Potential protective effect of curcumin in high-fat diet-induced nonalcoholic fatty liver disease in rats

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Background and aim
Nonalcoholic fatty liver disease (NAFLD) is a global health problem. There is yet no effective therapy for NAFLD. This study investigated the effects of curcumin, the active ingredient of turmeric (a spice), in the prevention of high-fat diet (HFD)-induced NAFLD model in rats.

Materials and methods
NAFLD was induced by feeding rats with HFD composed of standard rat chow supplemented with 2% cholesterol and 10% lard. Rats were allocated into three groups and treated once daily for 16 weeks a follows: The normal control group was fed standard chow diet and received the vehicle; HFD fed rat (HFD-FR) control group (model group of NAFLD) and HFD-FR group were medicated with curcumin (60 mg/kg).

Results
Development of NAFLD was demonstrated by necroinflammatory injury in the liver tissue, elevation in the level of the liver enzyme alanine aminotransferase together with increased liver index. Meanwhile, fatty liver was associated with body weight gain, visceral obesity, disturbances of oxidative stress parameters (malondialdehyde and glutathione peroxidase) and increased levels of the inflammatory parameters (tumor necrosis factor-α, C-reactive protein) alongside with decreased level of the anti-inflammatory, antiobesity, insulin-sensitizing and antilipogenic, adiponectin. Treatment with curcumin significantly attenuated the development of these cardinal features of NAFLD.

Conclusion
Curcumin exhibited a kind of protection against HFD-induced NAFLD in rats. The protective effect relies at least in part on its antiobesity, antioxidant, and anti-inflammatory effects. Confirmation of the present findings warrants further animal and human studies.

Keywords:
Nonalcoholic fatty liver disease, curcumin, adiponectin, tumor necrosis factor alpha, histopathology

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide [1]. It may progress from simple steatosis to nonalcoholic steatohepatitis, fibrosis and cirrhosis [2], and specific pharmacological treatment is so far lacking [3] and hence, optimizing new therapeutic strategies that could effectively and safely control the disease remains an important medical challenge.

Curcumin the bioactive phenolic component of spice turmeric has recently established to exert surprisingly activities including antioxidant, anti-inflammatory, antiproliferative, insulin sensitizing, hepatoprotective, and cardioprotective properties with excellent safety profile [4]. As such curcumin might hold promise in the treatment of NAFLD. Indeed, the available data in the literature regarding the efficacy of curcumin in NAFLD are scanty and contradictory [5].

This study was conducted to evaluate the protective effect of curcumin and its possible mechanism (s) of action in a high-fat diet-fed rat (HFD-FR) model of NAFLD. The effects of curcumin on body weight gain and both liver and visceral fat indices were determined. Its influence on alanine aminotransferase (ALT) activity and histopathological features of hepatic tissues were investigated. In addition, the effects on oxidative stress [malondialdehyde (MDA), glutathione peroxidase (GPx)] and inflammatory parameters [tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and adiponectin] were assessed. To the best of our knowledge, the interrelationship between the effectiveness of

curcumin in HFD-induced NAFLD and these parameters has not been evaluated simultaneously thus far.

Materials and Methods

Drugs and chemicals

Curcumin was provided as powder from Columbus Chemical Industries Inc. (Columbus Chemical Industries, Columbus, Ohio, United States of America) and was freshly prepared as suspension in 2% aqueous solution of carboxymethyl cellulose (CMC). All other chemicals and solvents were of highest grade obtained from commercial sources.

Animals used and induction of NAFLD

Adult male albino Wistar rats were purchased from the animal house of Faculty of Medicine, Assiut University. They were allowed free access to tap water and standard laboratory chow and left to acclimatize for 1 week before the start of the experiments under standard laboratory conditions of normal light–dark cycle and temperature. All experimental procedures were approved by the Animal Care and Use Committee of the Faculty of Medicine, Assiut University (17100982) and coincide with international guidelines.

A HFD model was followed for induction of NAFLD in rats. It implies feeding rats with HFD consisting of standard chow diet supplemented with 10% lard and 2% cholesterol for consecutive 16 weeks [6].

Experimental design

Rats were randomly assigned into three groups of 12 animals each. Rats of all groups were individually weighed at the start of experiments and once weekly to adjust the doses. They received the following treatments once daily orally by gavage for 16 consecutive weeks. Group I, the normal control group were fed the standard chaw diet and received 2 ml CMC. Group II, the positive control group was fed HFD and received 2 ml CMC. Group III, HFD-FR treated with curcumin in a dose of 60 mg/kg [7].

At the end of the experimental period, animals were individually weighed and the weight gain was determined (final body weight – initial body weight). Rats were deprived of food for 12 h, anesthetized with diethyl ether, sacrificed, and the blood samples were withdrawn from the abdominal aorta and centrifuged (5000 rpm for 10 min). Sera were separated and stored at –20°C till used for estimation of ALT, CRP, and adiponectin.

ALT activity was measured spectrophotometrically using commercially available kits (Randox Laboratories, UK, [Crumlin, Northern Ireland, United Kingdom]), adiponectin by Elisa kit, and CRP by latex kits.

Visceral fat and liver were dissected, rinsed with saline, and weighed. Both visceral fat and liver indices were calculated according to the following equation:

Organ weight (g)/body weight (g)×100 [8].

Specimen from each liver was separately weighed and homogenates in ice-cold potassium phosphate buffer (pH 7.4). The homogenates were centrifuged at 10 000 rpm for 10 min. The supernatant was used immediately for determination of the content of lipid peroxidation end product MDA by the reaction with thiobarbituric acid [9], GPx using kinetic GPx activity kits [10], and TNF-α by Elisa kit [11].

Histopathological examination of hepatic tissue

Samples from the liver tissue were fixed in 10% formalin solution and embedded in paraffin. Sections (5 μm thick) were taken, stained with hematoxylin and eosin stain, and examined under light microscope in a blind manner. The severity of liver steatosis, inflammation, and hepatocyte ballooning were assessed according to the NAFLD activity score (NAS) system [12] as follows: Steatosis (0: <5%, 1: 5–33%, 2: 33–66%, 3: >66%). Inflammation (0: none, 1: <2 foci per 100 × field, 2: 2–4 foci per 100 × field, 3: >4 foci per 100 × field). Hepatocyte ballooning (0: none, 1: few mild, 2: many moderate marked).

Results

Effects on body weight gain, visceral fat and liver indices, and alanine aminotransferase activity

There was significant increase in body weight gain, visceral fat index, liver index, and ALT activity in the HFD-FR group model of NAFLD compared with the normal control group. The HFD-FR group treated with curcumin showed significant decrease in the levels of above-mentioned parameters compared with the HFD-FR control group (Table 1).

Effects on hepatic levels of oxidative stress parameters

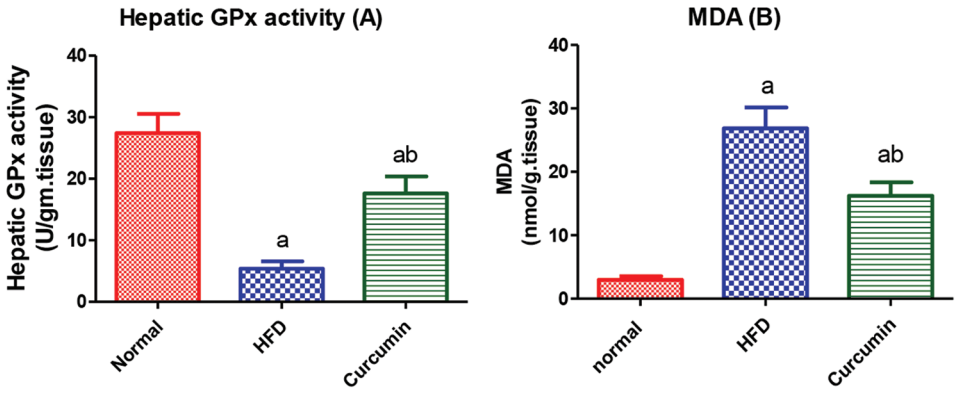
Feeding rats with HFD produced significant increase in hepatic levels of MDA alongside with significant reduction in GPx activity compared with the normal control group. These disturbances in the tested parameters were significantly corrected in HFD-FR treated with curcumin (Fig. 1a and b).

Table 1 Effects of curcumin administration on body weight gain, visceral fat index and liver index, and alanine aminotransferase activity

Groups	Body weight gain (g)	Visceral fat index (%)	Liver index (%)	ALT (IU/l)
Group I: normal (control)	140.7±13.23	1.400±0.134	1.875±0.084	5.89±1.317
Group II: HFD-FR control	361.8±10.78[a]	5.386±0.39[a]	3.125±0.08[a]	52.60±4.15[a]
Groups III: HFD-FR+curcumin (60 mg/kg/day) (treated)	290.3±10.46[a,b]	3.729±0.28[a,b]	2.54±0.059[a,b]	25.96±2.9[a,b]

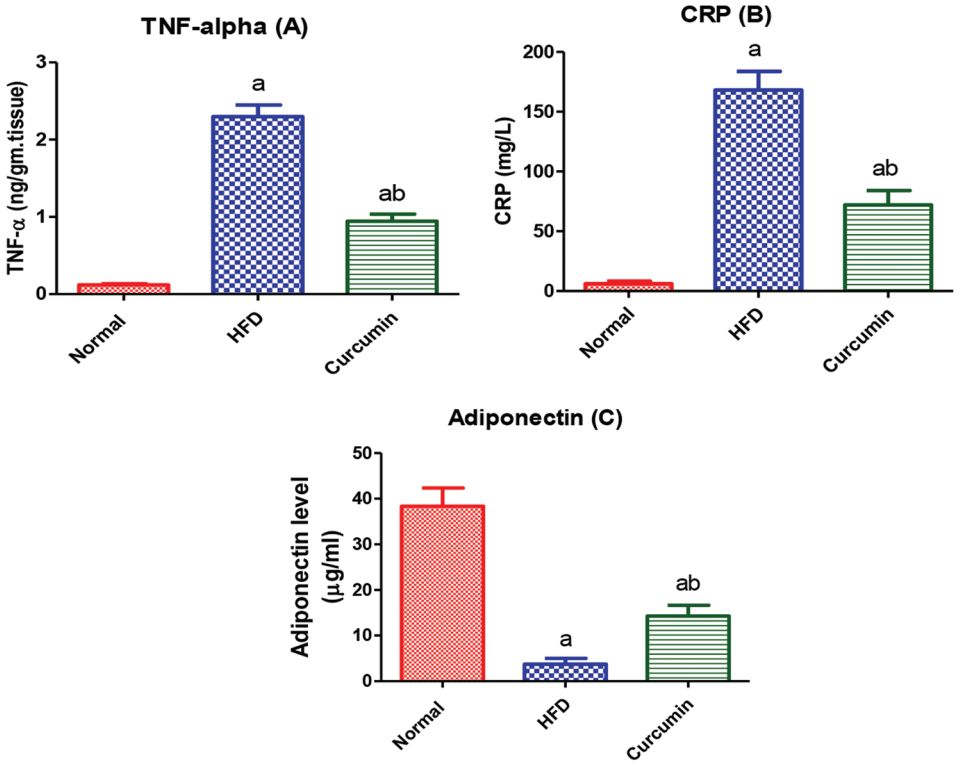
Data represent the mean±SEM (n=8–10).ALT, alanine aminotransferase; HFD-FR, high-fat diet-fed rat.[a,b]Significant difference (at P<0.05) from normal control and high fat diet-fed rat group, respectively.

Figure 1



Effects on hepatic MDA and GPx levels. Data represent the mean ± SEM (N = 8–10). [a,b]Significant difference (at P < 0.05) from normal control and high-fat diet-fed rat group, respectively. GPx, glutathione peroxidase; MDA, malondialdehyde.

Figure 2

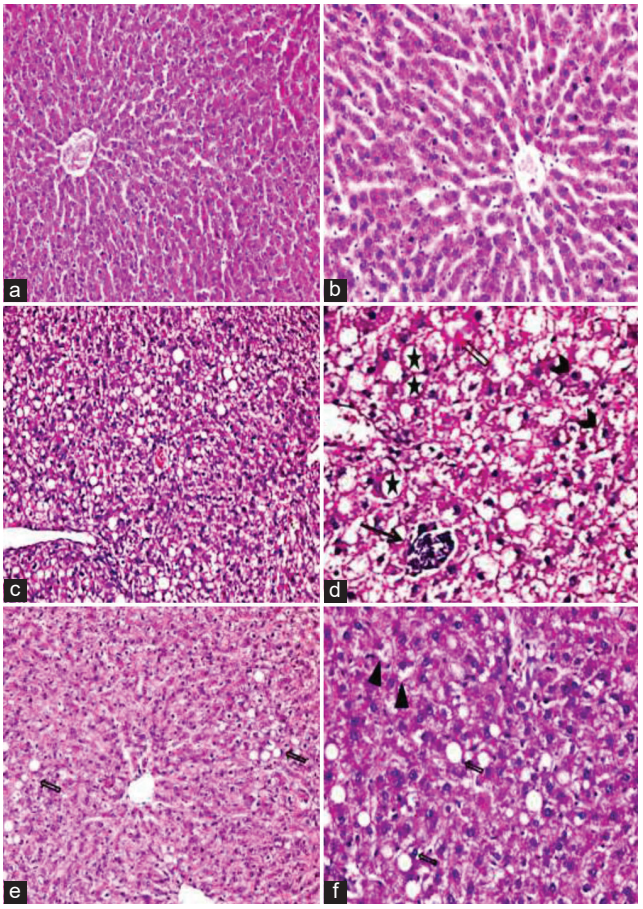


Effects on hepatic TNF-α (a) and serum levels of CRP (b) and adiponectin (c). Data represent the mean ± SEM (N = 8–10). [a, b]Significant difference (at P < 0.05) from normal control and high-fat diet-fed rat group, respectively. CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

Effects on inflammatory parameters

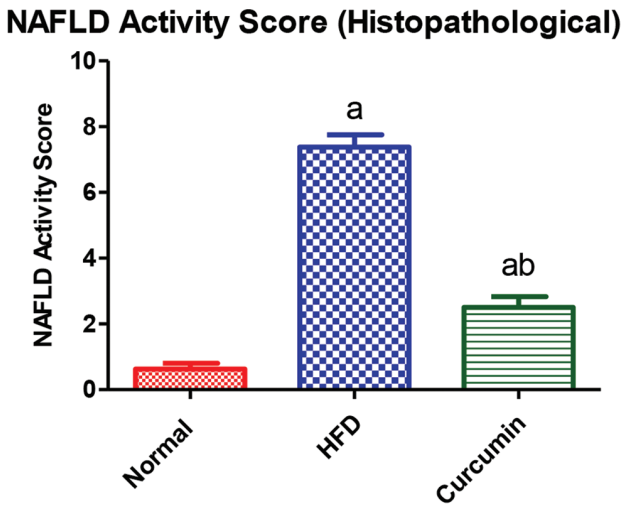
Induction of NAFLD was accompanied by elevation in hepatic level of proinflammatory cytokines, TNF-α, and serum levels of the inflammatory marker CRP concomitantly with decreased serum level of the anti-inflammatory, adiponectin compared with their

Figure 3



Photomicrographs of liver tissues: (a) H and E × 200 and (b) H and E stain × 400 normal control group with normal liver histology. (c) H and E × 200 and (d) H and E stain × 400 HFD-FR group showing macrovesicular steatosis with signet ring morphology (stars), ballooned hepatocytes (arrow heads), mallory hyaline bodies (outine arrow), and scattered necroinflammatory foci. (e) H and E × 200 and (f) H and E × 400 HFD-FR group treated with curcumin showing improvement in liver histology evident by a reduction of steatosis with few signet ring cells (outline arrow) and ballooned cells (arrow heads). H and E, hematoxylin and eosin; HFD-FR, high-fat diet-fed rat.

Figure 4



Effects on NAFLD activity score in liver specimens. Data represent the mean ± SEM (N = 8–10). [a, b]Significant difference (at $P < 0.05$) from normal control and high-fat diet-fed rat group, respectively. NAFLD, nonalcoholic fatty liver disease.

respective levels in normal control group (Fig. 2a–c). Treatment of the HFD-FR group with curcumin (60 mg/kg/day) caused significant decrease in TNF-α and CRP together with an increase in adiponectin levels compared with the HFD-FR group (Fig. 2a–c). Notably, the achieved levels of all the assessed parameters were still higher than those of the normal control group, following their treatment with curcumin.

Effects on liver histopathology

Photographs of rat liver tissues of the normal control group (Fig. 3a and b) showed normal lobular architecture; the hepatocytes radiated from the central vein. The HFD-FR control group showed marked steatosis in a diffuse manner all over the hepatocytes associated with focal necrosis and hepatocellular ballooning with massive cytoplasmic reticulum (Fig. 3c and d). These histopathological findings were of greater NAS grade (Fig. 4). These histopathological findings were obviously improved in the HFD-FR group treated with curcumin, which showed a marked reduction in steatosis of hepatocytes, few inflammatory cell infiltration, and traces of ballooned hepatocytes (Fig. 3e and f) with lower NAS grade (Fig. 4).

Discussion

In this study, feeding rats with HFD induced the main features of NAFLD. Rats showed visceral obesity and disturbances in the levels of the assessed oxidative stress and inflammatory parameters as compared with normal control rats. These alterations were associated with hepatic disorders as evidenced by the significant increase in liver index and liver enzyme ALT activity, indicating hepatocellular damage in agreement with de Castro *et al.* [13]. Development of steatohepatitis was confirmed by histopathological changes observed in liver sections in the form of marked steatosis, inflammation, and ballooned hepatocytes of higher NAS grade. Together, these abnormalities verified the successful induction of NAFLD which is in harmony with previous reports in animal models [14] and clinical situations [15] of NAFLD.

Mechanistically, obesity, oxidative stress, and inflammation are likely key factors in the progression of these abnormalities [16]. Thus overnutrition with fats favor accumulation of free fatty acids and triglycerides in visceral tissues, skeletal muscles, and liver with consequent development of obesity and IR [17]. Accumulated fats in the liver could undergo

oxidation releasing free radicals such as reactive oxygen species (ROS) [18]. ROS induces an increase in lipid peroxidation, by destroying unsaturated fatty acids in cell membrane and causes a decrease in endogenous antioxidants leading to liver tissue injury [19]. This agrees with the results of the current study which showed an increase in lipid peroxidation indicators MDA and the reduction in GPx activity in liver tissues of HFD-FR, substantiating the notion that increased oxidative stress plays a pivotal role in the pathogenesis of NAFLD [20].

Additionally, oxidative stress might release inflammatory mediators such as TNF-α that participate in the pathogenesis of NAFLD-associated liver injury. Increasing evidence indicate that inflammation represents a trigger for nonalcoholic steatohepatitis progression [21]. In the same line, present results showed that HFD-FR exhibited increased hepatic levels of TNF-α and the serum level of the inflammatory marker CRP together with decreased serum level of the anti-inflammatory adiponectin in consistence with the study of Hui *et al*. [22]. This imbalance in these inflammatory parameters could be assumed to be linked to the development of visceral obesity in HFD-FR as evidenced by increased weight gain and visceral fat index. This assumption gained support from the concept that adipose tissue particularly visceral fats, an endocrine tissue, produce adipokines including TNF-α, adiponectin, and others. These adipocytokines contributed to increased oxidative stress and proinflammatory state associated with NAFLD [23].

The data of the present study consistently with previous studies documented the crucial role of TNF-α in the pathogenesis of NAFLD [24]. Stimulation of nuclear factor κB (NF-κB), induction of hepatic stellate cell activation and liver fibrosis [16], antagonizing adiponectin secretion while stimulating CRP production [25] are among the previously postulated deleterious effects of TNF-α. Conversely, the reported anti-inflammatory mechanisms of adiponectin include suppression of NF-κB activation and macrophage functions [26], TNF-α antagonistic effect [27], and induction of the anti-inflammatory cytokines interleukin-10, interleukin-IRA [28].

In addition to its anti-inflammatory effects, the role of adiponectin in obesity and its complications has been established. In this respect, obesity was found to be associated with decline in the expression of adiponectin receptors (adip R1 and adip R2) that was improved by weight loss [29]. Substantiating our observation in the current study, reduced plasma levels of adiponectin have been noticed in obese individuals [30]. Adiponectin has been shown to have a broad range of other biological activities such as insulin sensitizing and antilipogenic effects [31].

This study demonstrated that administration of curcumin to HFD fed rats provided protection against hepatic disorders as indicated by the improvement in the activity of the liver enzyme ALT and confirmed by amelioration of severity grade of liver injury as well as by reduction in liver index. These results are in good concern with several studies in different animal models of NAFLD including HFD [32] and the available limited clinical trials [33]. Throughout these studies, curcumin improved liver histopathology, reduced oxidative stress, and ameliorated inflammation.

In the same direction, our results obtained in the present investigation indicated the attenuation of the assessed inflammatory parameters in HFD-FR treated with curcumin. This was deduced by a significant decline in the elevated levels of TNF-α and CRP and in contrary raising the reduced adiponectin level. The observed potential anti-inflammatory efficacy of curcumin is supported by previous numerous reviews [34]. Curcumin has been suggested to interrupt signal transduction between TNF-α and its receptors [35] and can modulate TNF-α expression [36]. Suppression of NF-κB in adipocytes via enhancement of adiponectin expression has been also postulated [37]. Interestingly, curcumin was found to dramatically increase the expression of adiponectin in animal models of IR [38].

It is likely to speculate that the observed positive effects of curcumin in the assessed inflammatory parameters in the present study particularly concur with the improvement of obesity as evidenced by decreased body weight gain and visceral fat index. These results are in accordance with those observed when curcumin was administered to obese individuals [39]. Curcumin supplementation showed an ability to inhibit angiogenesis of adipose tissues, decrease differentiation of preadipocytes, and reduce accumulation of lipids in adipocytes which all aid in lowering body weight [40]. As previously mentioned in this discussion, visceral fat is the main source of adipokines that constitute the major mediator in the inflammation process [23].

In this study it has been observed that the protective effect of curcumin was accompanied with abrogation of oxidative stress manifested by decreasing the elevated level of MDA alongside with increasing the activity of GPx. These results are in consistence with previously reported studies [41]. The accepted antioxidant mechanisms of curcumin include inhibition of ROS generation, scavenging of free radicals, and chelation of oxidative metals such as iron and copper [42].

Importantly, several investigators have advocated the correlation between oxidative stress and inflammation, one of each can easily be induced by other in a vicious cycle [43]. Considering this view, it is likely conceivable to speculate that the demonstrated beneficial effects of curcumin in the present study could be at least in part be possibly mechanistically relevant to the coexisting antioxidant and anti-inflammatory effects.

Conclusion

In conclusion, the present study showed that HFD-induced NAFLD was associated with hepatic disorders, visceral obesity, and disturbances of the assessed inflammatory and oxidative stress parameters. Administration of curcumin ameliorated the development of these abnormalities. The protective effect of curcumin relies at least in part on its anti-inflammatory and antioxidant effects as well as on the improvement of obesity. Further large-scale animal and human studies are required to confirm the present findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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