterol, ratio total cholesterol/HDL-cholesterol, ratio LDL cholesterol/HDL cholesterol and triglycerides levels were significantly decreased compared with those of HFD group ($p<0, 05$) (Fig.2). Similarly, fenofibrate treatment could alleviate the dyslipidemia, leading to 52% reduction in plasma cholesterol level and 45% reduction in triglyceride level, as well as reduced LDL-C and HDL-C levels in monosodium glutamate induced obese rats.[46] On the other hand, in human, fibrate reduces significantly the concentration of plasma triglycerides and increases the high density lipoprotein HDL. This decrease in plasma lipid is linked with modulation of the cholesterol metabolism pathways in the liver.[47] We found a notable reduction in plasma glucose level after fenofibrate treatment as shown in (Fig. 3). PPAR alpha is expressed in pancreatic islets and its agonist has been reported to improve pancreatic beta cell function in insulin-resistant rodents.[48] Many reports suggested that PPAR alpha activation could improve the peripheral insulin resistance by relieving lipid-mediated inhibition of insulin-stimulated glucose disposal in both rodents and humans.[49, 50] Aromatic plants are frequently used in traditional medicine and essential oils extracted from them are widely used as antioxidants and antidiabetic agents for the prevention and treatment of different human diseases. In the present study, we observed that the blood glucose levels after injecting the glucose were decreased at (t=120 min) compared with the control group with administration of *cinnamon* oil for 30 days in obese rats (Fig.3). The possible mechanism by which *cinnamon* brings about its anti-hyperglycemic effect was stimulation of surviving cells to release more insulin.[51] In our study, the oral administration of *cinnamon* oil not only

significantly lowered the blood glucose levels, but also caused improvement in lipid profile. Other investigators, showed that, *cinnamon* reduced serum glucose, triglyceride, total cholesterol levels in people with type 2 of diabetes. Similarly, the study showed that the addition of cinnamaldhehyde diminishes visceral fat deposition in high fat and high sucrose diet fed mice by stimulating interscapular brown adipose tissue.[52] Since cinnamaldhehyde is a main compound of *cinnamon* oil. This is in accordance with the results of the study by which found that the administration of *cinnamon* oil at dose 100 mg/kg decreased serum triglyceride and total cholesterol, but it significantly increased the level of the serum high density of lipoprotein (HDL)-cholesterol, after 35 days.[53] So, *cinnamon* is beneficial for the treatment of diabetes and hyperlipidemia.[54]

## CONCLUSION

In this research, we report the results of the first study on the treatment of obesity induced by high fructose-diet in wistar rat by using cinnamon oil which produce the same effects of reference drug peroxisome proliferator-activated receptor alpha agonist (fenofibrate). These results are very interesting suggesting the potential for development of new medicinal plants for treatment of patients with obesity.

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