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Comparative study between effects of ethanol extract of Zingiber officinale and Atorvastatine on lipid profile in rats

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Zingiber officinale **is known for its cholesterol-lowering and antioxidant properties. The use of traditional medicine reduces the use of drugs with a risk of toxicity. This study aims to assess the effects of ethanol extract of *Z. officinale* and atorvastatin on lipid parameters in rats fed with high-fat diet. The experiment was carried out on 40 rats during 9 weeks. The animals were divided into 4 groups; group 1 (normal healthy controls), group 2 (hypercholesterolemic diet controls), group 3 (treated with ethanol extract of *Z. officinal* at 500 mg / kg / day) and group 4 (treated with Atorvastatin at 20 mg/kg/day). It has been shown, respectively in groups 3 and 4, a stable body weight (289 vs 282 g) and a highly significant reduction of cholesterol (295.9 vs 275.1 mg/dl), total triglycerides (46.8 vs 41.9 mg/dl) and LDL (278.2 vs 259.1 mg/dl), but not a significant increase in HDL (8.6 vs 7.8 mg/dl). Results showed that *Z. officinale* is similar to Atorvastatin as a cholesterol-lowering agent in the treatment of patients exposed to risk of obesity and cardiovascular disease. Therefore, combination regimens containing ginger and low dose of statins could be advantageous in treating hypercholesterolemic patients.**

Key words: *Zingiber officinale*, cholesterol, antioxidant, Atorvastatine, cardiovascular disease.

INTRODUCTION

Metabolic syndrome, including obesity and dyslipidaemia that predisposes type 2 diabetes, is becoming more prevalent in many countries (Ascaso and Carmena, 2015). In developed countries metabolic syndrome appears to affect around 25 % of the population (Salas et al., 2014). The modern lifestyle of increased intake of high-calorie food contributes to the rising prevalence of obesity and type 2 diabetes (Isordia-Salas et al., 2012; Salas et al., 2014). Epidemiological studies also revealed that 90% of all patients with type 2 diabetes have been overweight, and indicated that obesity is a strong risk factor, and cause of type 2 diabetes and associated with metabolic disturbances (Salas et al., 2014). The therapeutic options such as dietary modification or a

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combination of synthetic antidiabetic, hypolipidaemic drugs have their own limitations and undesirable side-effects (Heeba and Abd-Elghany, 2010). There is an increased demand to search and evaluate traditional approaches for the treatment of metabolic disorders, particularly the use of herbal medicines. *Zingiber officinale* is widely used around the world in foods as a spice (Das et al., 2012). For centuries, it has been an important ingredient in herbal medicines for the treatment of rheumatism, nervous diseases, asthma, stroke, and diabetes (Kim et al., 2012). The major chemical constituents of essential oil *Z. officinale* rhizome include various terpenoids such as shogaols, paradols and zingerone (Jelled et al., 2015).

In laboratory experiments, ethanolic extract of *Z. officinale* has been shown to reduce plasma lipids in cholesterol-fed hyperlipidaemic rabbits (Zhang et al., 2011). It has been shown previously that long term dietary feeding of ginger has hypoglycemic and hypolipidemic effects in rats (Zhang et al., 2011). Besides, Z *officinale* has also been shown to reduce lipid parameters in streptozotocin induced diabetic rats (Ibrahim and Shathly, 2015).

Statins are group of drugs that have been recognized as the most efficient drugs for the treatment of hyperlipidemia. Atorvastatin differs from other statins in that it has a longer action and presents active metabolites which are biotransformed mainly by cytochrome P3A4 in the liver. Previous studies have reported severe AT-induced hepatotoxicity (Heeba and Abd-Elghany, 2010). Natural products and their active principles, as sources for new drug discovery and treatment of diseases, have attracted attention in recent years. Herbs and spices are generally considered safe and proved to be effective against various human ailments (Heeba and Abd-Elghany, 2010). *Zingiber officinale* is one of the commonly used medicinal plants around the world (Heeba and Abd-Elghany, 2010). In this study, we aim to compare the effects of *Zingiber officinale* and Atorvastaine on lipid profile in rats fed with high fat diet.

MATERIAL AND METHOD

Plant material and extraction

Zingiber officinale rhizomes were purchased from a local market in Saida, Algeria, during February 2013, and authenticated by Prof. M. Terras of the Biology Department, Moulay Tahar University, Saida, Algeria. The plant was dried in the shade. The dried rhizomes were powdered mechanically. Pulverised *Z. officinale* rhizomes (3 kg) were added to 5 L of 95% ethanol at room temperature for 7 days. The ethanol extract of *Zingiber officinale* rhizomes (EEZO) was evaporated to dryness under reduced pressure, for the total elimination of alcohol, followed by lyophilisation, yielding 500 g of dry residue. The EEZO was kept at - 20 °C until use and suspended in distilled water.

Preparation of animals

Male Wistar rats, 2 months of age and with mean weight of 180 g, were obtained from the Laboratory Animal of Biology Department (University of Oran, Algeria). They were maintained in a temperature-controlled room (25 ± 1°C) on a 12:12 h light–dark cycle in the Biology Department, University of Saida, Algeria. The rats were divided into four groups (10 rats / group); group 1 as a normal healthy control (NHC), group 2 as pathogenic hypercholesterolemic diet control (HDC), group 3 as HDC and treated with EEZO, and group 4 as HDC treated with Atorvastatine (ATV). Food and water were available ad libitum. Regular rat diet with 19% protein, 58% carbohydrate, and 7% fat was used as the maintenance and control diet. Hypercholesterolemia was induced by force feeding orally of 0.5 g cholesterol in 5 ml hydrogenated vegetable oil (Hemn et al., 2015) for 9 weeks along with normal rats feed in groups 2, 3 and 4. All animal procedures were performed according to the Guide for the Care and Use of Laboratory Animals as well as the guidelines of the Animal Welfare Act. The EEZO (500 mg / kg b.w. in 2 % water) and ATV (20 mg / kg b.w.) were administrated daily orally from the 7th week to groups 3 and 4, respectively. Group 2 served as pathogenic hypercholesterolemic diet control (HCD) and group 1 was kept as a normal healthy control (NHC).

Body weight data and biochemical parameter analysis

The daily body weights were recorded in all groups of rats during 9 weeks. After having heated the tail of the animal to cause vasodilation of the veins, an incision was practiced at the extremity of the tail (Sanchez et al., 2010). The blood samples were collected after every week during all the period of experimentation. Diagnostic kits (VIDAS) for the measurement of total cholesterol (TC) and total triglycerides (TG) were purchased from Bio Merieux Company (Lyon, France). Lipid parameters as TC, TG and high density lipoprotein-cholesterol (HDL-C) were measured using the semi-automatic analyzer mini-VIDAS, while low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) were measured using the Friedewald equations:

$$LDL = TC - HDL - (TG/5)$$
$$VLDL = TG/5$$

Statistical analysis

Data are expressed as the difference between the initial and final values (± SD) with a value of $p < 0.05$ considered statistically significant. Statistical evaluation was performed by one way analysis of variance (ANOVA). The Tukey-test was used for all pairwise multiple comparisons of the mean ranks of the treatment groups. All analysis was carried out with the statistical software SigmaPlot *version 11.0.*

RESULTS

The changes in the mean body weight of the experimental groups of rats during 9 weeks treatment period are shown in Table 1. During the period of experimentation, there was no significant difference in the body weight in

Table 1. Weight and biochemical parameters of pathogenic hypercholesterolemic diet control (HDC) and normal healthy control (NHC) rats.

Parameters (Mean ± SD)	Group 1 (NHC)	Group 2 (HDC)	Group 3 (HCD+EEZO)	Group 4 (HDC+ATV)
Body weight (g)	226.33±22.68	282.22±69.6	289.44±57.75	280.55±54.34
Serum TC (mg/dL)	186.1±8.01	*327.84±105.83	295.9±84.71	275.16±85.57
Serum HDL-C (mg/dL)	***14.75±0.84	8.01±1.93	8.26±2.5	7.86±2.33
Serum LDL-C (mg/dL)	*166±6.74	307.7±101.1	287.26±83.82	259.08±86.38
Serum VLDL-C (mg/dL)	5.32±0.83	*10.42±4.63	9.36±3.37	8.38±3.11
Serum TG (mg/dL)	26.63±4.18	*52.14±23.67	46.84±16.87	41.93±15.55

SD: standard deviation; NHC: normal healthy control; HDC: hypercholesterolemic diet control; EEZO: ethanol extract *Zingiber officinale*; ATV: atorvastatine, TC: total-cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol, VLDL-C: very low density lipoprotein-cholesterol; TG: total-triglyceride.***: p = 0,0009 (highly significant different). *: p = 0.02 (statistically different).

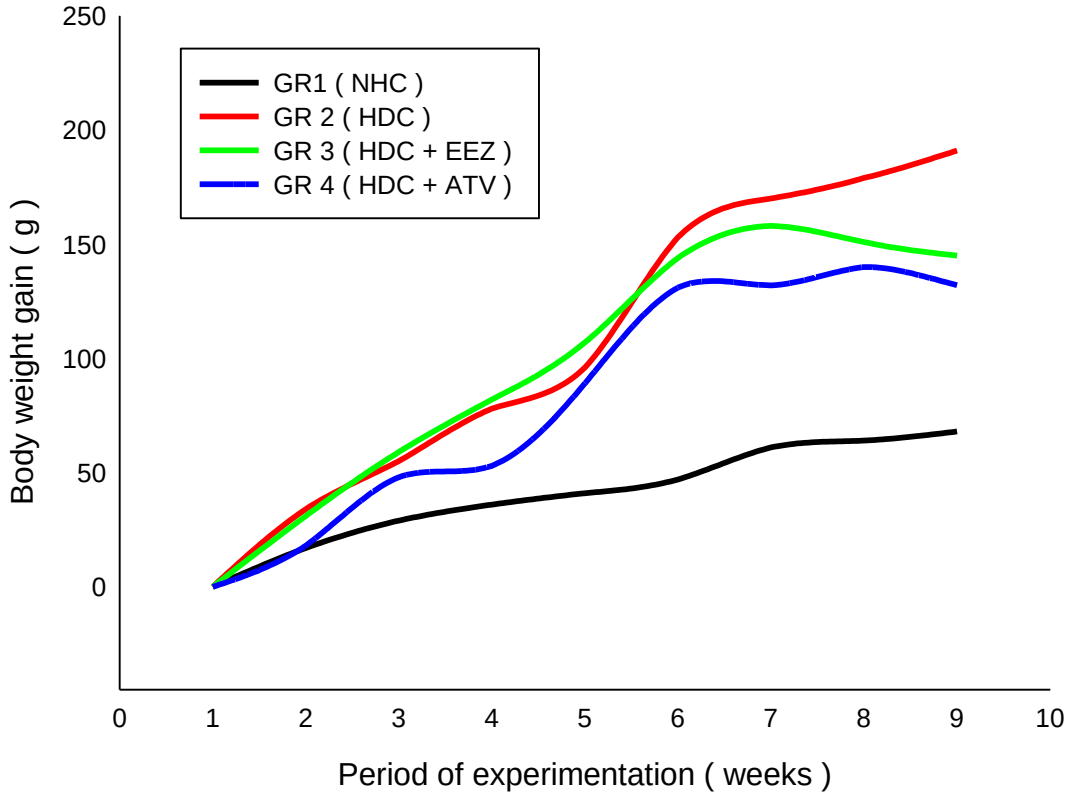

Figure 1. Variation of body weight gain in rats feed high fat diet and treated with ethanol extract of *Zingiber officinale* rhizomes (EEZO) and Atorvastatine (ATV).

different groups ($p = 0.08$) (Figure 1). Table 1 shows that serum T-cholesterol concentration was higher in three groups of rats (HDC, HDC+EEZO and HDC+ATV) than NHC rats, whereas these concentrations were not significantly different among the 3 groups of rats mentioned previously. The solution of the EEZO (500 mg / kg b.w. / day), administrated to rats from the 7th week, had induced a significantly decrease of serum T-C in comparison with hypocholesterolemic diet control rats untreated with OOZE ($p = 0.008$) (Figure 2).

Atorvastatine drug (20 mg / kg b.w./ day), administrated to animals from the 7th week, caused a high significantly reduction of serum TC level in comparison with the HDC rats, but the decrease of this parameter was not higher than that of HDC rats treated with OOZE. The mean values of serum HDL-C concentrations observed in

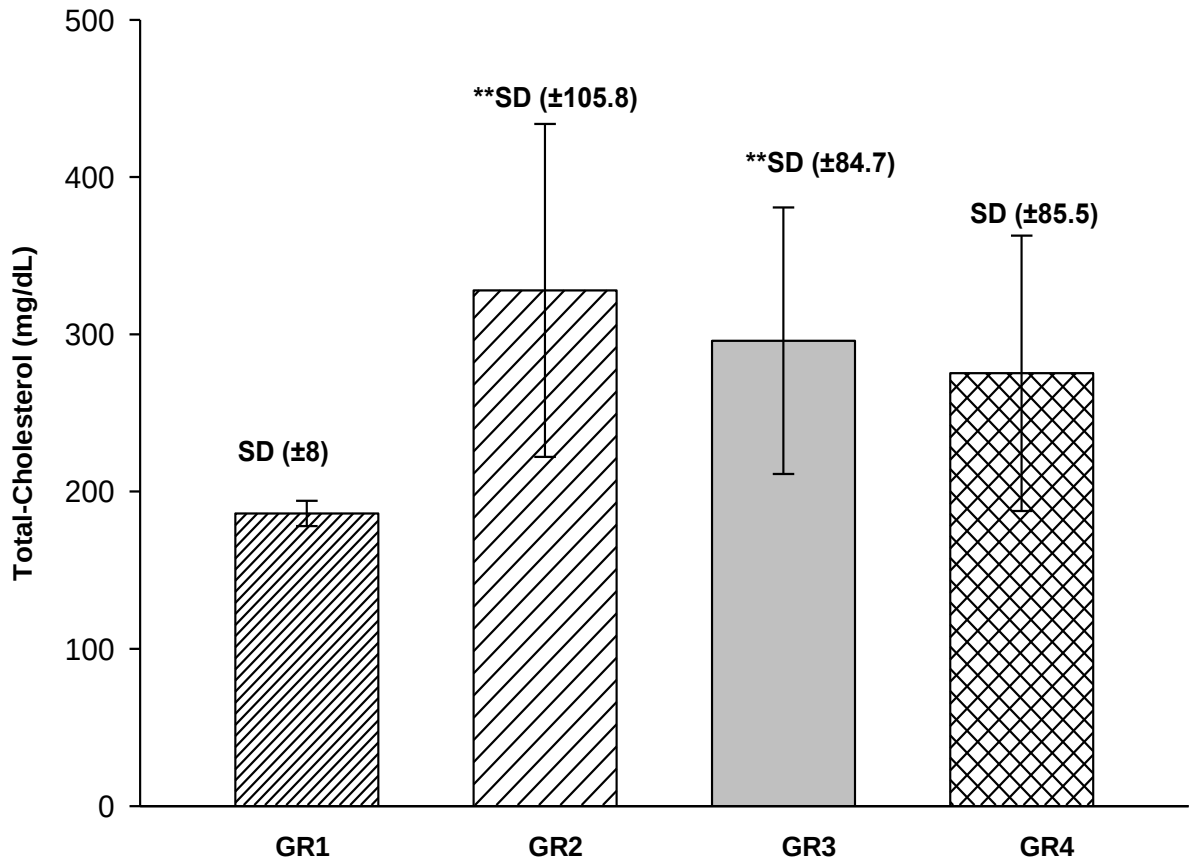

Figure 2. Variation of serum Total-Cholesterol concentration in rats feed high fat diet and treated with ethanol extract of *Zingiber officinale* rhizomes (EEZO) and Atorvastatine (ATV). GR1: NHC, GR2: HDC, GR3: HDC+EEZO and GR4: HDC+ATV.

different groups of rats are shown in Table 1. The serum HDL concentrations before the treatments were not significantly different among the HDC, (HDC+EEZO) and (HDC+ATV) groups of rats (Figure 3). Serum HDL-C levels, among 3 groups of animals cited previously, were significantly lower than that of NHC rats. The treatment of hypercholesterolemic diet animals of groups 3 and 4, respectively with EEZO (500 mg / kg b.w./day) and ATV (20 mg / kg / day) from the 7th week, had significantly caused an increased serum HDL-C level in comparison with the group 2 (HDC untreated) ($p = 0.0009$). Whereas NHC rats, fed with low-fat diet, showed significantly increased serum HDL-C levels (Figure 3). The levels of LDL-C as calculated by Friedewald's equation in various groups of experimental rats are shown in Table 1. The serum LDL-C concentrations, before the treatments, were not statistically different among the groups 2, 3 and 4 (Figure 4). Rats fed high-fat diet (HDC) showed significant elevation of serum LDL-C compared with the serum LDL of normal control rats ($p = 0.002$) at the end of 6 weeks treatment. But the pathogenic hyper-cholesterolemic diet rats, treated separately with EEZO and ATV from the 7th week of experimental period, showed high significant reduction in LDL-C compared with the high-fat diet-fed control (HDC). Furthermore, the serum LDL-C concentrations, in EEZO treated group, were not significantly different from the normal control group at the end of the treatment. The EEZO and ATV produced significant anti-hyperlipidaemic action. The test drug and standard drug significantly reduced the levels of serum VLDL-C ($p = 0.025$) (Figure 5) and total-triglycerides (TG) ($p = 0.026$) (Figure 6) when compared with group 2, that is, pathogenic hypercholesterolemic diet control (HDC).

DISCUSSION

In this study, we investigated the protective effects of ethanolic extract of *Z. officinale* in high-fat diet-fed rats, a

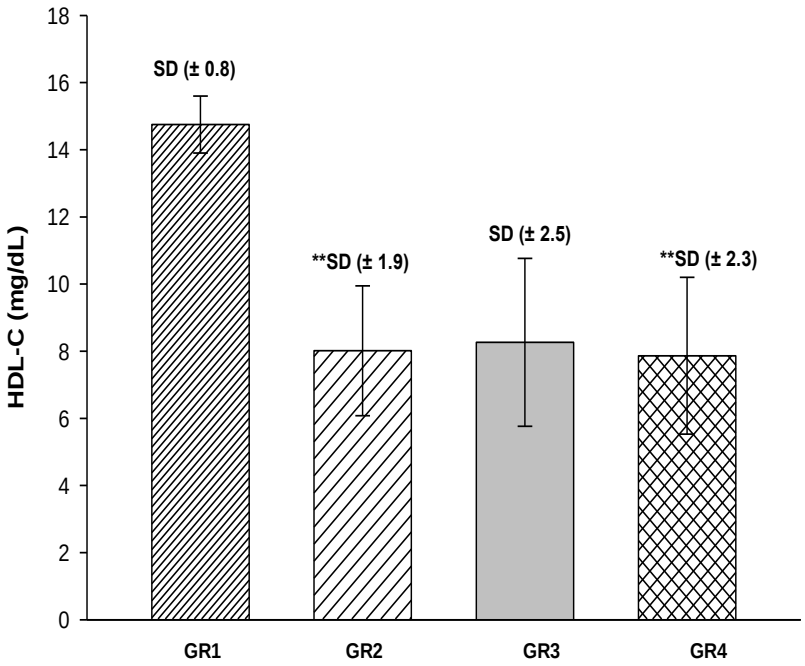

Figure 3. Variation of serum HDL-Cholesterol concentration in rats feed high fat diet and treated with ethanol extract of *Zingiber officinale* rhizomes (EEZO) and Atorvastatine (ATV).

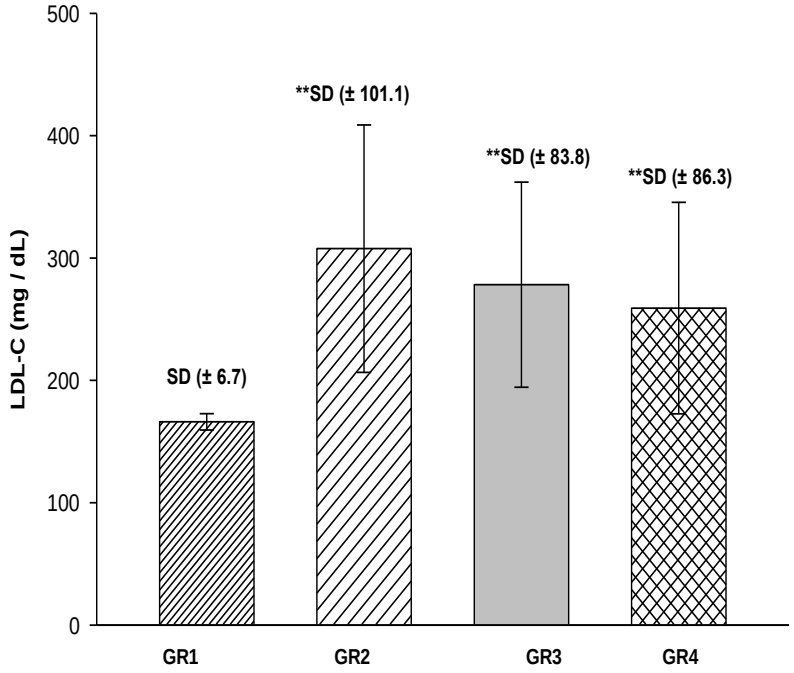

Figure 4. Variation of serum LDL-Cholesterol concentration in rats feed high fat diet and treated with ethanol extract of *Zingiber officinale* rhizomes (EEZO) and Atorvastatine (ATV).

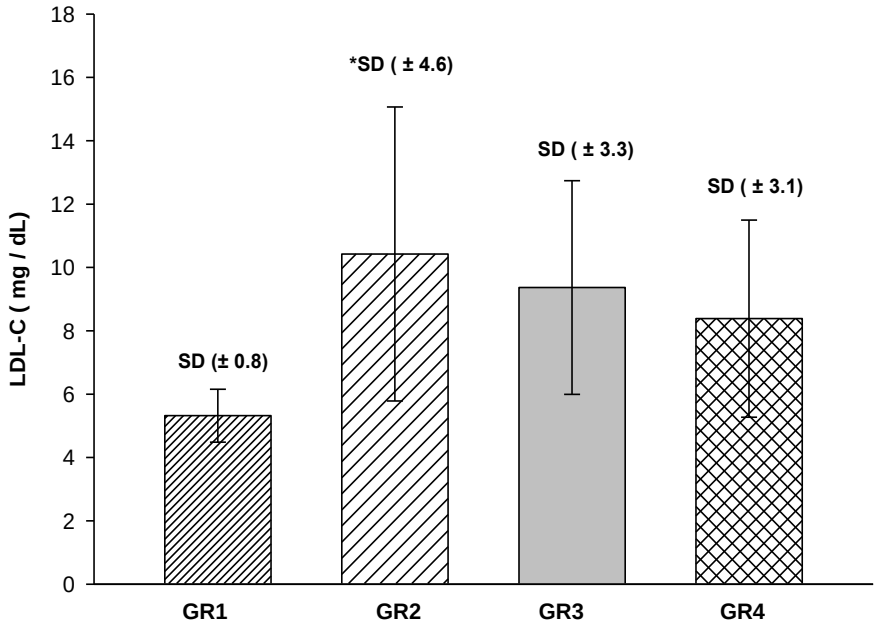

Figure 5. Variation of serum VLDL-Cholesterol concentration in rats feed high fat diet and treated with ethanol extract of *Zingiber officinale* rhizomes (EEZO) and Atorvastatine (ATV).

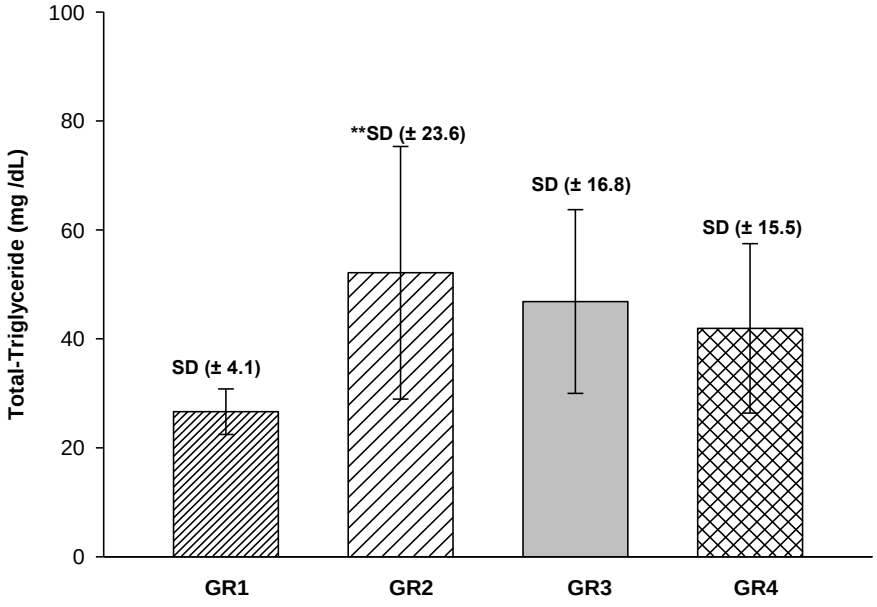

Figure 6. Variation of serum Total-Triglyceride concentration in rats feed high fat diet and treated with ethanol extract of *Zingiber officinale* rhizomes (EEZO) and Atorvastatine (ATV).

metabolic model of hyperlipidaemia, which according to Heeba and Abd-Elghany (2010), is similar to human metabolic syndrome**.** Dyslipidaemia is the most important risk factor contributing to the development of

atherosclerosis in type 2 diabetes (Meaney et al., 2013). The development of metabolic syndrome is influenced by a combination of genetic and environmental factors. Among the environmental factors, long-term high-fat intake is most intensively studied because of its contribution to the development of metabolic syndrome in human beings and rodents (Salas et al., 2014).

Results of this study are consistent with results of previous research works that have shown the anti-hypercholesterolemic effects of *Z. officinale* (Prasad et al., 2012). The ethanolic extract of *Zingiber officinale* rhizome, administrated to animals with the high-fat diet effectively reduced the serum total cholesterol, LDL-C, total triglycerides and raised HDL-C. Earlier studies (Al-Noory et al., 2013) have demonstrated that *Z. officinale* through its activity on hepatic cholesterol-7α-hydroxylase, stimulates the conversion of hepatic cholesterol to bile acids. More recently, Poorrostami et al. (2014) found that *Z. officinale* increased the faecal excretion of cholesterol, suggesting that this species may block the absorption of cholesterol in the gut. The increase in LDL-C may be due to the reduced expression or activity of the LDL-receptor sites in response to high-fat diet treatment as advocated by Brown and Goldstein (2012). Essential oil of *Z. officinale* is rich in antioxidants and anti-inflammatory components as α-zingiberene, β-sesquiphellandrene, curcumene, β-phellandrene, β-bisabolene and camphene (Yanagisawa et al., 2012). The powdered *Z. officinale* rhizomes contains aromatic components mainly gingerol and shogaols (Li et al, 2012; Asami et al., 2010). Pharmacological activities, mainly hypolipidimic effects, have been attributed to molecules of gingerol (Yanagisawa et al., 2012). Statins, overhung by Atorvastatin, slow the progression of hyperlipidemia. It has been suggested as an association of low HDL-C with a greater cardiovascular risk. This drug, as inhibitor of transfer of cholesteryl ester protein, increases from 40 to 60% of serum HDL-C and moderately reduces the serum LDL-C (Larach et al., 2013) **.** Although atorvastatin drug is rich in synthetic bioactive molecules and acts quickly and precisely at specific molecules, *Zingiber officinale* showed comparable effects on hyperlipidemia or hypercholesterolemia.

Conclusion

The ethanolic extract of *Zingiber officinale* protects from the high-fat diet induced metabolic disorders by strongly decreasing the body weight gain, protection from hyperlipidaemic conditions. The results confirm that *Z. officinale* is an antihyperlipidaemic agent, and possesses a potential medicinal value. Its traditional consumption in foods as a spice is beneficial in the prevention of metabolic disorders caused by high-fat diet. However, further detailed clinical studies are required to establish its application.

Conflict of interests

The authors have not declared any conflict of interest.

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