Curcumin acts as Cardiovascular Protector *via* Improving Leptin and Insulin Resistance in Obese Male Rats

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Abstract: Obesity is one of the leading causes of cardiovascular disease (CVD).This study was designed to evaluate the protective activity of curcumin against incidence of this disease in obese male rats . Rats (175 ± 5g) became obese by feeding high fat diet (HFD) for duration of 3 months ,while curcumin was given orally at dose(20 mg/kg b.wt) for the same period . Feeding rats on HFD caused elevation of the body weight gain and weights of aorta and heart . Meanwhile, HFD-fed rats exhibited marked hyperglycemia, with raised lipid profile as reflected by significant elevation of serum, aorta and heart total lipids (TLs), total cholesterol (TC) and triglycerides (TGs),accompanied by increased serum values of LDL-C, vLDL-C and atherogenic index (AI), with decreased HDL-C level. An increased serum levels of leptin and insulin were also observed. The study also showed marked reduction in the antioxidants, superoxide dismutase (SOD) and reduced glutathione (GSH), along with elevation in the levels of hydrogen peroxide (H_2O_2) and lipid peroxidation product, malondialdehyde (MDA) in both heart and aorta of HFD-fed rats. Further changes, including elevation of serum aminotranseferases (AST and ALT), lactic dehydrogenase (LDH) and creatinine kinase (CK), with a reduction in their activities in heart and aorta were demonstrated. Also, a reduction in the level of nitric oxide (NO) in the same organs were recorded which together with the above mentioned alterations may indicate developing of CVD in the obese rats. On the contrary, administration of curcumin to HFD-fed rats tended to prevent hyperglycemia, hyperlipidemia and other changes relevant to cardiovascular disease mainly through improving leptin and insulin resistance. Thus, curcumin can be prescribed as a natural dietary product for reducing CVD associated with obesity.

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1. Introduction:

Obesity is a metabolic health problem with increasing prevalence worldwide. Physiologically, obesity arises from an imbalance between energy intake and energy expenditure, which in turn results in increased fat accumulation in adipose tissue**.** Such fat accumulation predisposes the individual to development of several health problems, including cardiovascular disease (CVD) **(Lehrke and Lazar, 2004).** In this context, a causal role of hormonal alterations has been indicated. Previous studies suggested an important role of leptin, a peptide hormone produced by adipose tissue in obesity-associated CVD **(Vincent and Taylor, 2006).** Leptin is primarily involved in the regulation of food intake and energy expenditure, however leptin also has vasodilator effect through stimulating endothelial nitric oxide (NO) production **(Vecchione *et al*., 2002).** Plasma leptin concentration is increased in animals with dietary induced obesity and vast majority of obese humans**.** Thus, increased leptin with resistance to its effect as seen in obesity leads to vasoconstriction and elevation of blood pressure **(Rodriguez *et al*., 2006).**

In other studies, insulin resistance coupled with a number of metabolic abnormalities has been suggested to be involved in the pathogenesis of obesity-associated CVD **(Hodnett** and **Hester, 2007).** In addition, a clustering of events including increased free radicals production, inadequate antioxidant defenses and oxidative stress have been suggested as responsible factors **(Dobrian *et al*., 2001).**

Nowadays, there is increased interest for using natural dietary products to manage obesity and related health problems due to their safety, efficacy and cost effectiveness **(Shin *et al*., 2011).** One of these compounds is curcumin which is derived from the rhizomatous herb, turmeric (*Curcuma longa)*. It has shown to possess a broad spectrum of medicinal activities through its antioxidant (**Naik *et al*., 2004)**, antimicrobial **(Aggarwal *et al*., 2003)** and anticarcinogenic properties **(Chainani-Wu, 2003).** Curcumin has also observed to lower blood glucose and cholesterol levels in diabetic patients **(Arun and Nalini, 2002),** as well as to improve insulin resistance in diabetic rats **(Weisberg *et al*., 2008).**

Although curcumin has been investigated widely for various medicinal activities, detailed studies on its ability to protect against obesity-induced cardiovascular disorders are still lacking. Therefore, the main objective of this study was to investigate the effect of prolonged intake of curcumin on the risk of cardiovascular disease in male rats with dietary-induced obesity, in terms of selected hormonal and metabolic parameters, as well as NO level.

2. Materials and methods

2.1. Animals

This study was performed on thirty male albino rats of Wistar strain, initially weighing 175±5g. Rats were obtained from the Institute of Ophthalmic Disease Research, Cairo. They were housed in stainless steel cages at a well ventilated animal house. Rats were permitted adequate standard diet and given water *ad libitum* for one week of adaptation period prior to the experimental work. Care and use of the animals were conducted under supervision of the Animal Care Committee of Mansura University, Egypt.

2.2. Chemicals

Curcumin[1.7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5dione] the active constituent of the dietary spice turmeric was purchased from El-Gomhria Company for Chemicals, Mansoura, Egypt. All other reagents were of analytical grade and were purchased from local standard suppliers.

2.3. Research design

After one week of adaptation, rats were randomly divided into five equal groups. The first was considered as control group, in which rats received normal laboratory diet (NLD) whitout supplementation. The second group was fed NLD and received 5% DMSO as vehicle orally with gastric tube at a dose 0.1 ml/100 g b.wt. In the third group, rats were received curcumin orally at dose of 20 mg/kg b.wt dissolved in 5% DMSO**.** Rats of the fourth group were fed on high fat diet (HFD) consisted of NLD in powder form mixed with melted animal abdominal fat (30%) and extra pure cholesterol (2%) **(Goupta and kaushik, 2010),** while rats of the fifth group were fed HFD and received curcumin orally at the same way and doses as described in the above groups. Rats administrated NLD and HFD daily for three months, while DMSO and curcumin were given every alternate day **(Kalpana and Menon, 2004)** for the same period. The animals were weighed at the start of the experiment then weekly to adjust the dose and to obtain the body weight changes.

2.4. Samples collection

At the end of the study period, all rats were fasted overnight and sacrificed by cervical dislocation under ether anesthesia. Blood samples were collected and sera were separated by centrifugation at 855g for 15 minutes for further biochemical analysis. After collecting blood, the heart and aorta from each rat were removed, weighed and stored at -20 ° C until being analyzed.

2.5. Biochemical analysis

Total lipids (TLs) (**Zollner and Kirsch, 1962),** total cholesterol (TC) **(Allain *et al.*, 1974),** triglycerides (TGs) (**Fassati and Prencipe, 1982),** HDL-C (**Zoppi and Fellini 1976),** superoxide dismutase (SOD) (**Niskikimi *et al*, 1972),** hydrogen peroxide (H_2O_2) (**Aebi, 1984),** and nitric oxide (NO) (**Montgomery and Dymock, 1961),** as well as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (**Reitman and Frankel, 1957),** were estimated using kits supplied by **Biodiagnostic Co**. (Mansoura, Egypt). LDL-C and vLDL-C were calculated according to the equations applied by **Ahmedi *et al.*, (2008); Satheesh and pair, (2008)** respectively, while atherogenic index (AI) was calculated based on the formula of **Pandya *et al.*, (2006).**

Creatine kinase (CK) activity was determind as described by **Young (1995)** using SEPPIM kit, while lactate dehydrogenase (LDH) activity was determined according the method of **Witt and Trendelenburg (1982)** using Clinical Chemistry Liquid kit. Levels of insulin and leptin were estimated using Enzyme Immunoassay kits, as described by **Frier *et al.*, (1981)** and **Dagogo-gack *et al.*, (1996),** respectively. The level of malondialdehyde (MDA) "the end product of lipid peroxidation" was determined as thiobarbituric acid reactive substance (TBARS) according to the modified method of **Ohkawa *et al.*, (1982),** while reduced glutathione (GSH) content was estimated by the method of **Prins and Loose (1969).**

2.6. Statistical analysis

All data were analyzed by one way analysis of variance (One–way ANOVA) followed by Least Significant Difference (LSD) test, using SPSS statistical package, version 17.00 software. The results were expressed as means ± S.E and values were considered to be statistically significant at $P<0.05$ **(Snedecor and Cochran, 1980).**

3. Results

As shown from (Table 1, 2, 3, 4) administration of curcumin to normal rats did not produce any significant changes in all tested parameters in comparison to normal rats indicating its non toxic effect at applied dose. Feeding rats on high fat diet (HFD) tended to exhibit obesity features, as evidenced by a significant increase in the body weight gain and weights of aorta and heart compared to control rats. On the other hand, administration of curcumin to animals fed on HFD showed significant reduction in the body weight gain and weights of

tested organs compared to obese rats (Table 1). The present obesity model also showed significant increase in serum levels of glucose, insulin, leptin, LDL-C, vLDL- C and AI, with decreased HDL-C level. This goes along with elevation in serum heart and aorta TLs, TC, and TGs. Treatment of HFD-fed rats with curcumin significantly decreased serum glucose, insulin, leptin and various lipid indices compared to obese rats, however the results revealed significant increase in the level of HDL-C (Table 2). The present data also showed significantly increased serum activity of AST, ALT, CK and LDH, accompanied by reduction in their activities in aorta and heart of the obese rats compared to the control group. Treatment of HFD-fed rats with curcumin significantly improved all motioned enzymatic changes compared to obese rats (Table 3).

Present data showed significant increase in the levels of lipid peroxidation product, MDA and H_2O_2, concomitantly with a significant reduction in the activity of SOD and the level of GSH, as well as NO concentration in both aorta and heart tissue of the obese rats. Treatment of HFD-fed rats with curcumin significantly increased mentioned NO, SOD and GSH compared to obese rats (Table 4).

Table (1): Effect of curcumin on body weight gain and tissue weights in high fat diet fed rats.

Parameters	Animal groups				
	Control	DMSO	CUR	OB	OB+CUR
Body weight gain (g)	118.67 ±3.21	117.83 ±3.26	117.00 ±3.37	176.17 ±3.53 [a]	151.67 ±1.45 [abc]
Aorta weight(g)	0.15 ±0.009	0.15 ±0.004	0.14 ±0.002	0.18 ±0.007 [a]	0.16 ±0.007 [b]
Heart weight (g)	0.85 ±0.02	0.85 ±0.02	0.80 ±0.01	1.12 ±0.07 [a]	0.87 ±0.02 [b]
ANOVA	P<0.05				

Values are means± SE of six animals for each group. DMSO= dimethylsulphoxide, CUR= curcumin, OB= obese. a: significant when compared different groups with control. b: significant when compared (OB+CUR) with obese . c: significant when compared (OB+CUR) with curcumin.

Table (2): Effect of curcumin on serum glucose, insulin and leptin , as well as serum and tissue lipid profile in high fat diet fed rats.

Parameters		Control	DMSO	CUR	OB	OB+CUR
SERUM	Leptin (ng/ml)	18.93 ±0.73	18.62 ±0.42	18.30 ±0.41	29.50±1.32 [a]	23.38 ±0.54 [abc]
	Insulin µIU/ml	1.86 ±0.13	1.82 ±0.12	1.94 ±0.05	3.39 ±0.18 [a]	2.61±0.18 [abc]
	Glucose (mg/d)	96.71 ±3.11	96.37 ±0.84	96.01 ±0.76	198.46 ±2.61[a]	135.97 ±5.92 [abc]
	TLs (mg/dl)	439.54±8.01	438.28±11.91	433.08±8.48	873.64±17.92 [a]	676.36±10.83 [abc]
	TC(mg/dl)	101.96 ±1.75	102.35 ±2.45	101.15 ±1.86	131.41±1.76 [a]	116.86±3.41 [abc]
	TGs(mg/dl)	94.98 ±4.07	94.37 ±4.83	94.05 ±1.90	147.03 ±4.87 [a]	127.29 ±4.46 [abc]
	HDL-C (mg/dl)	40.29 ±0.53	40.06 ±0.36	40.81 ±0.66	32.55 ±0.69 [a]	37.55 ±1.36 [b]
	LDL-C (mg/dl)	42.68 ±1.69	43.41 ±2.96	41.37 ±2.57	69.45 ±1.41 [a]	53.85 ±3.87 [abc]
	vLDL-C(mg/dl)	18.99 ±0.81	18.87 ±0.97	18.31 ±0.38	29.41 ±0.98 [a]	25.46 ±0.89 [abc]
	AI	1.53 ±0.04	1.56 ±0.08	1.47 ±.0 07	3.04 ±0.08 [a]	2.13 ±0.14 [abc]
AORTA	TLs (mg/g)	68.74 ±1.69	68.56 ±1.45	68.09 ±1.71	90.44±1.31 [a]	81.94 ±1.73 [abc]
	TC (mg/g)	32.74 ±1.32	32.59 ±1.67	32.28 ±1.54	48.02 ±1.21 [a]	41.28 ±0.82 [abc]
	TGs (mg/g)	26.56 ±2.12	26.38 ±1.90	26.09 ±1.38	40.59 ±1.34 [a]	34.55 ±1.87 [ac]
HEART	TLs (mg/g)	63.43 ±0.98	63.29 ±1.00	63.06 ±0.77	80.27±1.42 [a]	70.66±1.82 [abc]
	TC (mg/g)	26.97 ±1.81	26.72 ±0.48	26.41 ±1.01	42.61±2.80 [a]	35.88±1.40 [abc]
	TGs (mg/g)	25.56 ±1.36	25.24 ±1.03	25.10 ±0.90	35.93 ±1.40 [a]	31.67 ±0.95 [ac]
ANOVA	P < 0.05					

Values are means ± SE of six animals for each group. DMSO = dimethylsulphoxide, CUR= curcumin, OB = obese. a: significant when compared different groups with control. b: significant when compared (OB+CUR) with obese . c: significant when compared (OB+CUR) with curcumin.

Table (3): Effect of curcumin on serum and tissue aminotransferases (AST&ALT), creatine kinase (CK) and lactic dehydrogenase (LDH) activities in high fat diet fed rats.

Parameters		Control	DMSO	CUR	OB	OB+CUR
SERUM	AST (U/L)	52.63 ±1.79	52.58 ±1.77	52.04 ±0.51	77.75 ±1.94 [a]	66.75 ±2.36 [abc]
	ALT (U/L)	15.58 ±0.35	15.42 ±0.30	15.13 ±0.33	33.25 ±0.58 [a]	22.63 ±1.15 [abc]
	CK (U/L)	142.77 ±4.08	142.32 ±0.78	142.01 ±1.46	252.20 ±2.22 [a]	179.43 ±2.00 [abc]
	LDH (U/L)	94.98 ±1.63	94.71 ±3.22	94.16 ±2.55	141.40 ±1.69 [a]	119.40 ±3.13 [abc]
AORTA	AST (U/g)	63.54 ±0.48	63.37 ±0.63	63.94 ±0.81	45.14 ±1.48 [a]	55.83 ±0.82 [abc]
	ALT (U/g)	24.46 ±0.72	24.21 ±0.48	24.94 ±0.40	14.45 ±0.57 [a]	18.00 ±0.64 [abc]
	CK (U/g)	316.42 ±4.29	316.15 ±5.07	316.91 ±1.65	215.93 ±3.37 [a]	277.70 ±2.53 [abc]
	LDH (U/g)	53.54 ±0.94	53.48 ±0.86	53.93 ±1.52	33.25 ±0.42 [a]	44.37 ±0.84 [abc]
HEART	AST (U/g)	63.29 ±0.82	63.17 ±0.83	63.92 ±1.01	43.46 ±0.68 [a]	55.38 ±1.17 [abc]
	ALT (U/g)	20.49 ±0.45	20.04 ±0.34	20.92 ±0.44	12.25 ±0.53 [a]	15.75 ±0.46 [abc]
	CK (U/g)	339.30 ±1.72	339.08 ±1.07	339.93 ±1.27	248.86 ±4.44 [a]	286.64 ±4.13 [abc]
	LDH (U/g)	50.62 ±1.26	50.51 ±0.75	50.86 ±1.36	36.43 ±1.01 [a]	41.83 ±1.86 [ac]
ANOVA		P < 0.05				

Values are means ± SE of six animals for each group. DMSO = dimethylsulphoxide, CUR = curcumin, OB = obese.
a:significant when compared different groups with control. b: significant when compared (OB+CUR) with obese .
c: significant when compared (OB+CUR) with curcumin..

Table 4: Effect of curcumin on tissue nitric oxide (NO) and oxidative stress markers in high fat diet fed rats.

Parameters		Control	DMSO	CUR	OB	OB+CUR
AORTA	NO(µmol/g)	49.43 ±1.30	49.11 ±0.94	49.96 ±1.82	30.81 ±2.09 [a]	42.30 ±0.82 [abc]
	H_2O_2(mM/g)	25.67±1.50	25.30±1.42	25.07±0.91	36.80 ±1.02 [a]	26.82±1.51 [bc]
	MDA (nmol/g)	327.74±4.59	327.36±2.41	327.01±8.02	568.15 ±9.75 [a]	416.16 ±5.86 [abc]
	GSH(mg/g)	3.11±0.13	3.10±0.17	3.24±0.02	2.03 ±0.10 [a]	2.72±0.19 [b]
	SOD (U/g)	131.46±2.71	131.38±2.78	131.93 ±0.57	111.04 ±4.33 [a]	122.83 ±2.17 [b]
HEART	NO(µmol/g)	59.29 ±0.97	59.18 ±1.77	59.92 ±1.32	39.50 ±1.85 [a]	47.83 ±1.54 [abc]
	H_2O_2(mM/g)	29.57±0.44	29.71±1.52	29.01 ±0.22	35.94 ±1.00 [a]	31.38 ±0.76 [bc]
	MDA (nmol/g)	368.53 ±3.12	368.37 ±2.81	368.01 ±5.75	519.87 ±10.10 [a]	426.41 ±2.57 [abc]
	GSH(mg/g)	4.29±0.10	4.28±0.11	4.46±0.07	2.29±0.20 [a]	3.49±0.12 [abc]
	SOD (U/g)	174.19 ±3.20	174.02 ±1.80	174.98 ±1.05	135.42 ±2.38 [a]	148.00 ±2.35 [abc]
ANOVA		P < 0.05				

Values are means± SE of six animals for each group. DMSO = dimethylsulphoxide, CUR= curcumin, OB= obese.
a: significant when compared different groups with control. b: significant when compared (OB+CUR) with obese .
c: significant when compared (OB+CUR) with curcumin.

4. Discussion

Obesity refers to abnormal or excessive fat accumulation with an increase in the body weight**.** Changes in dietary pattern, such as increased consumption of high fat diet (HFD) are considered a primary cause of this problem**.** In the present study, rats fed on HFD for duration of 3 months tended to exhibit obesity features characterized by an increase in the body weight gain, with elevation in the weights of heart and aorta if compared to normal rats. Similarly, it was reported that long term exposure to HFD can increase body weight and adiposity in human and animals as consequence of body fat storage enhancement **(Thaler *et al.*; 2012).**

Recently, there is great evidence suggesting obesity as an independent risk factor for a number of

health problems, including cardiovascular disease (CVD) **(Chandrasekaran *et al.*, 2012).** Obesity is characterized by hormonal changes with a number of metabolic abnormalities which in all may contribute to development of cardiovascular disorders **(Vecchione *et al*., 2002).** Leptin, a peptide hormone secreted by adipocytes is strongly implicated in this problem **(Hall *et al*., 2001).** Leptin is primary involved in the regulation of body weight by centrally inhibiting food intake and stimulating energy expenditure**.** Leptin enters the circulation and crosses the blood-brain barrier to reach its primary target receptors in the hypothalamus. Binding of leptin to these receptors triggers intracellular pathways in the hypothalamus satiety centers which in turn signal brain for restricting food intake and regulating body weight **(Ahima and Osei, 2004).**

There is evidence that serum leptin is elevated in obese human **(Orel e*t al*., 2004)** and animals **(Scarpace and Zhang, 2008)** as seen in the present study which is correlated to the increase of body fat**.** Positive correlation between body fat and serum leptin is probably explained by the increased release of leptin from the large fat mass. Thus, leptin can serve as an indicator of fat content and its level may be decreased by reduction of body weight **(Masoud and Adel, 2006).** Prior studies suggested that early during high fat feeding, animals are sensitive to the food lowering effect of leptin. However, despite the reduction in food intake, animals become fat as a result of the increase in food efficiency leading to an increase in plasma leptin levels, followed by resistance to its action **(Lin *et al* ., 2000).**

Recent investigation suggested leptin resistance as contributing factor for incidence of hypertension and cardiovascular complications in obese subjects, which in turn may be linked to impairment of vascular endothelial function **(Singh *et al*., 2010a).** On this issue, it was demonstrated that leptin receptors are present on endothelial cells and that increasing doses of hormone are able to exert vasorelaxant response through increasing endothelial production of nitric oxide (NO) **(Shiuchi *et al.*, 2001).** However, the chronic condition of hyperleptinemia typical of obesity could be accompanied by impaired endothelial vasorelaxation through deficiency of NO production **(Tripathy *et al*., 2003).**

Normally, NO functions to maintain vascular homeostasis, while decreased production of NO is associated with vasoconstriction that accelerates development of atherosclerosis with increased myocardial injury (**Dubey *et al.*, 2008).**When myocardial cells are injured, many enzymes such as (CK, LDH, ALT, and AST) can be released from the myocardial cells to the extracellular fluid as a result of alterations in plasma membrane integrity and/or permeability **(Ramadan *et al*., 2012).** Accordingly, it can said that various events, such as hyperleptinemia, decreased NO level and increased serum ALT, AST, LDH and CK, with reduction in their activities in aorta and cardiac tissue, as seen in this study may indicate incidence of CVD as consequence of obesity.

Additional trials have identified insulin resistance as contributing factor for increased cardiovascular disease in obesity. Insulin resistance is a state in which higher concentration of insulin is required to maintain normoglycemia **(Eckel *et al*., 2005).** The action of insulin is initiated by binding to its receptors and activation of intrinsic protein tyrosine kinase activity of the receptors, resulting in initiation of intracellular signaling cascades that eventually related to glucose and lipid metabolism **(Westerbacka *et al*., 2002).** It is well established that increased availability and utilization of free fatty acids (FFAs) play a critical role in the development of insulin resistance. Excess adipose tissue has been shown to release an increased amount of FFAs which directly affect insulin signaling, diminish glucose uptake in muscles, drive exaggerated triglyceride synthesis and induce gluconeogenesis in the liver **(Mlinar *et al*., 2007)** leading to elevated levels of glucose and lipids. Accordingly, the increased insulin level as seen in this study may indicate a state of insulin resistance which in turn may contribute to incidence of hyperglycemia and raised lipid profile in serum, heart and aorta of the obese rats.

Elevation in serum levels of glucose is intimately linked to the rising incidence of CVD in the obese subjects**.** This is because hyperglycemia can activate the formation of deleterious products derived from protein or lipid structures named as advanced glycation end products (AGEs) which can deeply affect the function of cardiovascular system **(Grillo and Clombatto, 2008).** Increased lipid profile has also suggested to be a major risk factor predisposing obese subjects to develop CVD**.** In different obese states, level of TC is frequently increased possibly through decreased level of HDL-C, together with increased LDL-C concentration**.** As reported earlier, LDL-C is the major cholesterol carrier in the blood, about 60-80% of cholesterol is carried by LDL-C**.** Some of cholesterol is used by tissues and other returned to liver **(Quinet *et al*., 2009)** but if there is much LDL-C in blood, cholesterol may be deposited. On the other hand, HDL-C picks up cholesterol and takes it back to liver for reprocessing or excretion by a pathway called reverse cholesterol transport **(Xie *et al*., 1999).** Consequently, decreased HDL-C is associated with decreased cholesterol removal from extra hepatic tissues and increased risk of developing

cardiovascular disorders**.** Events of cardiovascular disorders may also involve elevations of serum vLDL-C and TGs with subsequent accumulation of TGs in the vascular wall and cardiac tissue **(Vallance and Chan, 2001).** Based on this, the present findings that HFD-fed rats showed raised lipid profile characterized by elevation in levels of serum, heart and aorta TLs, TGs and TC, as well as serum vLDL-C, LDL-C and AI with decreased HDL-C concentration may indicate development of CVD.

Increased lipid profile could also contribute to increased oxidative stress in obesity, where increased lipid substrate in the tissues may increase the mechanical and metabolic load on such tissues, thus increasing oxygen consumption. A negative consequence of the elevated oxygen consumption is the production of reactive oxygen species (ROS) **(Vaz *et al*., 1997)**. Under normal physiological conditions, ROS can be eliminated or inactivated by different antioxidant systems**.** In obesity, both human **(Noeman *et al*., 2011)** and animals **(Olusi, 2002)** are unable to provide adequate levels of antioxidants to compensate for the production of free radicals, thereby generating a state of oxidative stress, coupled with increased lipid peroxidation. As such, the present obesity model showed increased oxidative stress characterized by a reduction in the antioxidants, GSH and SOD with subsequent elevation in the level of H_2O_2 and lipid peroxidation in both aorta and cardiac tissues.

Lipid peroxidation is a marker of cellular damage initiated by ROS. In obesity, lipid peroxidation is thought to play a role in the etiology of existing health problems, such as cardiovascular disorders. Increased lipid peroxidation is considered responsible for impairment of endothelial cells, capillary permeability and vascular integrity **(Keidar *et al*., 2004).** Moreover, increased lipid peroxidation in the heart leads to loss of cellular membrane integrity due to oxidative modification of lipids and proteins that can ultimately lead to cardiac arrhythmias, poor contractility, infarction, cardiac failure or sudden death **(Vincent *et al*., 2001).** Accordingly, the present elevation of lipid peroxidation in both aorta and heart tissues is probably involved in initiation and progression of cardiovascular injury in the obese rats.

In this research area, one of the recent approaches is applying various plant products as alternative therapy for controlling obesity and related health problems. In the present study, administration of curcumin to HFD-fed rats was found to lower body weight gain and weights of the tested organs (heart and aorta). Curcumin showed an ability to inhibit angiogenesis in adipose tissue, decrease differentiation of preadipocytes and reduce accumulation of lipids in adipocytes which in all aid in lowering body weight **(Ejaz *et al*., 2009).** This latter effect provided benefits toward decreasing leptin concentrations in parallel with elevation of NO levels **(Ciardi *et al*., 2012).** Since it is known that patient with hyperlepitinemia are at increased risk for cardiovascular disease through impaired NO production, action of curcumin such as decreased leptin and increased NO availability as shown in the present study appears to play important role in preventing cardiovascular disease associated with obesity. A result which is further supported by the present finding of normalized activities of ALT, AST, LDH and CK in serum, heart and aorta of curcumin administered HFD-rats. Thus, indicating the protective activity of curcumin against obesity-induced CVD.

The present study demonstrated also the ability of curcumin to lower the elevated serum insulin in the HFD- fed rats. Thereby, indicating improved insulin resistance **(Seo *et al*., 2008).** An effect that seemed to stimulate glucose utilization by tissues resulting in normalized serum glucose as observed in the present study following curcumin administration to the HFD-group. Additionally, curcumin served as hypolipidemic agent, as evidenced by reducing the elevated lipid profile in the HFD-fed animals. In this concern, curcumin plays a pivotal role via stimulating fatty acids B−oxidation and suppressing fatty acids biosynthesis which seemed to be related to the hypolipidemic activity of curcumin **(Babu and Srinivasan, 1997).**

Moreover, curcumin has shown to possess potent antioxidant activity **(El-Wakf *et al*., 2011)** through scavenging a variety of ROS, including $O2^{-}$**,** OH^{-}**,** nitrogen dioxide radicals and non-free radical species , such as H_2O_2 **(Kapakos *et al*., 2012).** It was claimed that the presence of phenolic groups in the structure of curcumin is fundamental in its ability to eliminate ROS. Further, it has been shown that phenolic and methoxy groups on phenyl rings and 1, 3-diketone groups are important structural features that contribute to the antioxidant effect of curcumin **(Singh *et al*., 2010b)**. A role of the H-atom donation from the phenolic group is also shown to be critical for its strong antioxidant and ROS scavenging properties **(Ak and Gulcin, 2008).** In this concern, **Tirky *et al*., (2005)** indicated that curcumin improved renal GSH levels in arsenite treated rats. Besides, treatment with curcumin brought back lipid peroxidation markers near normal levels in streptozotocin (STZ) diabetic rats, which could be as a result of improved antioxidant status **(Majithiya and Balaraman, 2005).** Accordingly, the present results of increased antioxidants (SOD and GSH), with reduction in the levels of H_2O_2 and MDA in both aorta and cardiac tissue of curcumin

administrated HFD-rats, could indicate a beneficial effect of curcumin against oxidative stress -induced CVD in obesity.

In conclusion, the present study demonstrated that curcumin administration to HFD-fed rats helped in controlling obesity and the related events contributing to CVD. Thus, curcumin can be considered as a natural dietary product suitable for reducing the risk of developing CVD in obesity.

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