

Therapeutic Effects of Curcumin against Obesity and Obesity Induced Renal Pathology in Experimental Animal Models

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Abstract:

Obesity and its associated metabolic disorders are considered a growing global epidemic. Curcumin is used as a flavoring agent and food colorant, this polyphenol has been shown to possess many pharmacological properties. The current study was and designed to assess the protective effect of curcumin extract on HFD-induced obese rats. Thirty male albino rats were used in the current study and divided into five groups; control Diet group (CD), High Fat Diet - group (HFD), High Fat Diet + curcumin (HFDC), Vegetable Diet group (VEG) and Vegetable Diet group + Curcumin (VEGC). Body weight was measured 2 times per week during the experiment period (56 days); specimens from kidneys were taken for histopathological studies. The results showed the body weight of HFD-group was increased while decreased in both HFDC and VEG-group. Moreover, severe histopathological changes of kidney were detected in the HFD-group. We conclude, treatment with curcumin extract was effectively alleviated the obesity and obesity induced renal pathology.

Keywords: Curcumin, Obesity, Body weight, kidney

1- INTRODUCTION

Obesity is a multifactorial disease; it is typically defined quite simply as excess body weight for height. Obesity is characterized by an excess of adiposity or body fatness and an overconsumption of dietary fat that can manifest metabolically and not just in terms of body size (Hruby and Hu, 2015). Weight gain and abnormal body fat storage at or after middle age were associated with declines in walking ability, hearing and vision, memory and decision making. Multiple studies have identified obesity as a possible risk factor for impairments in physical and mental functional status especially for those over 70 years old (Zhu et al., 2018).

Excess weight gain is a major risk factor for metabolic disease, cardiovascular disease such as hypertension, *diabetes mellitus* and renal disease, particularly end-stage renal disease (Amann and Benz, 2013).

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Triglycerides (TGs) are the major storage form and transport of fatty acids in the plasma and within cells. However, excessive fat accumulation adversely affects almost all physiological functions of the human body and it directly or indirectly increases health risks linked to obesity (Zou et al., 2020).

Obesity increases the progression potential of preexisting renal disorders and is itself considered an independent risk factor for development of chronic renal disorders. It causes various structural, hemodynamic, and metabolic alterations in the kidney (Tsuboi et al., 2017). They reported that, glomerular hypertrophy in obesity may be largely attributable to compensatory changes accompanying glomerular hyper-filtration. Furthermore, Lee et al. (2019) found that HFD induced renal injury as evidenced by increased proteinuria, basement membrane thickness, glomerular hypertrophy and abnormal glomerular structure.

Curcumin is the most important phenolic compound of turmeric (*Curcuma longa*) and has a yellow color. Curcumin is a natural phenolic antioxidant, because its phenolic hydroxyl group can directly capture or scavenge free radicals. Curcumin and its related phenolics have been shown to be accompanied with the inhibition of lipid peroxidation, DNA damage and generation of free radicals (Farzaei et al., 2018). Curcumin is used as a flavoring agent and food colorant, this polyphenol has been shown to possess many pharmacological properties such as anti-inflammatory, hypoglycemic, antioxidant, wound-healing, anti-lipid peroxidation, anti-tumor, and antimicrobial activities among others (Inzaugarat et al., 2017).

Long term dietary curcumin administration blocked HFD-induced body-weight gain and obesity in chronic HFD mouse model. Also, the administration of curcumin significantly prevented HFD-induced body weight gain along with improved serum lipid profile (Mahmoud et al., 2021).

Experimental evidence supports the potentiality of curcumin as supplement promoting body weight loss and reducing the incidence of obesity-related disorders. Several studies demonstrated the potential anti-obesity and anti-inflammatory effects of this phytotherapeutic to prevent chronic inflammatory diseases and to suppress weight gain (Silva et al., 2020). Using curcumin as a dietary supplement showed its ability in inhibiting angiogenesis and differentiation of adipocytes which is a main factor aid lowering body weight (Zhou et al., 2011).

Based on the above-mentioned literatures, the present study was scheduled to examine the possible therapeutic effects of curcumin as an anti-obesity induced renal alteration in the experimental animals model of obesity and obesity-related disorders.

2- MATERIALS AND METHODS

2.1- Chemicals

The *Curcuma longa* (Turmeric) powder used for this experiment was purchased from Merck, CAS Number 458-37-7. All other chemicals were of highest quality.

2.2-Animals

Thirty male albino rats weighed 50-60 gm at the beginning of the experiment. Rats were obtained from Qena Breeding Center and acclimatized for one week before the beginning of study. Rats were randomly divided into five groups. All groups were kept under the same environmental conditions at temperature 25°C and 12h dark/light cycle. Feeding regimens and water supplementation were constant among the control and all tested groups. Animals were housed in well-ventilated cages with sawdust bedding, under standard air conditioned

environment. Care of the animals and experimental procedures were approved by the Animal Ethical Committee of Aswan University, Egypt, in accordance with the guide for the care and use of laboratory animals.

2.3- Experimental Design

The rats were randomly divided into five groups, 6 rats each. The groups were assigned to a food type as follow:

- I. **Control Diet group (CD):**-This group feed on 40 g Mash
 - II. **High Fat Diet group (HFD):**- This group feed on 20 g Mash + 20 g Beef grease (50% fat, wt. /wt.) (Woods et al., 2003).
 - III. **High Fat Diet + Curcumin (HFDC):**-This group feed on High Fat Diet + 100 mg /kg body weight curcumin (Ding et al., 2016).
 - IV. **Vegetable Diet group (VEG):**-This group feed on 20 g Mash + 20 g Vegetable.
 - V. **Vegetable Diet group + Curcumin (VEGC):**-This group feed on Vegetable Diet + 100 mg /kg body weight curcumin (Ding et al., 2016).
- All the above treatments were repeated daily for 56 days.

Note:

- **Mash components** were (51.7 g crude carbohydrate, 30.2 g crude protein, 6.4 g crude lipid, 4.3 g crude fiber, 5.8 g mineral mixture, and 1.6 g vitamin mixture/100 g diet).
- **Vegetable components** were fresh green vegetables (lettuce, arugula, coriander).
- We used (20 gm) of vegetables in the VEG-group similar to that (20 gm) of beef grease which used in the HFD-group to unify the diets amount used in different types of groups.

2.4- Body weight measurement

Experimental rats were assigned by equal initial body weight to the experimental diet for 56 days. Body weight was measured every week and the measurements were continued until the last week of the experiment. At that point all groups were allowed free access to their respective diets (Bravo et al. 2014, Marques et al. 2015).

2.5- Histological studies

Pieces of kidney were collected from all groups and were washed in sterile saline and kept in 10% neutral phosphate-buffered formalin (PH 7.0). For microscopic preparations, specimens were dehydrated in gradual ethyl alcohol (50-99%), cleared in methyl benzoate and embedded in molten paraffin wax at 58-62°C. Tissue sections in 5µm of thickness were prepared and stained with Hematoxylin and Eosin for microscopic investigation (Gabe, 1976). Examination of the sections to assess histological and histopathological alterations was performed under high-power light microscope (Olympus BX43F, Tokyo 163-0914, Japan). Image analysis was performed using a personal computer, a camera, software (Olympus DP74 Tokyo 163-0914, Japan) and an optical microscope.

2.6- Statistical analysis

The obtained data were expressed as means \pm standard deviation (SD). Differences between means were tested by one-way analysis of variance ANOVA followed by the Student-Newman-Keuls T-test using Minitab 12 software so that the data obtained can be compared and statistically evaluated. Statistical significance was considered when $p < 0.05$.

3- RESULTS AND DISCUSSION

3.1-Body weight

Data from the table (1) shows that, HFD-group exhibited a significant increase ($P < 0.05$) of the body weight when compared with CD- group. However, the HFDC-group exhibited a significant decrease ($p < 0.05$) of the body weight comparing with the HFD- group. Also, the VEG-group showed a highly significant decrease of the body weight ($p < 0.01$) comparing with the CD-group. However, VEGC-group group showed non-significant change of body weight as compared with the VEG-group. High-fat diets (HFD) have been used to induce obesity in animals. In both rats and mice a positive relationship has been found between the level of fat in the diet and body weight or fat gain (Hariri and Thibault, 2010). In the present study we focus on studying the differential changes of using different food regimens on the health status and health welfare. Moreover, we tried to examine the therapeutic effect of curcumin against HFD-induced obesity. The data of the present work revealed the occurrence of a significant increase in the body weight of experimental group feed on HFD compared with those of the normal group. These results are in a harmony with Andrich et al. (2018) who observed alterations in body composition and weight gain in HFD group. They illuminated that obesogenic diets greatly contribute to a positive energy balance and their fat content provides approximately twice the caloric load of carbohydrates and proteins. Interestingly, curcumin induction decreased the body weight significantly in the HFDC- group comparing with HFD-group. These findings are in agreement with Ding et al. (2016) who reported that, *in vivo*, curcumin ameliorated HFD-induced body weight gain and fat accumulation in liver or adipose tissues, and improved serum lipid levels and insulin sensitivity in HFD-induced obese mice. Curcumin, a major active component of *Curcuma longa* could be a potential leading compound for development of drugs for the prevention of obesity and insulin resistance.

Table 1: Mean values of body weight after 8 weeks in the control and different treated groups.

Groups	Parameter	Body weight (gm)
Control diet group (CD)		190.88 ± 22.88
High fat diet group (HFD)		227.22 ± 25.88 ^a
High fat diet group+ curcumin (HFDC)		199.25 ± 14.33 ^b
Vegetable group (VEG)		140.73 ± 17.36 ^c
Vegetable group+ curcumin (VEGC)		140.72 ± 19.59 ^d

Values are means ± S.D. of 10 animals in each group.

^a significant increase ($p < 0.05$) compared with the CD group.

^b significant decrease ($p < 0.05$) compared with the HFD group.

^c highly significant decrease ($p < 0.01$) compared with the CD group.

^d non-significant change ($p > 0.05$) compared with the VEG group.

Zhao et al. (2011) indicated that curcumin exerted a potent effect on the prevention of adipocyte differentiation, a significant reduction in leptin and a significant increase in adiponectin levels. Also, the effect of curcumin on energy metabolism may suppress anabolic pathways and stimulate catabolic pathways, resulting in higher energy expenditure, probably a higher basal

metabolism and a higher body temperature in HF-fed mice. In addition, Ejaz et al. (2009) showed that curcumin suppression of angiogenesis in adipose tissue together with its effect on lipid metabolism in adipocytes collectively appear to be responsible for the lower body fat, lower body weight gain and obesity. The favorable effects of curcumin are due to the enhancement of glucose and lipid catabolism, anti-inflammatory effect and ultimately caused a lower weight gain (Panzhinskiy et al., 2019).

3.2-Histopathological findings

H&E staining and microscopic examinations of the kidney of the CD- group (Figure 1) revealed the renal cortex with normal appearance of glomeruli, the proximal and the distal convoluted tubules.

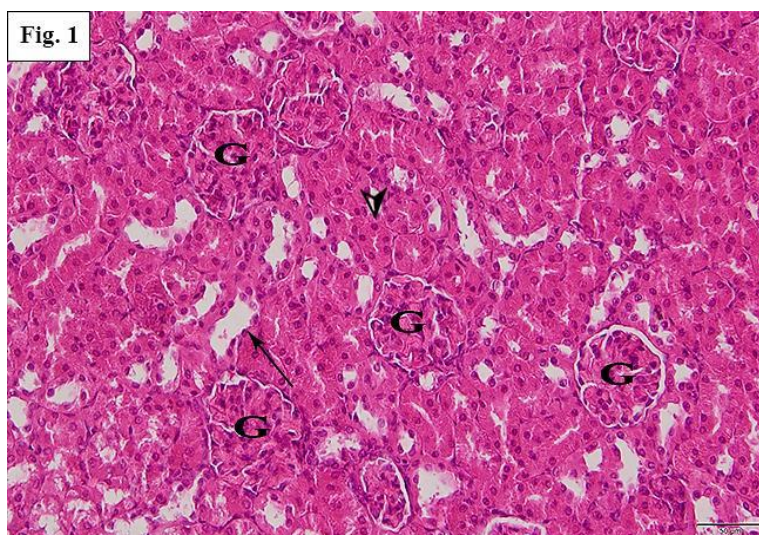


Fig. 1: A photomicrograph of a kidney section of CD-group rats showing the renal cortex with normal appearance of glomerulus (G), the proximal convoluted tubules (arrowhead) and the distal ones (arrow).
(H&E, X 400)

Kidney sections of HFD-group rats showed several alterations in the renal tissue (Figure 2). These alterations included dilatation of blood vessels and interstitial inflammatory cell infiltration. Degeneration of glomerular cells with mild dilatation of Bowman's space and some renal tubules contained a considerable amount of debris in their lumen were also detected. In addition, some necrotic changes were detected in some renal tubular cells.

Co-treatment with curcumin showed improvements in renal tissues of HFDC-group (Figure 3). These improvements represented by normal structure of the glomeruli, proximal and distal convoluted tubules, while mild congestion of blood capillaries was noticed. Microscopic examinations of the kidneys of both VEG- group (Figure 4) and VEGC- group (Figure 5) revealed a normal histological structure that was similar to that of the control group.

The site of storage of fat in obesity is properly in adipose tissue. However, in some instances excess fat may sometimes be deposited in other tissues such as heart, kidney and liver. HFD induces alteration of renal lipid metabolism by an imbalance between lipogenesis and lipolysis in the kidney, as well as systemic metabolic abnormalities and subsequent renal lipid accumulation and lipid peroxidation leading to renal injury (Altunkaynak et al., 2008). The result of this study is in accordance with the findings of earlier research studies carried out by Futatsugi et al. (2016) who summarized the histology of kidney sections from HFD-fed rats as follows:

dilatation in glomerular capillaries and other blood vessels, mononuclear cell infiltration in the renal cortices. Degeneration in nephrons including glomerulosclerosis, segmental necrosis and tubular defects was found in the kidneys of the HFD-fed rats. They concluded that a fatty diet is responsible for the rats' obesity and may lead to renal deformities as a result of histopathological changes such as dilatation, tubular defects, inflammation and connective tissue enlargement of the kidney.

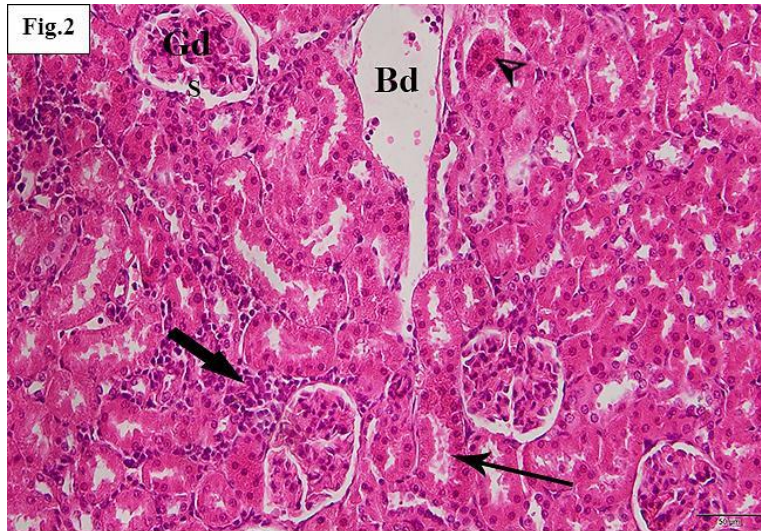


Fig. 2: A photomicrograph of a kidney section of HFD-group rats showing dilatation of blood vessels (Bd) and interstitial inflammatory cell infiltration (thick arrow). Degeneration of glomerular cells (Gd) with mild dilatation of Bowman's space (S) and some renal tubules contained a considerable amount of debris (arrow) in their lumen were viewed. Some renal tubular cells underwent necrotic changes (arrow head) were noticed. (H&E, X 400)

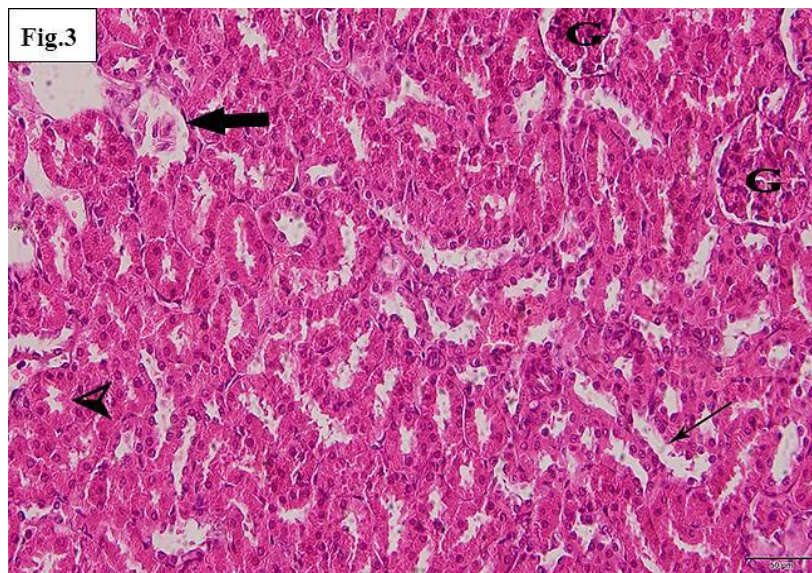


Fig. 3: A photomicrograph of a section of the renal cortex of the HFDC-group, showing normal structure of the glomerulus (G), both convoluted tubules; proximal (arrow head) and distal (arrow) and congestion of blood capillaries (thick arrow). (H&E, X 400)

Wang et al. (2018) showed obvious renal histological lesions including tubular hypertrophy, basement membrane thickening, mesangial expansion and glomerulosclerosis in addition to sustained inflammation and cell apoptosis in the kidney of HFD-group compared to controls.

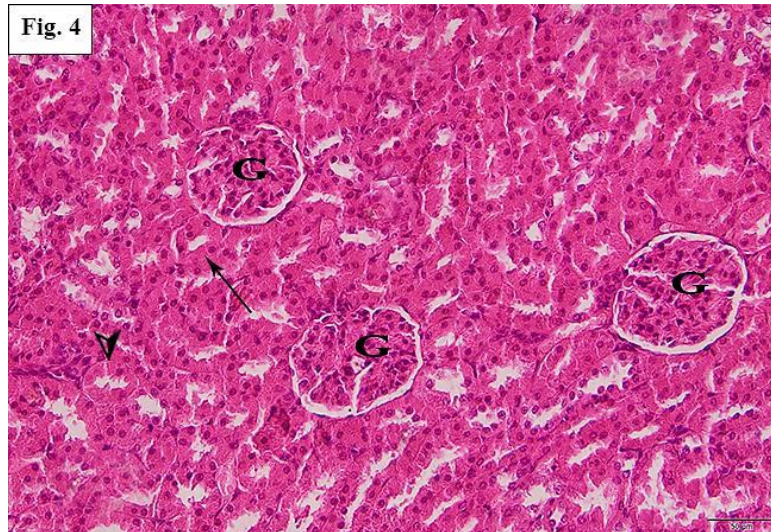


Fig. 4: A photomicrograph of a kidney section of VEG-group rats displaying the renal cortex containing a number of healthy glomeruli (G), proximal (arrow head) and distal (arrow) convoluted tubules. (H&E, X 400)

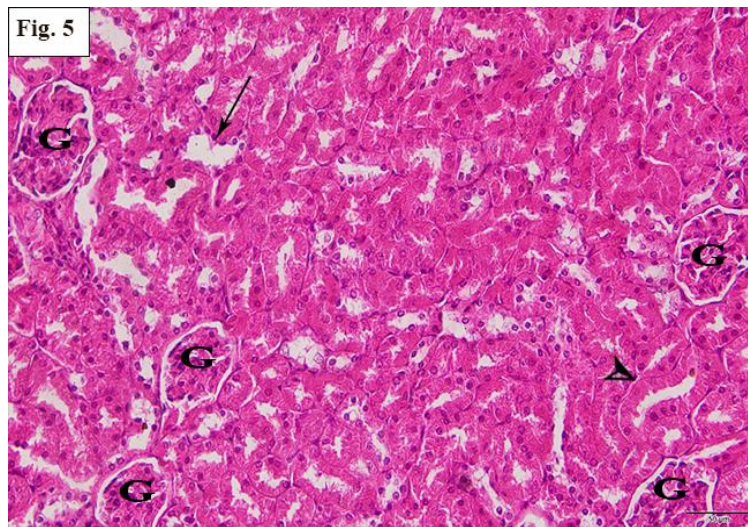


Fig. 5: A photomicrograph of a section of the renal cortex of the VEGC-group, showing healthful structure of the glomerulus (G), proximal (arrow head) and distal (arrow) convoluted tubules. (H&E, X 400)

This assumption gained support from the concept that the accumulated adipose tissue around the kidneys penetrates into the medullary sinuses, increases intra-renal pressures causing damage to the renal tissue. Damaged renal tissue acts as a source of reactive oxygen species (ROS) generation and develops lipid peroxidation. An increased lipid peroxidation in the kidney tissue is probably involved in the onset of kidney lesions in the rodent models of obesity (Muthulakshmi and Saravanan, 2013).

Again, the examination of kidney sections of treated HFD-fed rats with curcumin showed that supplementation with curcumin resulted in a good protection to the renal architecture. Curcumin exerted anti-inflammatory effects; the renal cortex of HFDC-kidney revealed general normal structure of the most renal corpuscles and tubules comparing with those of the HFD-group. The renal tubules retained their normal appearance as the proximal convoluted tubules were lined by a single layer of cubical cells with a well-developed brush border. Also, the lumens of distal convoluted tubules were clearly defined. In addition, the renal corpuscles appeared with almost normal shape as it was formed of a central tuft of capillaries surrounded by Bowman's capsules. These observations are in a harmony with Ye et al. (2021) who demonstrated that visible pathological changes which showed significantly higher amorphous pink eosin staining in the Bowman's capsules indicating increased hyalinization and higher hematoxylin blue staining indicating pronounced infiltration of lymphocytes in the HFD-fed in comparison to the LFD-fed mice, which was significantly reduced in curcumin-treated HFD-fed mice.

Conclusion

Thanks to curcumin extract that is able to present protective activity against obesity and obesity-induced renal pathology. Therefore, we can recommend that it is better to add curcumin to the daily nutritional content to prevent obesity and its associated health problems.

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