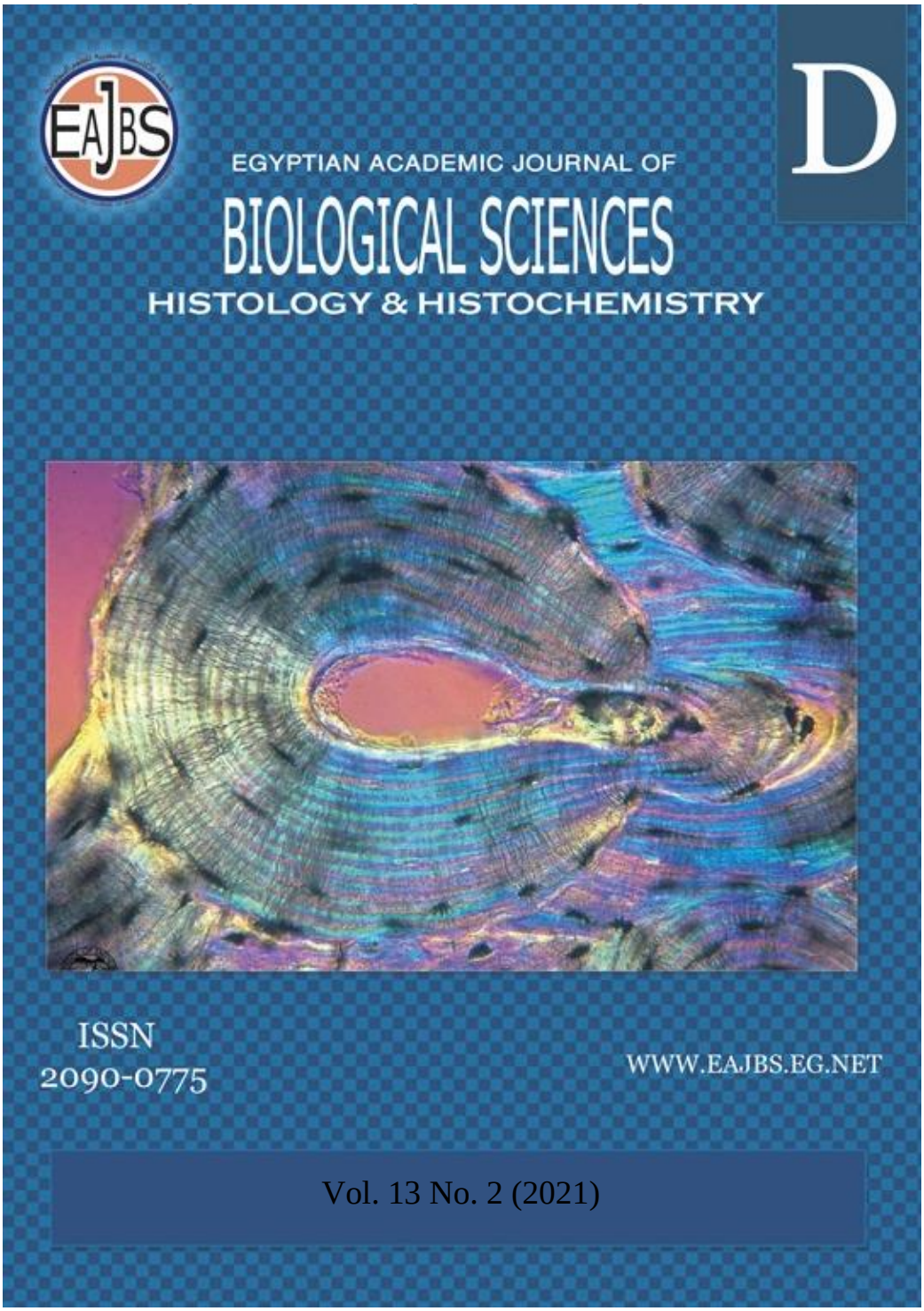

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Effect of Dietary Enrichment with Curcumin on Collagen and Glycogen in Some Organs of The Obese Adult Male Albino Rat

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ABSTRACT

Background: Obesity is an important health concern facing our world for a while. Curcumin is a yellow substance produced by curcuma plant, with antioxidant, anti-inflammatory and insulin-like actions in animals. It showed very promising results in the control of rheumatoid arthritis more than the non-steroidal anti-inflammatory drugs which may give new hope.

Aim of the work: Herbal medicine has been proved to be effective in the reduction of comorbidity of some diseases. Based on the previous reports; liver, lung and heart were selected to be studied in this article to investigate the effect of obesity on these vital organs and the possible protective role of curcumin**.**

Material and Methods: Eighteen rats were equally divided into control, obese and curcumin-treated groups. The control rats received a standard diet, the obese group received a high-fat diet, the curcumin group was fed a fatty diet mixed with curcumin. After 8 weeks, all rats were anaesthetized, liver, heart and lung were dissected. The specimens were processed for paraffin sections. The slides were stained with hematoxylin-eosin (HE), Masson's trichrome and periodic acid schiff stains. Oxidative marker; malondialdehyde (MDA) was measured in the tissues of the liver, lung and heart.

Results: The liver in obese rats showed degenerated cells, increased collagen and glycogen percent. However, the curcumin-treated group showed less fibrosis and glycogen deposition. The lung sections showed fibrosis and increased mucin in obese rats but the curcumin-treated group exhibited less fibrosis and secretions. In contrast to the previous organs, the heart showed less glycogen content in obese rats, this decline was improved in the curcumin-treated group.

Conclusion: the current study highlighted the structural changes that could be induced in some organs by obesity and clarified the possible protective role of curcumin as one of the novel agents in herbal medicine.

INTRODUCTION

Obesity is an important health concern facing our world for a while (Jen *et al.,* 2010). It has been listed as a risk factor for diseases like asthma. It was reported that weight loss could reduce asthma complications (Yuliana *et al.,* 2011). However, obesity is also linked to additional health problems, like diabetes, fatty liver disease and dementia (Semenkovich, 2006).

Curcumin is a substance produced by curcuma plant. It is the basic curcuminoid in turmeric (Curcuma longa) (Manolova *et al.,*2014). Previous studies proved that curcumin can exert antioxidant, anti-inflammatory and insulin-like actions in animals (Jang *et al.,* 2008).

Interestingly, curcumin showed very promising results in the control of rheumatoid arthritis more than the non-steroidal anti-inflammatory drugs which may give a new hope (Shehzad and Lee, 2010). In addition, It was reported that curcumin inhibited myofibrilis degeneration and collagen fibers deposition in the heart and skeletal muscles in atorvastatin-treated rats (Elshama *et al.,*2016). Moreover, curcumin exhibited antifibrotic actions in the liver of carbon tetra chloride-treated rats (Zheng and Chen,2006).

Curcumin has a poor bioavailability in vivo, which may interfere with its use as a therapeutic agent in certain conditions (Ireson *et al.,* 2002). It is metabolized and excreted by the liver in a short time (Jurenka, 2009).

Herbal medicine has been proved to be effective in the reduction of co-morbidity of some diseases. Based on the previous reports; liver, lung and heart were selected to be studied in this article to investigate the effect of obesity on these vital organs and the possible protective role of curcumin.

MATERIALS AND METHODS

Experimental Animals & Design:

After approval of preliminary protocol from IRB, Faculty of Medicine, Mansoura University, adult male rats (≈ 4months old and 300gm weight) were bought from AL-Nile Experimental Animal Center, Mansoura, Egypt. Animals were maintained in a well-aerated area provided with light-dark cycle and thermal regulation systems. The animals were supplied with fresh food and water ad libitum daily. All animals were supervised daily for any sign of infection.

The 18 rats were equally divided into control, obese and curcumin-treated groups. The control rats received a standard diet; 18% protein, 7% fat, 70% carbohydrates and 2% vitamins and minerals for eight weeks.

To induce obesity, a high-fat diet was prepared; 30% fat (animal source), 18% protein, 50% carbohydrates, 2% vitamins and minerals for eight weeks (Alturnkaynak, 2005).

To determine the achievement of obesity, Lee obesity index method was used by measuring rats' body weight and naso-anal length (Bellinger LL, Bernardis, 1999).

The curcumin group was fed a high-fat diet and 1.5% curcumin 95% (Monsley *et al.,* 2015), for eight weeks. The high percent of curcumin to overcome its low oral bioavailability **(**Prasad *et al*., 2014). Curcumin was obtained in powder form from Sigma Aldrich Company, USA.

Histological Analysis:

After 8 weeks, all rats were anaesthetized with Ketamine (60 mg/kg /intraperitoneal injection), the liver, heart and lung were dissected. The specimens were processed for paraffin sections. The slides were stained with hematoxylin-eosin (HE) as a routine, Masson's trichrome (to detect collagen fibers) (Chen *et al.*, 2017) and periodic acid schief (PAS) stains to detect glycogen (polyscharides) (Hui *et al.*,2017). Oxidative marker; malondialdehyde (MDA) as a lipid peroxidation marker was measured in the tissues of liver, lung and heart using a kit (Biovision, cat. K739-100, USA).

Quantitative Analysis:

Histomorphometry of blue-stained collagen fibers in Masson's sections and PAS-positive cells were determined using 40 × magnification through Image J analysis software. It was reported as the area covered by staining, compared to the total area of the tissue in the image (Zhang *et al.*, 2015). Statistical analysis was carried out by SPSS program version 22. The data obtained were subjected to statistical analysis using One way ANOVA and post-hoc Tukey for independent variables. $P<0.05$ was accepted as a significant difference.

RESULTS

Histological Results:

I-Liver:

H&E-stained control liver slides showed classical hepatic lobules with anastomosing cords of hepatocytes around the central vein. The blood sinusoids were lined by von-kupffer cells between hepatocytes (Fig.1A).

In the obese group, the portal vein was congested. Hepatocytes showed vacuolated cytoplasm with pyknotic nuclei (Fig.1B). The curcumin-treated group showed less congested central vein (Fig.1C). Masson's Trichrome stained slides exhibited slight collagen fibers between hepatocytes in control rats, obese rats showed higher collagen fibers around blood vessels, while the curcumin-treated group exhibited less percent of fibers when compared with the obese group (Fig.3A, B, C), Table.2, Histogram 1.

PAS slides showed positive granules in the hepatocyte cytoplasm of the control group. Obese rats exhibited increased PAS staining in the hepatocyte. Curcumin group showed a reduction in the percent of glycogen granules in comparison to obese rats (Fig.3D, E, F), Table.3, Histogram 2.

II-Lung

H&E-stained control sections showed a spongy structure with normal clear alveoli (Fig.2A). Obese rat's lungs showed congested blood vessels and collapsed alveoli (Fig.2B). Masson trichrome stain showed classic deposition of collagen fibers in the bronchial wall and inter-alveolar septa in control sections (Fig.4A). Obese rat sections showed a higher percent of collagen fibers (Fig.4B), while the curcumin treated group exhibited less percent of fibers when compared with the obese group (Fig.4.C), Table.2, Histogram 1.

In PAS sections, obese rats expressed a significant increase in mucin (Fig.4E), while the curcumin-treated group expressed a significant reduction in mucin when compared to the control group (Fig.4F), Table.3, Histogram 2.

III-Heart:

H&E-stained sections in obese rats showed distorted muscle fibers with deeply stained nuclei and thickened blood vessels that contained haemolysed blood cells (Fig. 2B). Highly deposited collagen bundles were observed in

the obese rat cardiac tissue especially around vessels (Fig.5B). Somewhat normal deposition of collagen fibers in the cardiac muscle of curcumin-treated rats was observed (Fig.5C), Table.2, Histogram 1. In contrast to liver sections, cardiac glycogen was significantly decreased in obese rats (Fig.5E). Curcumin treatment improved glycogen distribution in cardiac tissue (Fig.5F), Table.3, Histogram 2.

Oxidative Marker:

The (MDA) is significantly increased in the liver, lung and heart of obese rats when compared to the control group, while it reports a significant reduction in the same organs of the curcumin treated groups when compared to the obese rats (Table.1).

Table 1. MDA values are listed as mean ± Standard erro.

MDA (nmol/gm)	*Control*	*Obese*	*Curcumin*
Liver	45.5±7.93	70.2±12.4^{w}	50± 10^{y}
Lung	39.8±6.1	81±20.3^{w}	44.1± 9.7^{y}
Heart	32.29±5.53	90±23.8^{w}	38.2± 11.6^{y}

w : p<0.001 compared to control, ^{y}: P<0.001 compared to obese group.

Morphometric Result:

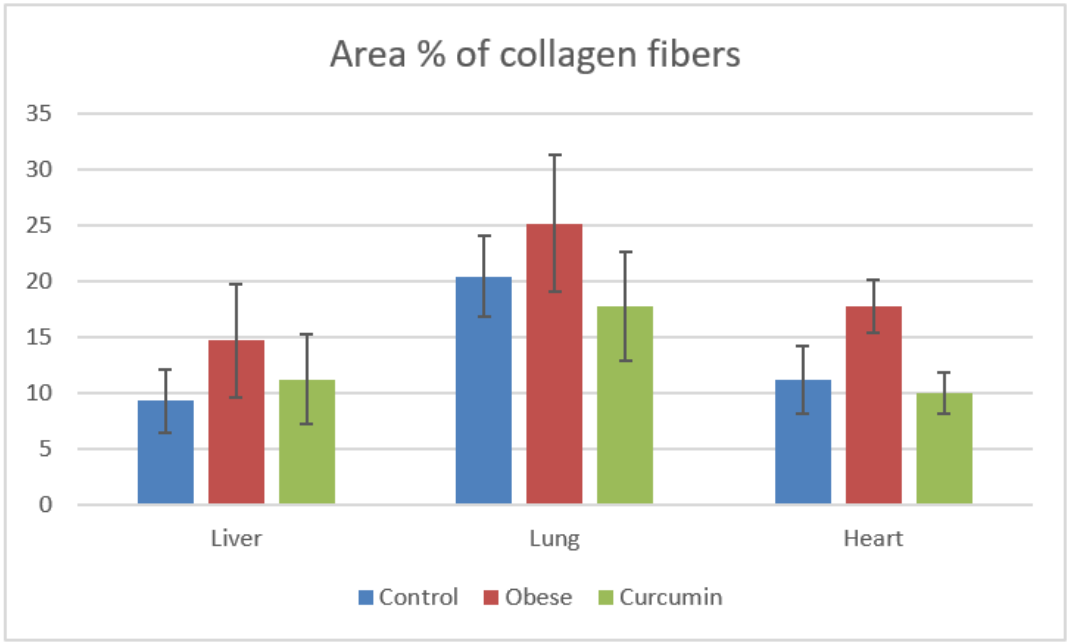
1.Area % of Collagen Fibers:

The area % of the collagen fibers is significantly higher in the liver, lung and heart of obese rats when compared to the control group, while it shows significant reduction in the same organs of the curcumin treated groups when compared to obese rats (Table.2, Histogram .1).

Table 2. Area% of collgen fibers, results are listed as mean ± Standard error.

Organs	Control	Obese	Curcumin
Liver	9.3±2.76	20.45±5.1^{w}	12.8±4^{y}
Lung	14.7±3.6	25.2±6.1^{w}	16.9±4.9^{y}
Heart	11.2±3%	17.8±2.4^{w}	10±1.9^{y}

w: p<0.001 compared to control, ^{y}: P<0.001 compared to obese group.



Histogram 1. Area% of collagen fibers in control, obese and curcumin-treated groups.

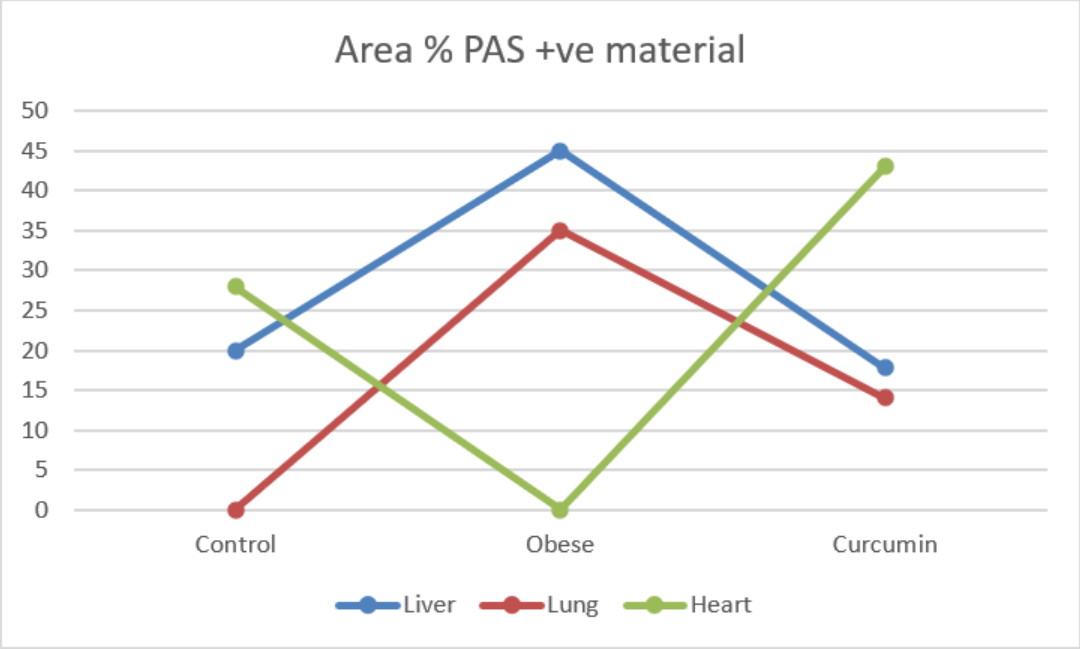
2.Area % of PAS +ve Material:

The area % of the PAS+ve area is significantly higher in the liver and lung of obese rats when compared to the control group, while it shows significant reduction in the same organs of the curcumin treated groups when compared to obese rats. In contrast, the heart shows absence of PAS +ve material in the obese rats and significant increase in the curcumin treated rats (Table.3, Histogram .2).

Table 3. Area% of PAS+ve area, results are listed as mean ± Standard error.

Organs	Control	Obese	Curcumin
Liver	20±3.7	45±4.5 ^{w}	17.8±5.8 ^{y}
Lung	0.00±0.00	35±14.2 ^{w}	14±4.1 ^{y}
Heart	28±2.48	0.00±0.00 ^{w}	43±12.3 ^{y}

^{w} : p<0.001 compared to control, ^{y}: P<0.001 compared to obese group.



Histogram 2. Area% of PAS +ve area in control, obese and curcumin treated groups.

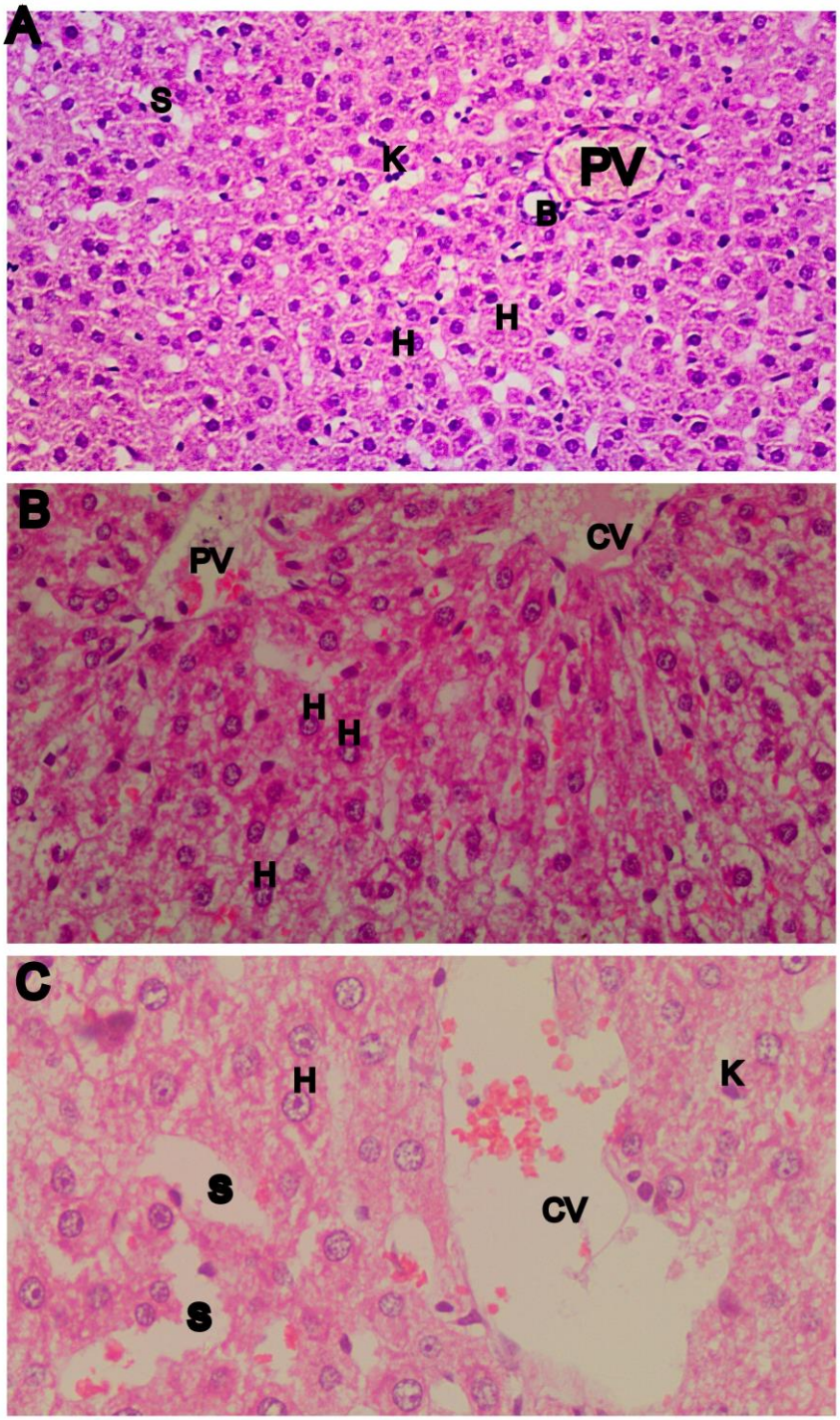


Fig1. The section in the control liver showing hepatocytes cords (H), surrounding the portal vein (PV), bile duct branch (B), sinusoid (s), Von Kupffer cells (K). **B.** Obese liver shows congested central vein (CN), congested portal vein (PV), vacuolated hepatocytes with pyknotic nuclei (H). **C.** Curcumin-treated liver shows less congested central vein (CN), hepatocytes(H), Von Kupffer cells (K), sinusoids (s) *(H&E X 400).*

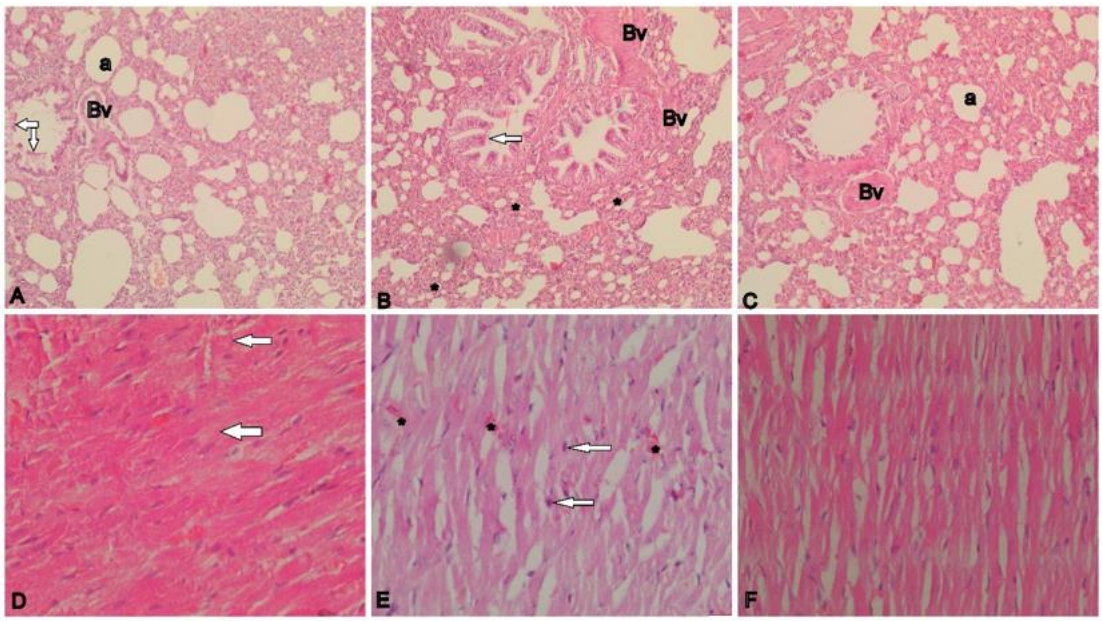


Fig.2. A. Control lung showing normal alveoli (a), bronchi with cilli (arrow), normal blood vessel (BV).**B.** Obese lung shows some collapsed alveoli (*), congested vessels(BV), Lost cilia in bronchial lumen (arrow).**C.** Curcumin treated lung with normal alveoli (a) and blood vessels (BV). **D.** Control cardiac tissues showing normal muscle fibers, intercalated discs (arrows). **E.** Obese cardiac tissue reveals distorted muscle fibers, pyknotic nuclei (arrows), hemolysed blood (*). **F**. Curcumin-treated cardiac tissue shows somewhat normal nuclei and fibers. *(H&E X 400).*

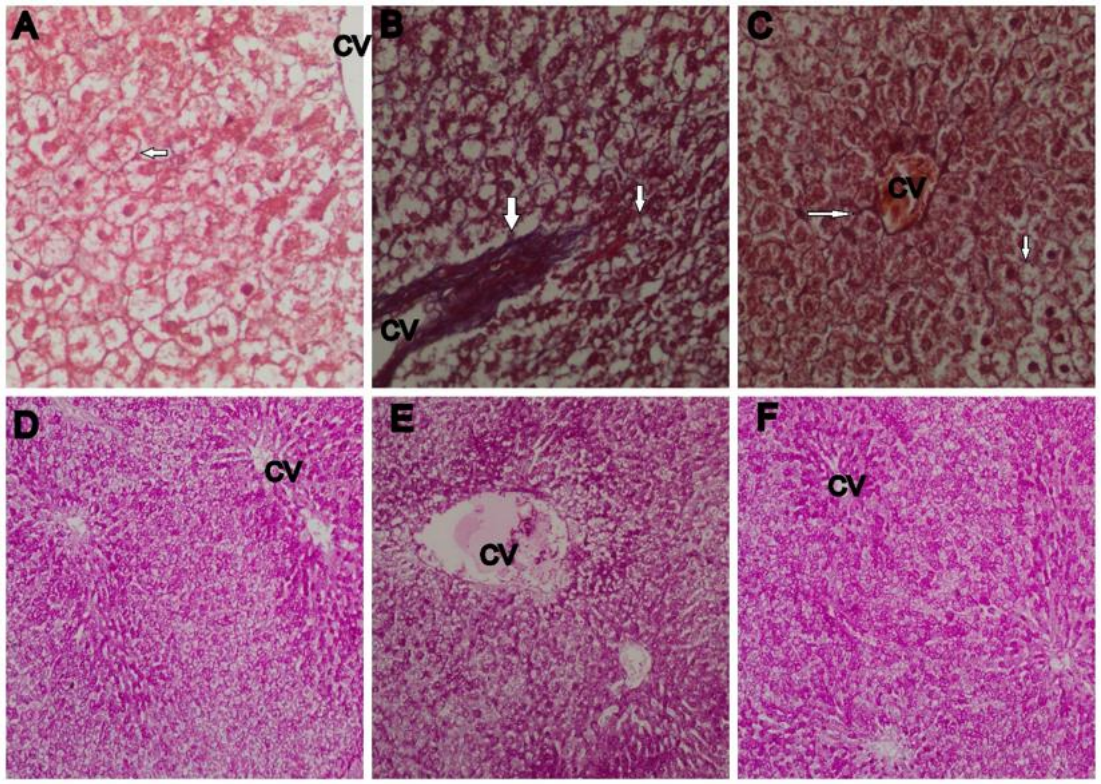


Fig.3. A. Control liver shows slight collagen fibers between hepatocytes (arrow) **B.** Obese rats showed higher collagen fibers around the central vein (arrows), **C**. Curcumin treated group shows less percent of fibers (arrows). *(Masson TrichromeX400).***D.** Control liver shows moderate stain PAS +ve stained material (arrows) **E**. Obese rat liver section shows intense +ve PAS stained material (arrows) **F**. Curcumin treated liver shows moderate stain PAS +ve stained material (arrows). *(PAS X 400).*

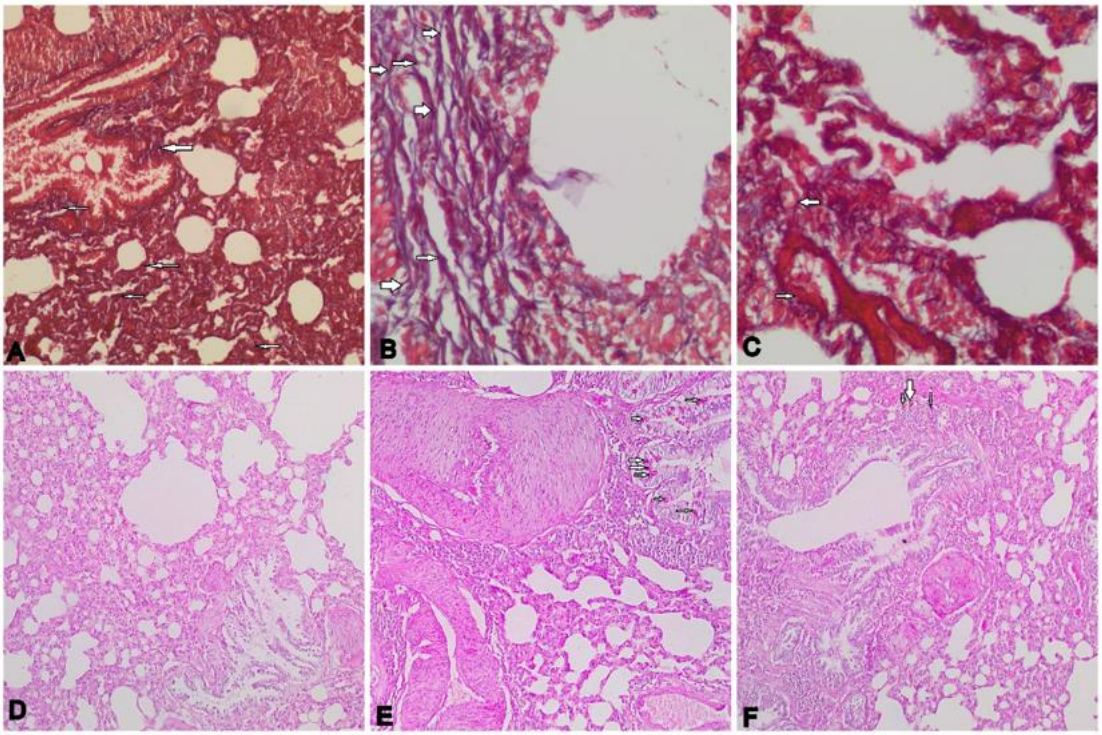


Fig.4. A. Control lung shows collagen fibers in the bronchial wall and inter-alveolar septa (arrows). **B**. Obese rat sections show a higher percentage of collagen fibers (arrows), **C.** Curcumin treated group exhibits less percent of fibers (arrows) *(Masson TrichromeX400).***D.** Control lung shows –ve PAS stain **E.** Obese lung sections show intense +ve PAS stain (arrows)**. F.** Curcumin treated group shows less +ve PAS stain (arrows). *(PAS X400).*

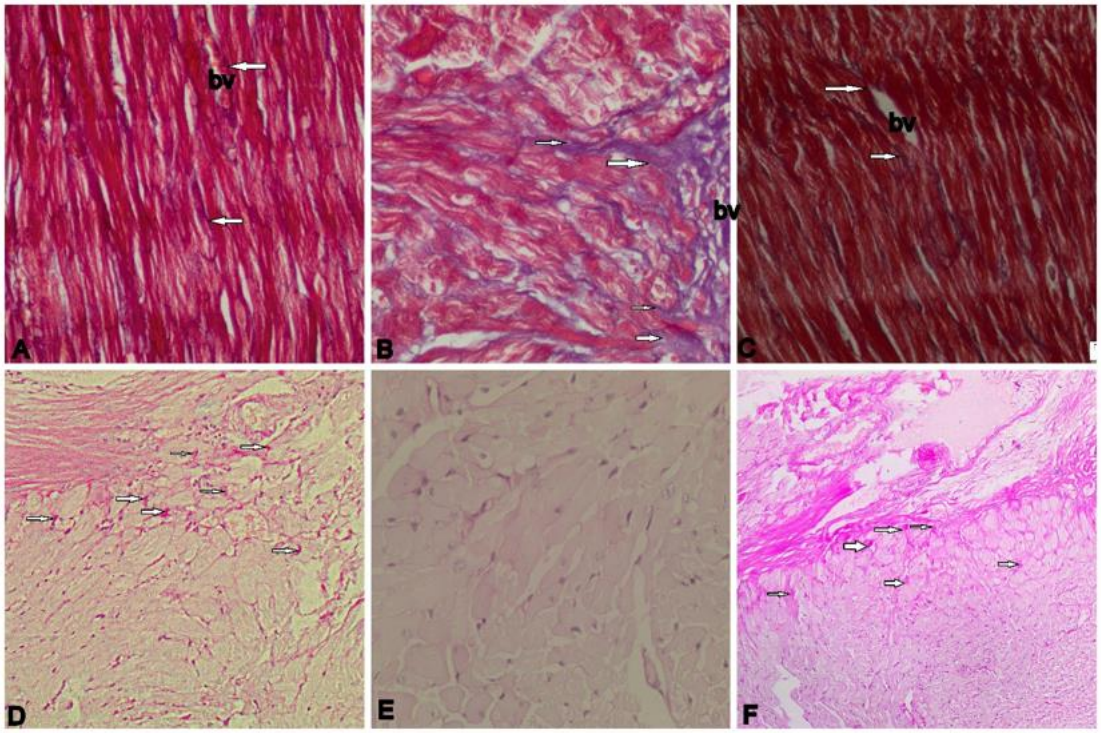


Fig.5. A. Control heart shows collagen fibers between muscle fibers and vessels (bv) (arrows). **B.** Obese rat sections show a higher percentage of collagen fibers around vessels (bv) (arrows). **C.** Curcumin treated group exhibits less percent of fibers (arrows) *(Masson TrichromeX400).* **D.** Control heart shows +ve PAS stain (arrows) **E.** Obese heart sections -ve PAS stain. **F.** Curcumin treated group shows +ve PAS stain (arrows). *(PAS X400).*

DISCUSSION

Obesity is a metabolic disorder, linked to other complications like coronary heart disease (Abu-Abid *et al.,* 2002), sleep apnea, stroke, cystic and hepatic disease, and impaired wound healing (Pi-Sunyer, 2002). Previous reports have concluded that regular use of herbs may prevent some chronic diseases (Hung *et al.*, 2006).

Lipid peroxidation is known as an obesity-induced pathology (Amirkhizi *et al.,* 2007). The current study revealed increased lipid peroxidation in the liver, lung and heart expressed by a high level of MDA. This increase was reversible after the utilization of curcumin on a regular regimen.

In addition, the current study revealed structural changes in some organs of obese rats. The liver in obese rats showed degenerated hepatocytes, increased fibrosis, and glycogen store in the cells. In line with our finding, It was reported that obesity could induce portal fibrosis, and hepatocellular ballooning, this was also induced by oxidative stress (Brent *et al.,* 2003). Also, obese mice showed a higher level of hepatic glycogen (Chen *et al.,*1993). One possible mechanism for obesity-induced collagen production was reported earlier by Friedman *et al.,* (1985), that hepatic lipocyte (fat cells) are the principal source of collagen fibers synthesis in normal and obese rats. In the case of obesity, the adipocytes become hypertrophied, with defective blood supply result in tissue hypoxia and cell death (Cinti *et al.,* 2005). The cellular debris attracts macrophages to the tissue which produces cytokines like IL-6 (Kim *et al.,* 2007). This causes the systemic inflammatory process and stimulates adipocyte to produce more collagen (Tilg and Moschen, 2008).

Interestingly, the curcumin-treated rats in our study showed a reduction in hepatic collagen and glycogen. A similar result was documented by Rajagopalan *et al.* (2010) who showed that curcumin analogue is an effective antifibrotic agent that caused a reduction of collagen deposition in the liver. In contrast to our finding, Bustanji *et al.* (2009) reported significant increased liver and muscle glycogen in curcumin-treated animals, but they used a different dose in mice (60mg/kg) which may explain the different result.

Regarding the lung, our results revealed Obese rat's lungs showed congested blood vessels and collapsed alveoli. Collagen fibers were distributed in the bronchial wall and inter-alveolar septa in control sections. Obese rat sections showed a higher percent of collagen fibers, while the curcumin-treated group exhibited less percent of fibers when compared with the obese group. This comes in line with the finding of Saraiva *et al.* (2011) who reported that mice obesity led to alveolar septa fibrosis and alveolar collapse. A possible mechanism for increased collagen expression is IL-4,5 stimulation in obesity (Wen *et al.,* 2003). Moreover, Ghobashy *et al.* (2010) reported that collagen fiber deposition may be reduced when inflammation subsides. In this study, the obese rat's lung showed increased mucin in the PAS-stained section. This finding could be explained according to the fact that inflammation of the mucosa is the cause of increased mucous production (Maestrelli *et al.,* 2001), this also might explain why curcumin-treated rats showed less mucus production by acting as an

anti-inflammatory agent in the lung tissue. Another possible mechanism is that curcumin could inhibit mucus production in the lung by activation of Nrf2 which stimulates antioxidant proteins (Lin *et al.,* 2018).

In the heart, we found distorted muscle fibers, deeply stained nuclei sections and deposited collagen bundles were observed in the obese rat cardiac tissue especially around blood vessels. Somewhat normal deposition of collagen fibers in the cardiac muscle of curcumin-treated rats was observed. In contrast to liver sections, cardiac glycogen was significantly decreased in obese rats. Curcumin treatment improved glycogen distribution in cardiac tissue.

Carroll *et al.* (2006) reported an insignificant increase in cardiac collagen in obese rats. However, rabbits that received a fatty diet for 12-weeks showed increased fibrosis in coronary arteries, and deposition of collagen in the cardiac tissue (Carroll and Tyagi, 2005). Also, Leopoldo *et al.* (2010) reported that obesity caused more collagen deposition in the heart. One mechanism for collagen deposition in heart of obese rats was reported by Brands *et al.* (1995) that it might be linked to insulin metabolism as insulin growth factor induces collagen expression. Pretreatment with curcumin in a dose of 75mg/kg/d for one week prior to aortic banding surgery attenuated cardiac hypertrophy and fibrosis in murine through blockage of collagen synthesis (Li *et al.,* 2008) In addition, cardiac glycogen was significantly decreased in obese rats. This finding suggests different regulations of glycogen accumulation in the heart and liver (Leopoldo *et al.,* 2010).

In conclusion, the current study highlighted the structural changes that could be induced in some organs by obesity and clarified the possible proactive role of curcumin as one of the novel agents in herbal medicine.

Ethical Approval

All applicable international, national, and institutional guidelines for the care and use of animals were followed. We respected the welfare of animals and excluded situations when animals were in pain.

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ARABIC SUMMARY

تأثير التعزيز الغذائي بالكركمين على الكولاجين والجليكوجين فى بعض أعضاء ذكر الفأر الابيض البالغ السمين

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ان الكركمين هو مادة كيمائية نباتية الاصل ينتمي لعائلة الزنجبيل. على الرغم من أن الكركمين له عدد من الأثار المفيدة، إلا أن التوافر الحيوي للكركمين يكون ضعيفًا في الجسم الحي، والذي قد يكون عقبة مهمة في استخدامه كأداة علاجية. كما يعتبر الكركمين نقطة انطلاق مثالية في البحوث الصيدلانية لاكتشاف أدوية جديدة. على الرغم من استخدام في الكركمين في بعض الحالات المرضية، فقد ثبت أن له تأثير مفيد كعامل مضاد للأكسدة ومضاد للالتهابات.

أثبت طب الأعشاب فعاليته في الحد من الأمراض المصاحبة لبعض الأمراض. بناء على التقارير السابقة. تم اختيار الكبد والرئة والقلب لدراستها في هذه الدراسة للتحقيق في تأثير السمنة على هذه الأعضاء الحيوية والدور الوقائي المحتمل للكركمين.

تم تقسيم ثمان عشرة من الفئران إلى مجموعات: مجموعة ضابطة ومجموعة سمينة ومجموعة معالجة، 6 جرذان لكل منهم. المجموعة السمينة حصلت على وجبة مرتفعه الدهون لمدة ثمان اسابيع. المجموعة المعالجة حصلت على وجبة عالية الدهون بالاضافة الى الكركمين. بعد ثمان اسابيع تم تخدير الفئران من كل مجموعة، أستخرجت عينات من الكبد والرئة والقلب وتم صبغها بالصبغات الروتينية والمناسبة للكولاجين والجليكوجين

أظهرت النتائج ان السمنة أدت لوجود تغيرات فى أنسجة الكبد والرئة والقلب، كما أدت الى زيادة ألياف الكولاجين فى هذه الاعضاء وكذلك زادت نشبه الجليكوجين فى الكبد والرئة بعكس القلب. أظهر استخدام الكركمين تحسنا ملحوظا فى توزيع الياف الكولاجين وكذلك نسبة الجليكوجين فى الاعضاء المستخدمة.

سلطت الدراسة الحالية الضوء على التغييرات ا التي يمكن أن تحدث في بعض الأعضاء بسبب السمنة وأوضحت الدور الوقائي المحتمل للكركمين كأحد العوامل الجديدة في طب الأعشاب.

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