Biochemical study on the effect of alpha-lipoic acid on lipid metabolism of rats fed high fat diet.

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A B S T R A C T

Hyperlipidemia is a known risk factor for the development of cardiovascular disease including atherosclerosis. The present study was carried to evaluate the protective effects of alpha-lipoic acid against hyperlipidemia induced in rats fed high fat diet. Hundred male albino rats were divided into four equal groups. Group I:(control normal group) rats fed on normal diet. Group II: (hyperlipidemic group) rats fed hyperlipidemic diet (1% cholesterol, 0.5 % cholic acid and 5% hydrogenated fat/kg diet) for 8 weeks. Group III :(hyperlipidemia +Alpha-lipoic acid group) rats fed hyperlipidemic diet and treated with alpha-lipoic acid (54 mg/kg b.wt/day/ i.p). Group IV: (Alpha-lipoic acid group): normal rats treated with alpha-lipoic acid (54 mg/kg b.wt/day/ i.p). Blood samples for serum separation were used for total cholesterol (TC), triacylglycerol (TG), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), very low density lipoprotein-cholesterol (VLDL-c), phospholipids, glucose and insulin determination. In addition, liver tissue were processed for the determination of L-Malondialdhyde (L-MDA), catalase (CAT), superoxide dismutase (SOD) and reduced Glutathione (GSH). The obtained results revealed that, a significant increase in serum TC, TG, HDL-c, LDL-c, VLDL-c, glucose and insulin resistance in addition to liver L-MDA concentrations were observed hyperlipidemic rats. However, administration of alpha-lipoic acid exhibited a significant decreased in all mentioned parameters. On the other hand, serum phospholipids, antioxidant enzymes and GSH in liver tissue were significantly decreased in hyperlipidemic rats. Meanwhile, treatment with alpha-lipoic acid to hyperlipidemic rats resulted in significant increase in liver CAT activity and GSH concentrations. It could be concluded that, alpha lipoic acid has the potential in improving dyslipidemia and oxidative stress and may exert some protective effect on atherosclerotic vascular change in hyperlipidemic rats.

Key Words: Antioxidant enzymes, high fat diet, hyperlipidemia, oxidative stress, alpha-lipoic acid.

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1. INTRODUCTION

Hyperlipidemia is a condition associated with increased level of lipids in plasma leading to various disorders including coronary artery disease. Hyperlipidemia is a highly predictive risk factor for atherosclerosis, coronary artery disease and cerebrovascular disease (Mohale et al., 2008). Hyperlipidemia also induces oxidative stress and MDA is one of the end products of lipid peroxidation. Plasma MDA levels increased markedly in animals with obesity and diabetes mellitus that indicate elevations of lipid oxidation in tissues (Moussa, 2008). Humans with apparent increase in Malondialdehyde-Modified LDL were shown to be more predisposed to developing arteriosclerosis. Cardiovascular diseases such atherosclerosis, that are caused as a result of hyperlipidemia elevate mortality percent, and the age of death has reduced, so reducing serum hyperlipidemia is very important. 1% reduction in serum cholesterol concentration results in a 2% reduction in the prevalence of coronary artery diseases (Onyeneke et al., 2007). It is

clearly established that long-term consumption of a high fat diet accelerates the development of Coronary Heart Disease (CHD). Dietary cholesterol can increase the level of serum cholesterol to a rate which can place an individual at risk for developing or exacerbating of atherosclerosis. Coronary Heart Disease (CHD) increases dramatically as the plasma concentration of LDL cholesterol increases (Oluba et al., 2008). The approach of reducing dietary cholesterol suffers from two limitations, the first is that cholesterol is present in all animal fats and many people are unwilling to scarify their preferred diet. The second is that the liver and other tissues synthesize cholesterol de novo if the dietary supply is inadequate. Consequently, the development of methods for lowering LDL cholesterol levels has become a major focus of medical research. Antioxidants are known to play a vital role in preventing many of the health disorders associated with aging, including degenerative diseases such as diabetes, Alzheimer's disease, and cardiovascular disease. Medical researchers continue to discover new antioxidant compounds as well as new applications for these protective nutrients. A vitamin-like substance known as alpha-lipoic acid is now at the forefront of antioxidant research (Jim, 2005). Alpha lipoic acid (ALA), also known as 1,2-dithiolane- 3-pentanoic acid, 1,2-dithiolane-3-valeric acid or 6,8-thioctic acid has generated considerable clinical interest as a cellular thiol-replenishing and redox modulating agent(Marsh et al., 2005). Lipoic acid is a unique antioxidant because it has beneficial effects on fuel metabolism and also an essential cofactor of mitochondrial respiratory enzymes, including the pyruvate dehydrogenase complex (Siti et al., 2008). It is said that Lipoic acid offer advantages over other antioxidants as it increases the level of reduced glutathione (Osfor et al., 2010) and can also regenerate other antioxidants such as vitamin C and E (Cakatay et al., 2005). Accordingly, the present study was performed to investigate the improving effect of alpha lipoic acid administration on hyperlipidemic rats after 8 weeks of treatment by determination of the following biochemical parameters such as lipid profile, glucose and insulin. Moreover, liver antioxidant enzymes such as catalase enzyme (CAT), superoxide dismutase activity (SOD) and reduced glutathione (GSH) in addition to L-malondialdehyde (L-MDA) as oxidant substrate were also determined.

2. MATERIALS AND METHODS

2.1. Experimental animals

One hundred male albino rats of 6-8 weeks old and weighing 120 – 140 g were used in this study. Rats were housed in separated metal cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The animals were fed on constant ration and water was supplied ad- libitum. All rats were acclimatized for minimum period of two weeks prior to the beginning of study.

2.2. Chemicals and drugs:

Alpha- Lipoic acid (Thiotacid) ^{R}: Thiotacid was obtained as pack of five ampoules of 10 ml solution. Each ampoule contains thioctic acid (alpha lipoic acid) 300 mg. Alpha-lipoic acid (Thioctic acid) ® manufactured by EVA pharma for pharmaceuticals and Medical Apliances, Egypt. Alpha lipoic acid was injected intraperetineal in a daily dose of 54 mg/kg body weight (Gruzman et al., 2004).

Hyperlipidemic Induction: Rats were fed on normal diet and water for 14 days, group II and group III were fed on HFD (High Fat Diet) represented as Cholesterol 1%, Cholic Acid 0.5% and Hydrogenated Fats 5% / Kg diet.

2.3. Experimental design:

After acclimatization to the laboratory conditions, the animals were randomly divided into four groups, 25 rats each, placed in individual cages and classified as follow: Group I (Control normal): Rats

were fed on normal diet and received no drug; kept as negative control.
Group II (Hyperlipidemic group): Rats were fed on high-fat diet (1 % cholesterol, 0.5 % cholic acid and 5% hydrogenated fat) and received no drug allover the periods of the experiment. Group III (Hyperlipidemic+ alpha lipoic acid treated group): Rats were fed on hyperlipidemic diet and received alpha-lipoic Acid at a dose level of (54 mg/kg body weight/ day/ i.p) after 21 days from the onset of the experiment. Group IV (Alpha lipoic acid treated normal group): Rats were fed on normal diet and received alpha-lipoic Acid at a dose level of (54 mg/kg body weight/ day/ i.p) after 21 days from the onset of the experiment.

2.4. Sampling:

Blood samples were collected at the third, sixth and eighth weeks from the start of treatment with alpha-lipoic acid. Samples were collected from the venous plexus located at the medial canthus of the eye by heparinzed capillary tubes. The collected blood was allowed to clot at room temperature for an hour; and then refrigerated for further an hour for clot retraction. Clear serum were separated by centrifugation at 3000 r.p.m. for 10 minutes and then collected in Eppendrof's tubes using automatic micropipettes processed directly for glucose determination then kept in deep freezer at -20 ^{0}C for subsequent biochemical analysis. Tissue samples (Liver):
After blood samples collection the rats were sacrificed. Livers were removed, rinsed in ice-cold 0.9% sodium chloride solution, quick frozen in a deep freeze at -20°C for subsequent biochemical analyses. All liver samples were analyzed for the determination of L-malondialdehyde (L-MDA), antioxidant enzymes (Catalase and superoxide dismutase) and reduced Glutathione (GSH).

2.5. Biochemical analysis:

Serum total cholesterol, Triacylglycerol, HDL-c, LDL-c, VLDL-c and phospholipids were determined according to the method described by Meiattini et al, (1978); Buccolo and David, (1973); Lopes-Virella et al., (1977); Friedewald et al., (1972); Bauer, (1982); Takeyama et al, (1977); respectively. Moreover, Serum glucose, insulin and Homeostasis model assessment for insulin resistance (HOMA-IR) were determined according to the method described by Tietz, (1995); Sacks, (1994) and Haffner et al., (1997); respectively. In addition to liver antioxidant enzymes (CAT and SOD), reduced glutathione (GSH) and L-MDA were determined according to the method described by Xu et al., (1997); Paoletti and Macali, (1990); Beutler, (1963) and Mesbah et al., (2004) respectively.

2.6. Statistical analysis:

The results were expressed as mean±SE and statistical significance was evaluated by two way ANOVA using SPSS (version 10.0) program followed by the post hoc test, least significant difference (LSD). Values were considered statistically significant when $p < 0.05$.

3. RESULTS

The obtained data in table (1) revealed that, hyperlipidemic rats showed significant increase in serum glucose and insulin resistance concentration when compared with normal control group. Treatment with alpha-lipoic acid to hyperlipidemic rats caused significant decrease in serum glucose and homeostasis model assessment of Insulin Resistance (HOMA-IR) concentration when compared with hyperlipidemic group. The obtained data in table (2) revealed that, rats fed hyperlipidemic diet showed significant increase in serum total cholesterol and triacylglycerol concentrations and significantly decreased serum phospholipids concentration when compared with normal control group. Treatment with alpha-lipoic acid to

Table (1): Effect of treatment with alpaha lipoic acid on serum glucose and insulin concentrations and homeostasis model assessment of insulin resistance (HOMA-IR) in normal and hyperlipidemic male rats.

Parameters	Glucose (mg/dl)			insulin(mg/dl)			HOMA-IR		
Experimental groups	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks
Group I: (Control)	113.46 ± 3.68^{a}	90.39 ± 5.34^{b}	92.79 ± 8.85^{a,b}	2.25 ± 0.25^{a}	11.31 ± 3.57^{a}	16.54 ± 1.49^{a}	0.61 ± 0.06 ^{a}	2.40 ± 0.81 ^{a,b}	3.46 ± 0.43 ^{b}
Group II : (HFD)	117.31 ± 8.53^{a}	112.68 ± 8.40^{a}	112.65 ± 6.71^{a}	3.07 ± 0.54^{a}	15.13 ± 2.65^{a}	19.30 ± 0.74^{a}	0.95± 0.15 ^{a}	4.51 ± 0.95 ^{a}	5.61 ± 0.44 ^{a}
Group III: (HFD+ALA)	102.89 ± 1.84^{a}	83.99 ± 5.31^{b}	87.35 ± 5.09^{b}	1.95 ± 0.35^{a}	13.15 ± 2.63^{a}	16.98 ± 1.26^{a}	0.50 ± 0.08 ^{a}	2.53 ± 0.43 ^{a,b}	3.46 ± 0.24 ^{b}
Group IV: (Normal +ALA)	100 ± 7.19^{a}	85.69 ± 6.47^{b}	101.30 ± 5.94^{a,b}	2.71 ± 0.76^{a}	7.33 ± 3.53^{a}	18.35 ± 1.24^{a}	0.64 ± 0.19 ^{a}	1.56 ± 0.87 ^{b}	4.49 ± 0.61 ^{a,b}

Data are presented as (Mean ± S.E). S.E = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$).

Table (2): Effect of treatment with alpaha lipoic acid on serum total cholesterol, triacylglycerols and phospholipids concentrations in normal and hyperlipidemic male rats.

Parameters	Total Cholesterol (mg/dl)			Triacylglycerols (mg/dl)			Phospholipids (mg/dl)	
Experimental Groups	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks
Group I: (Control)	94.66 ± 1.33 ^{b}	71.43 ± 5.05 ^{b}	65.29 ± 3.74 ^{b}	87.50 ± 4.37 ^{b}	86.45 ± 3.24 ^{a,b}	76.17 ± 6.88 ^{b}	185.89 ± 18.47 ^{a}	81.98 ± 14.24 ^{a}
Group II : (HFD)	125.33 ± 11.62 ^{a}	97.88 ± 4.85 ^{a}	98.57 ± 11.70 ^{a}	145.71 ± 22.99 ^{a}	106.65 ± 9.16 ^{a}	105.81 ± 4.89 ^{a}	81.61 ± 10.07 ^{b}	73.33 ± 7.58 ^{a}
Group III: (HFD+ALA)	64.67 ± 8.92 ^{c}	63.33 ± 7.78 ^{b}	68.29 ± 5.86 ^{b}	63.57 ± 8.87 ^{b}	62.50 ± 5.89 ^{c}	57.26 ± 4.79 ^{b}	93.21 ± 20.42 ^{b}	96.67 ± 8.05 ^{a}
Group IV: (Normal +ALA)	57.33 ± 6.18 ^{c}	63.36 ± 2.55 ^{b}	65.00 ± 4.36 ^{b}	71.43 ± 11.74 ^{b}	67.38 ± 7.78 ^{b,c}	62.66 ± 7.89 ^{b}	115.08 ± 5.71 ^{b}	87.50 ± 12.94 ^{a}

Data are presented as (Mean ± S.E). S.E = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$).

Table (3): Effect of treatment with alpaha lipoic acid on serum high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c) and very low density lipoprotein- cholesterol (VLDL-c) concentrations in normal and hyperlipidemic male rats.

Parameters	HDL-C (mg/dl)			LDL-C (mg/dl)			VLDL-C(mg/dl)		
Experimental groups	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks
Group I: (Control)	36.48 ± 1.28 ^{a,b}	28.80 ± 1.01 ^{b}	21.00 ± 0.90 ^{b}	40.68 ± 2.17 ^{a}	25.34 ± 4.25 ^{a}	29.05 ± 3.56^{a}	17.50 ± 0.87 ^{b}	17.29 ± 0.65 ^{a,b}	15.23 ± 1.38 ^{b}
Group II : (HFD)	44.80 ± 4.17 ^{a}	37.12 ± 4.59 ^{a}	26.72 ± 1.38 ^{a}	51.39 ± 6.45 ^{a}	39.43 ± 6.57 ^{a}	50.69 ± 11.18^{a}	29.14 ± 4.60 ^{a}	21.33 ± 1.83 ^{a}	21.16 ± 0.98 ^{a}
Group III: (HFD+ALA)	32.64 ± 2.12 ^{b,c}	20.16 ± 1.87 ^{c}	19.20 ± 1.60 ^{b}	19.32 ± 9.58 ^{b}	30.67 ± 8.94 ^{a}	37.64 ± 7.38^{a}	12.71 ± 1.77 ^{b}	12.50 ± 1.18 ^{c}	11.45 ± 0.96 ^{b}
Group IV: (Normal +ALA)	24.32 ± 3.73 ^{c}	21.44 ± 1.72 ^{b,c}	18.72 ± 2.11 ^{b}	18.73 ± 2.43 ^{b}	28.44 ± 1.39 ^{a}	33.75 ± 5.23^{a}	14.29 ± 2.35 ^{b}	13.48 ± 1.56 ^{b,c}	12.53 ± 1.58 ^{b}

Data are presented as (Mean ± S.E). S.E = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$).

Table (4): Effect of treatment with alpha lipoic acid on catalase (CAT) and superoxide dismutase (SOD) activities, reduced glutathione (GSH) and L– Malondialdehyde (L-MDA) concentrations in liver of normal and hyperlipodemic male rats.

Animal Groups	CAT (mmol/min / g. tissue)			SOD (U/ g. tissue)			GSH(mg/min/ g. tissue)			L – MDA (nmol/g. tissue)		
	3 Weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks	3 weeks	6 weeks	8 weeks
Group I: (Control)	5.63 ± 0.29 ^{a}	3.46 ± 0.32 ^{a}	3.73 ± 0.46 ^{a}	0.64 ± 0.07 ^{a}	0.39 ± 0.01 ^{a}	0.44 ± 0.02 ^{a}	32.06 ± 0.98 ^{a}	28.54 ± 2.07 ^{b}	24.16 ± 1.17 ^{b}	73.46 ± 8.10 ^{b}	57.13 ± 2.86 ^{b}	53.59 ± 4.86 ^{b}
Group II : (HFD)	1.26 ± 0.13 ^{c}	1.20 ± 0.09 ^{b}	1.43 ± 0.13 ^{b}	0.47 ± 0.18 ^{b}	0.36 ± 0.02 ^{a}	0.40 ± 0.02 ^{a}	25.53 ± 1.06 ^{b}	24.41 ± 0.96 ^{b}	21.01 ± 1.18 ^{b}	108.66 ± 4.80 ^{a}	82.16 ± 5.20 ^{a}	75.76 ± 6.24 ^{a}
Group III: (HFD+ALA)	2.07 ± 0.22 ^{b}	1.47 ± 0.14 ^{b}	1.71 ± 0.28 ^{b}	0.37 ± 0.05 ^{b,c}	0.26 ± 0.02 ^{b}	0.26 ± 0.03 ^{b}	25.15 ± 1.76 ^{b}	46.90 ± 3.18 ^{a}	43.94 ± 1.26 ^{a}	66.25 ± 7.33 ^{b}	37.87 ± 3.86 ^{c}	38.62 ± 3.49 ^{c}
Group IV: (Normal +ALA)	2.10 ± 0.22 ^{b}	1.02 ± 0.08 ^{b}	0.90 ± 0.07 ^{b}	0.24 ± 0.03 ^{c}	0.39 ± 0.04 ^{a}	0.37 ± 0.04 ^{a}	32.54 ± 2.33 ^{a}	42.10 ± 2.23 ^{a}	45.16 ± 1.15 ^{a}	60.01 ± 5.21 ^{b}	73.08 ± 1.60 ^{a}	76.30 ± 3.03 ^{a}

Data are presented as (Mean ± S.E). S.E = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$).

hyperlipidemic rats caused significant decrease in serum total cholesterol and triacylglycerol concentration when compared with hyperlipidemic non treated group. The obtained data in table (3) revealed that, high fat diet induced hyperlipidemia in rats showed significant increase in serum high density lipoprotein–cholesterol (HDL-c) and very low density lipoprotein-cholesterol (VLDL-c) concentrations when compared with normal control group. Treatment with alpha-lipoic acid to high fat diet induced hyperlipidemia in rats caused significant decrease in serum high density lipoprotein –cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c) and Very low density lipoprotein-cholesterol (VLDL-c) concentrations when compared with high fat diet induced hyperlipidemic group. The obtained data in table (4) revealed that, rats fed high fat diet showed significant decrease in liver CAT, SOD and GSH and significantly increased L-MDA concentration when compared with normal control group. Treatment with alpha-lipoic acid to high fat diet induced hyperlipidemia in rats caused significant increase in liver CAT and GSH and significantly decreased liver SOD and L-MDA concentration when compared with hyperlipidemic non-treated group.

4. DISCUSSION

Hyperlipidemia, including hyper-cholesterolemia and hypertriglyceridemia, is a major risk factor for the development of cardiovascular diseases (Makni et al., 2008). Elevated levels of plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) as well as reduced levels of plasma high density lipoprotein cholesterol (HDL-C) are often associated with an increased risk of coronary heart disease (Smith et al., 2004). In addition, hyperlipidemia can induce oxidative stress in liver (Bolkent et al., 2005). High fat diet induced hyperlipidemic rats showed significant increase in serum total cholesterol concentration. This result is consistent with those achieved by Diaz et al., (2000) who reported that, rabbits fed with the atherogenic diet showed marked increase in plasma total cholesterol and triacylglycerols.The dramatic rise in serum TC observed in this study could be attributed to increase in HMG-CoA reductase activity in the liver of animals fed hypercholesterolemic diet and the reduced rate of the clearance of LDL from circulation due to defective LDL receptors, which associated with increase of plasma total cholesterol concentration (Zulet *et al*., 1999). Treatment with alpha-lipoic acid to hyperlipidemic rats caused significant decrease in serum total cholesterol concentration when compared with hyperlipidemic non treated group. The hypocholesterolemic effect of alpha lipoic acid may be explained on the basis of increasing the transfer of blood cholesterol to be used in bile synthesis and thus, biliary excretion of cholesterol or bile acids is increased resulting in reduced availability of cholesterol to be incorporated into lipoproteins (An et al., 1997). In present study a significant increase in serum triacylglycerol concentration was observed in rats fed high fat diet after three and eight weeks of the experiment when compared with normal control group. These results came in accordance with the recorded data of Brousseau *et al*., (2000) who reported that a hyperlipidemic diet caused a significant increase of the plasma triacylglycerols and an increased content of cholesterol in the liver, despite the fact that diet produced a cessation of endogenous cholesterol synthesis. Such significant rise in serum triacylglycerols level may be attributed to the decrease of activity of lipase which is an insulin-dependant enzyme involved in triglyceride clearance from plasma by mediating triglyceride lipolysis into glycerol and fatty acids (Yost *et al*., 1995). Another possibility is that such significant increase in triglycerides might be a consequence of over production of VLDL by the liver. Treatment with Alpha-lipoic acid to high fat diet induced

hyperlipidemia in rats caused a significant decrease in elevated serum triacylglycerol concentration all over the period of the experiment. Such decrease in serum triacylglycerols was explained by Bennani-Kabchi et al. (2000) who related them to the increase rate of lipolysis by increase of plasma lipase activity at the same periods of decrease plasma triacylglycerols. A significant increase in serum high density lipoprotein cholesterol (HDL-C) concentration was observed after six and eight weeks. Also, a significant increase in serum very low density lipoprotein cholesterol (VLDL-C) was observed after the third and eight weeks when compared with normal control group. These results are nearly similar to those reported by Abdel-Maksoud et al., (2002) who reported that, mice and rats received cholesterol-enriched diet showed severe hypercholesterolemia, elevated plasma serum LDL-C and VLDL-C compared to those fed a normal diet. Also Yushchenko, (1959) recorded that, rabbits fed on hyperlipidemic diet showed significant increase of the plasma lipid levels; total lipids, total cholesterol, triacylglycerols, phospholipids, alpha lipoprotein (HDL), pre-beta lipoprotein (VLDL) , beta lipoprotein (LDL) fraction, and an increased content of cholesterol in the liver, despite the fact that the diet produced a cessation of endogenous cholesterol synthesis. Treatment with alpha lipoic acid to rats fed high fat diet showed significant decreased in serum HDL-c concentration, significantly reduced serum LDL-c concentration after three weeks. Also, significantly reduced elevated serum VLDL-c level when compared with hyperlipidemic non treated group. This data may be consistent with that of Park *et al*., (2012) who observed significant differences for HDL cholesterol levels among the control and LA group and reported that, LDL cholesterol levels were highest in the HFD group, whereas the α-LA supplemented groups showed a significant decrease in LDL cholesterol levels in a dose-dependent manner. Feeding of high fat diet induced hyperlipidemia in rats showed significant increase in serum glucose concentrations after the six week of the experiment compared to the control group. These results came in accordance with the recorded data of Lee, (2014) who found that, high fat diet (HFD) caused a significant increase of the plasma glucose. Treatment with alpha-lipoic acid to high fat diet fed rats significantly reduced elevated serum glucose concentration after six and eight weeks of the experiment when compared with hyperlipidemic non treated group. These results came in accordance with the recorded data of Udupa et al., (2013) who reported that, alpha lipoic acid an essential cofactor of alpha-oxoacid dehydrogenase complexes, is a potent lipophilic free radical scavenger. Alpha lipoic acid was found to increase glucose transport in muscle cells culture by stimulating translocation of $GLUT_4$ from internal pools to the plasma membrane (Konrad et al., 2001). Hyperlipidemic rats showed a non significant increase in serum insulin concentration all over the period of the experiment when compared to the control rats that received basal diet. This result of hyperlipidemia is consistent to that have been reported previously by Choi et al., (2014) who reported that consuming the high-fat, high-sucrose (HFHS) diet elevated serum insulin and glucose levels, as well as HOMA-IR relative to the control group, suggesting that the HFHS diet induced insulin resistance. These results came in accordance with the recorded data of Gupte et al. (2009) they reported that, chronic lipoic acid administration increases heat shock protein expression and inhibits stress kinase activation to improve insulin signaling in skeletal muscle from high-fat-fed rats. High fat diet induced hyperlipidemic rats showed a significant increase in liver L-MDA concentration all over the period of the experiment when compared to the control rats that received basal diet. Lipid peroxidation is a marker of cellular oxidative damage initiated by reactive oxygen species (Farber *et al*.,

1990). This result of hyperlipidemia is consistent to that have been reported previously by Wang *et al*., (2014) who reported that hypercholesterolemia could increase the cholesterol content of platelets, polymorphonuclear leukocytes and endothelial cells; lead to the formation of oxygen free radicals; and accelerate the process of lipid peroxidation. Treatment with Alpha-lipoic acid to hyperlipidemic rats significantly reduced elevated liver L-MDA concentration all over the period of the experiment when compared with hyperlipidemic group. Similarly, Sena et al., (2007) reported that, treatment with Alpha-Lipoic acid (α-LA) significantly decreased the MDA level, which may be partly due to the ability of alpha-Lipoic acid to scavenge free radicals. This effect can be explained on the basis that, LA or its reduced form can prevent lipid peroxidation and protein damage via interaction with vitamin C and glutathione (Packer et al., 1995). Another action of LA is its antioxidant effect by donating electrons to the free radicals for neutralizing their reactivities. High fat diet induced hyperlipidemia in rats showed significant decrease in liver catalase and superoxide dismutase activities. Also, a significant decrease in liver reduced glutathione concentration was observed after three weeks of the experiment when compared with normal control group. These results are nearly similar to those reported by Vuković et al., (2014) who reported that, high fat diet decreased the activities of CAT, GR, and GST, as well as the level of GSH. Moreover, several studies suggested that disorders of lipid metabolism, hyperlipidemia and obesity are associated with overproduction of oxygen free radicals (Rehman et al., 2003). The enhanced accumulation of these free radicals and dysfunction of antioxidant defense system resulted in oxidative stress (Giao et al., 2008). These radicals can bind covalently to the macromolecules and induce peroxidative degradation of the membrane lipids rich in polyunsaturated fatty acids, leads to the formation of lipid peroxides followed by multiple pathological changes (Shyamala et al., 2003). Treatment with α-Lipoic acid to hyperlipidemic rats significantly increased liver catalase activity after three weeks of the experiment and significantly decreased liver superoxide dismutase (SOD) after six and eight weeks of the experiment. In addition, liver reduced glutathione level was significantly increased after six and eight weeks of the experiment when compared with hyperlipidemic non-treated group. Similarly, Akpinar et al., (2008) found that, LA contributes to antioxidant defense by increasing CAT activity in the stress group. The decline in CAT can be attributed to ineffective scavenging of H_2O_2 resulting in increased H_2O_2 levels, which can react with $O_2^{\cdot}$ to give OH radical and thus increased lipid peroxidation.

5. CONCLUSION

The results indicated that alpha lipoic acid produces potent antiatherogenic and antioxidant effects in hyperlipidemic rats. This study recommends that administration of lipoic acid may be beneficial for patients who suffer from hyperlipidemia, hypercholesterolemia and/or arteriosclerosis.

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