Effect of Curcumin on the Liver of Albino Rats in Experimental Obesity

El-Sayed Galal El-Sayed Khedr, Ahmad Mohmmad Abdel-Alem Desoky, Mohamed Yossry Ahmed Agwa

Histology Department, Faculty of Medicine, Al-Azhar University, Egypt
mohamedyossry532@gmail.com

Abstract: Background: Diets containing high amount of fats or cholesterol lead to both hyper-cholesterolemia and hyper-triglyceridemia which mostly induces oxidative stress is now believed to be an important factor in the development of nonalcoholic fatty liver disease. Nonalcoholic fatty liver diseases the most common liver disorder in the world which caused by obesity, its incidence reaches 70-90%. The disease is characterized by the accumulation of triacylglycerols inside liver cells and the condition can progress into more serious liver disease, such as non-alcoholic steato-hepatitis, liver fibrosis, cirrhosisand more rarely, liver carcinoma. Hypercholesterolemia is widely known as a dominant risk factor for the development of cardiovascular diseases, particularly coronary heart disease which is a leading cause of death in developing and developed countries. **Aim of the Work:** The aim of this study is to evaluate the hypolipidemic effect of curcumin extract (50 mg/kg/day) on the hepatic changes induced by obesity in albino rats that treated by intra-peritoneal injection of Triton (250 mg/kg) to induce obesity. **Materials and Methods:** This study was carried out at the Faculty of Veterinary Medicine, Alexandria University. 80 male albino rats weighing 120 ± 5 grams and aged 4-5 weeks were used throughout this study. The rats were housed in clean metallic cages with a metallic mish cover and dimension of 120 X 60X 60 cm. Each cage contained 10 rats. The animals were fed normal laboratory diet and with liberal supply of water. All animals were housed under the mentioned environmental condition and the basal diet for one week before experiment for acclimatization to ensure normal growth and behavior. Weight of animals was recorded every week. This study was carried out at the Faculty of Veterinary Medicine, Alexandria University. The experiment lasted for eight weeks. A total of 80 male albino rats (weighing 120 ± 5 gram body weights) were allocated in eight cages (10 rats/cage) and divided into four groups. Group I (Control group), group II (Obese group), group III (Curcumin group), group IV (Recovery group). **Results:** During period of triron WR 1339 injection rats were calm, easy to handle without injuries or deaths. Appetite was increased in obese group more than in control group, this indicated by increased amount of food needed for each group (about 20 grams/ rat/ day for obese group and 14 grrams/ rat/ day for control group). Appetite was lower in curcumin-treated group (about 13 grams/ rat/ day) than recovery group (about 17 grams/ rat/ day). The rats stool in curcumin group was greasy in comparison with recovery group. No changes occurred in the skin or hair. Obese group increased in weight by (up to 70 grams per week) while control group showd lower rate of weight gain (about 30 grams per week). At the end of the fourth week rats were weighed and we found a significant increase in body weight in obese group compared to control group. **Conclusion:** There are several stages of NAFLD natural history, ranging from simple steatosis to steatohepatitis (NASH), liver cirrhosis, and finally carcinoma of the liver. The first stage, which is steatosis, is characterized by the presence of lipid inclusion in the liver. In NASH, steatosis is accompanied by inflammatory cells, ballooning of the hepatocytes, and often elevation of liver enzymes. Fibrosis is present when cirrhosis develops and is due to liver cells death.

[El-Sayed Galal El-Sayed Khedr, Ahmad Mohmmad Abdel-Alem Desoky, Mohamed Yossry Ahmed Agwa. **Effect of Curcumin on the Liver of Albino Rats in Experimental Obesity.** *Nat Sci* 2018;16(10):82-88]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 12. doi:10.7537/marsnsj161018.12.

Keywords: Curcumin, Albino Rats, Experimental Obesity, Steatohepatitis

1. Introduction

Diets containing high amount of fats or cholesterol lead to both hyper-cholesterolemia and hyper-triglyceridemia which mostly induces oxidative stress is now believed to be an important factor in the development of nonalcoholic fatty liver disease [(1)].

Nonalcoholic fatty liver diseases the most common liver disorder in the world which caused by obesity, its incidence reaches 70-90% [(2)]. The disease is characterized by the accumulation of triacylglycerols inside liver cells and the condition can progress into more serious liver disease, such as non-alcoholic steato-hepatitis, liver fibrosis, cirrhosisand more rarely, liver carcinoma [(3)].

Hypercholesterolemia is widely known as a dominant risk factor for the development of cardiovascular diseases, particularly coronary heart disease which is a leading cause of death in developing and developed countries [(4)].

Today, oxidative stress is one of the major threats to our survival; it became the nutritional and medical buzzle for the 21St century [(5)].

Treatment of obesity needs diet control, exercise and using lipid-lowering compounds as fibrates, bile

acid sequestrates and statins. However, they have side effects and affect liver functions [6].

Nowadays, there is increased interest for using natural dietary products to manage obesity and related health problems due to their safety, efficacy and cost [7].

Therefore, search for natural compounds with lipid-lowering properties especially medicinal plants is warranted because of less toxicity, easy availability and easy absorption in the body that may be better treatment than currently used drugs. Plants that were once considered of no value are now being investigated, evaluated and developed in to drugs with no side effects [8].

One of these compounds is curcumin which is derived from the rhizomatous herb, turmeric (Curcuma longa), a member of the Zingiberaceae (ginger) family. Extensive scientific researches on curcuma have demonstrated a wide spectrum of therapeutic effects such as anti-inflammatory, antibacterial, antiviral, antifungal. It also has potent anti-oxidant, anti-carcinogenic and hypoglycemic properties [9].

Curcumin attenuates high fat diet-induced hepatic steatosis by regulating hepatic lipid metabolism via AMP-activated protein kinase activation, suggesting its use as a therapeutic for hepatic steatosis [10].

Curcumin at a dosage higher than 50 mg/kg/day can improve obesity-induced cardiac remodeling via anti-oxidative stress and anti-inflammatory mechanisms in mice [11].

Aim of the Work:

The aim of this study is to evaluate the hypolipidemic effect of curcumin extract (50 mg/kg/day) on the hepatic changes induced by obesity in albino rats that treated by intra-peritoneal injection of Triton (250 mg/kg) to induce obesity.

2. Material and Methods

This study was carried out at the Faculty of Veterinary Medicine, Alexandria University. 80 male albino rats weighing 120 ± 5 grams and aged 4-5 weeks were used throughout this study.

The rats were housed in clean metallic cages with a metallic mish cover and dimension of 120 X 60X 60 cm. Each cage contained 10 rats. The animals were fed normal laboratory diet and with liberal supply of water.

All animals were housed under the mentioned environmental condition and the basal diet for one week before experiment for acclimatization to ensure normal growth and behavior. Weight of animals was recorded every week.

Intra-peritoneal injection (IP) is the most frequently used parenteral route of administration in rats. The large surface area of the abdominal cavity and its abundant blood supply facilitate rapid absorption. Absorption from this route is usually one-half to one-quarter as rapid as that from the intravenous route.

Histological stains were purchased from El-gomhria company for chemicals, Mansoura, Egypt. They include Haematoxylin and eosin stain, PAS stain and Mallory trichrome stain.

Kits for liver function tests as (ALP, ALT, AST and GGT) were purchased from Vitro Scient Company.

This study was carried out at the Faculty of Veterinary Medicine, Alexandria University. The experiment lasted for eight weeks. A total of 80 male albino rats (weighing 120 ± 5 gram body weights) were allocated in eight cages (10 rats/cage) and divided into four groups (20 rats per each group) as the followings:

Group I (Control group): 20 rats will be fed normal laboratory diet for 4 weeks then sacrificed. This group was used as a negative control group.

Group II (Obese group): 20 rats will be treated by intra-peritoneal injection of Triton 250 mg/kg to induce obesity according to ***Walaa and Saad*** [12] and fed normal laboratory diet for 4 weeks then sacrificed. This group was used as a positive control group.

Group III (Curcumin group): 20 rats similar to the second group but treated with Curcumin 50 mg/kg/day according to ***Yuanyuan et al.*** [13] for another 4 weeks then sacrificed.

Group IV (Recovery group): 20 rats similar to the obese group but left without treatment for another 4 weeks (for spontaneous recovery) then sacrificed.

Rats of all groups were eviscerated after decapitated under di-ethyl ether anesthesia, liver was removed and washed by normal saline to remove the blood and then fixed in 10% formol saline.

After putting the tissues in the fixative (10% formol saline) for 24 hours, the fixed tissues is washed in running tap water to remove the fixative from them, dehydration was done gradually in ascending grades of alcohol by putting the tissues in 50% alcohol then in 70% alcohol and finally in 100% alcohol. Clearing of the tissues was done to remove alcohol and to allow the fixed tissues to be miscible with xylol.

Statistical analysis:

All analyses were run using SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) A probability value of 0.05 was considered significant.

3. Results

The results observed in Table (1) cleared that there is a significant increase in the body weight and

liver weight of rats in obese group when compared to the control one.

Table (1): Comparison between means, standard errors and P value of body weight and liver weight in varous groups.

Group	Body weight (grams)	Liver weight (grams)
Control	242 ± 04.37 [c]	04.54 ± 0.14 [d]
Obesity	358 ± 10.70 [a]	11.90 ± 0.21 [a]
Curcumin	260 ± 05.81 [c]	05.38 ± 0.22 [c]
Recovery	318 ± 08.15 [b]	07.04 ± 0.13 [b]

Means with different superscript differ significantly (P<0.05).

The results observed in (Table 2) cleared that there is a significant reduction of collagen area in recovery group compared to obese group but the decrease of collagen area was more in curcumin group than recovery group.

Table (2): Comparison between median, inter-quartile range and P value of collagen area and optical density of hepatocytes in varous groups.

Group	Collagen area %		Optical density (µm)	
	Median	IQR	Median	IQR
Control	1.802 [c]	2.726	0.241 [a]	0.057
Obesity	2.356 [a]	3.834	0.138 [d]	0.021
Curcumin	1.813 [c]	3.130	0.217 [a b]	0.052
Recovery	2.052 [b]	2.864	0.179 [c]	0.018

Groups with different superscript differ significantly (P<0.05). Analysis and comparisons based on non-parametric methods.

The results observed in table (3) and cleared that, there is a significant increase in liver enzymes (ALT, AST and GGT) in obese group when compared with control group.

Table (3): Comparison between means, standard errors and P value of liver enzymes in different groups.

Group	ALT (U/l)	AST (U/l)	GGT (U/l)
Control	19.96 ± 1.38 [c]	030.00 ± 1.23 [c]	05.85 ± 0.59 [c]
Obesity	84.76 ± 3.56 [a]	172.10 ± 9.22 [a]	25.60 ± 1.55 [a]
Curcumin	24.97 ± 1.52 [c]	042.90 ± 5.19 [c]	08.64 ± 0.47 [c]
Recovery	42.10 ± 2.55 [b]	072.70 ± 4.70 [b]	13.00 ± 0.70 [b]

Means with different superscript differ significantly (P<0.05); ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyl transferase

Histological Results

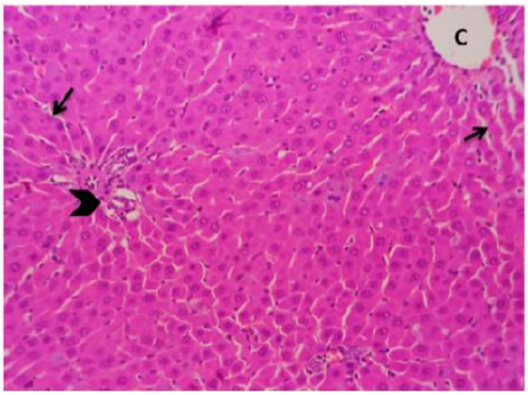

Figure (1): Photomicrograph of liver sections from control group showing. Normal liver architecture. A classic hepatic lobule containing central vein (c) and radiating cords of hepatocytes with blood sinusoids in between (arrow). Portal tract at the periphery of a classic hepatic lobule revealing a portal venule, a hepatic arteriole and abile ductile (head arrow) **(H & E X200).**

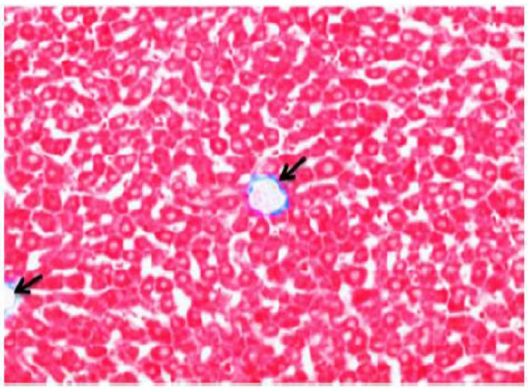

Figure (2): A photomicrograph of liver sections from control group showing collagen fibers with normal distribution of collagen fibers. Notice fin collagen bundles supporting the central vein (arrow) **(Mallory's trichrome stain X 400)**

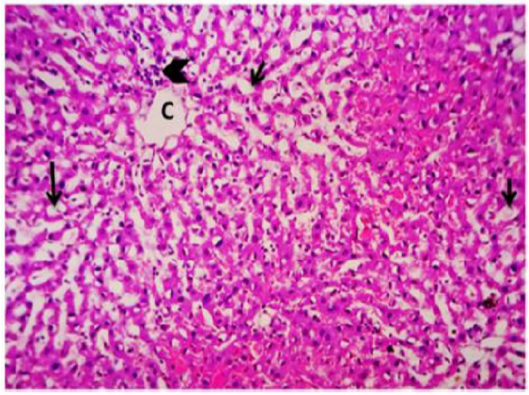

Figure (3): A photomicrograph of liver section from obese group showing disturbed liver architecture with apparently dilated vein. Notice vacuolation of most of hepatocytes (arrow), lymphocytic infiltration (head arrow) around the distorted central vein (C) **(H & E X200).**

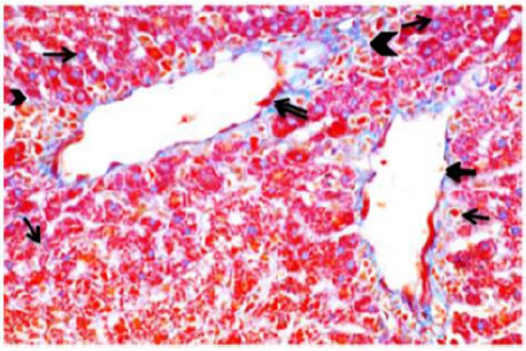

Figure (4): A Photomicrograph of liver section from obese group showing increased collagen fiber in all most of liver tissue (arrow), around dilated central vein (double arrow) and extending in between the cords of hepatocytes as well as between hepatic lobules (head arrow) **(Mallory's trichrome stain X 400)**.

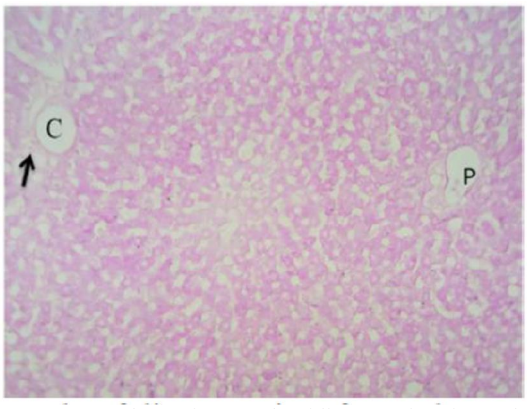

Figure (5): A Photomicrograph of liver section from obese group showing hepatocytes depleted from glycogen with highly reduced stain in the portal (p), central areas (c) and in endothelia lining of the central vein (arrow) **(PAS stain X 200)**.

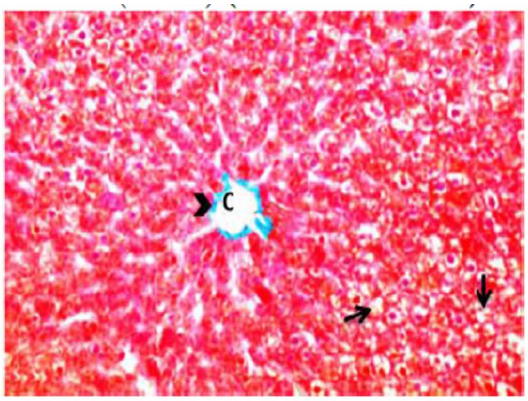

Figure (6): A Photomicrograph of liver section obtained from Curcumin group showing fine collagen fibers around central vein (head arrow) and some fat vacuole (arrow) **(Mallory's trichrome stain X 400).**

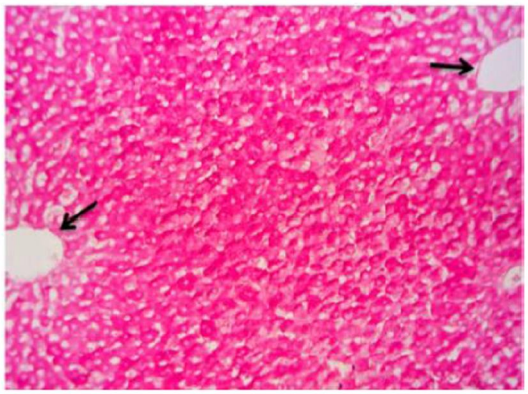

Figure (7): A Photomicrograph of liver section obtained from Curcumin group showing nearly normal glycogen content in hepatocytes of central and portal areas of hepatic lobule with dilated two central veins (arrow) **(PAS X 200)**.

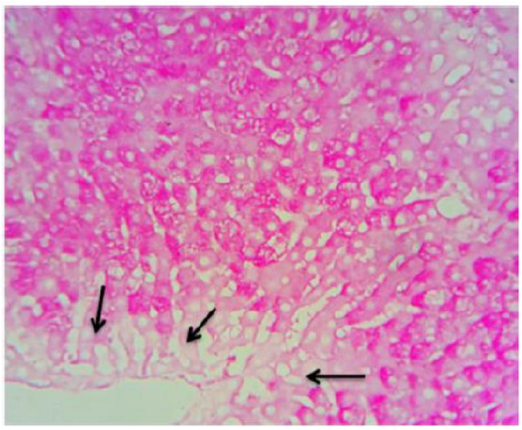

Figure (8): A Photomicrograph of liver section obtained from recovery group showing Moderate stain affinity of glycogen in hepatocytes with marked reduce stain affinity of glycogen around center vein (arrow) **(PASX 400)**.

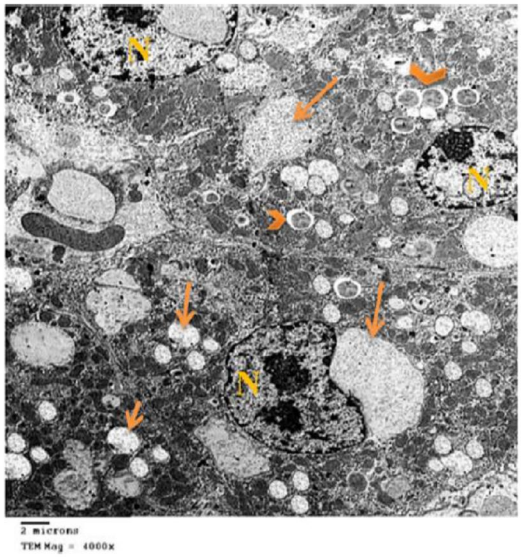

Figure (9): Electron micrograph of liver ultrathin section obtained from obese group showing hepatocytes with many lipid droplets variable in size and shape within nucleus and cytoplasm of hepatocytes (arrow). Some of mitochondria are engulfed by vacuole (head arrow). Nuclei of many hepatocytes show condensed chromatin, with widening of the perinuclear space (N).

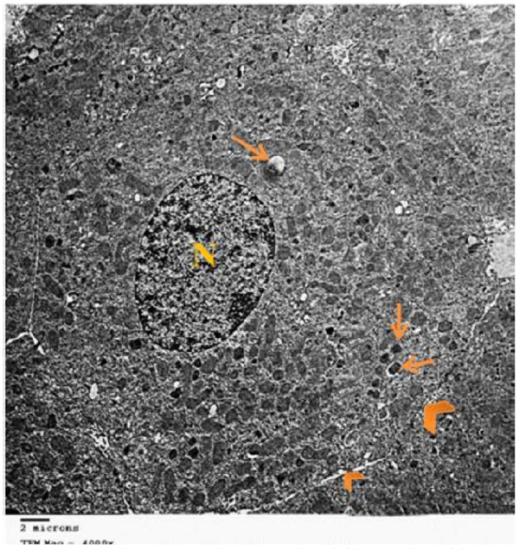

Figure (10): Electron micrograph of liver ultrathin section obtained from Curcumin group showing normal hexagonal shape of hepatocyte, large oval nucleus (N), primary and secondary lysosomes (arrow) and normal space of disse (head arrow).

4. Discussion

Obesity is a disorder characterized by a chronic energy imbalance, whereby energy expenditure is consistently lower than energy intake, necessitating the expansion of adipose tissue to allow the storage of excess energy [(14)].

Obesity is increasing in prevalence at a fast rate due to the rapidly increasing adoption of diets rich in saturated fats and simple carbohydrates, in combination with a sedentary lifestyle [(15)].

Obesity is associated with a spectrum of liver abnormalities, known as nonalcoholic fatty liver disease (NAFLD), characterized by an increase in intrahepatic triglyceride (IHTG) content (i.e. steatosis) with or without inflammation and fibrosis (i.e. steatohepatitis). NAFLD has become an important public health problem because of its high prevalence, potential progression to severe liver disease, and association with serious metabolic abnormalities, including type 2 diabetes mellitus (T2DM), the metabolic syndrome and coronary heart disease (CHD) [(16)].

In addition, the presence of NAFLD is associated with high risk of developing T2DM, dyslipidemia (high plasma TG and/or low plasma HDLc concentrations), and hypertension [(17)].

The pathogenesis of NAFLD and nonalcoholic steato-hepatitis (NASH) is not fully understood. It was explained as prolonged over-nutrition that leads to accumulation of free fatty acids and triglycerides within the liver (Steatosis) and progression of NAFLD to NASH that is associated with other factors such as oxidant stress, mitochondrial injury, fatty acids lipotoxicity, innate immunity and inflammatory cytokines. Steatosis is a characteristic histological feature of NAFLD results from increased fatty acid influx or impaired fatty acid utilization in the hepatocytes [(18)].

Why Rat Models in this study: NAFLD takes years and results from an interplay of several risk factors like over nutrition and/or an inappropriate dietary pattern (e.g., high fat and/or high sugar intake) as well as inadequate energy expenditure due to a sedentary lifestyle and probably genetic susceptibility, all leading to multiple molecular alterations in the human organism.

However as human behavior and biology are rather complex, it should be kept in mind when selecting an animal model to study NAFLD, and also when interpreting that data obtained in these models that other factors like physical activity, social environment, psychological stress factors and genetics may also be important contributors to the development of NAFLD in humans [(19)].

Accordingly, rat models used to study the onset of, but also progression of NAFLD to later stages of the disease like NASH or even fibrosis and cirrhosis, should incorporate the following criteria (I) the pathological patterns and histological alterations found in the different stages of the disease in humans and (ii) the general physiological alterations associated with the disease development in humans

(e.g., weight gain, insulin resistance but also impaired intestinal barrier function and adipocytokine release from adipose tissue) [20].

Also our results revealed that decreasing in the liver weight and the body weight in Curcumin group compared with obese group and recovery group due to ability of Curcumin to inhibit lipid synthesis and accumulation fat droplet in the liver or other area in the body.

Our results of the effect of Curcumin on histological structure of liver in induced rat's obesity showed by light microscope: cleared that many pathological changes in the liver tissue in obese group and recovery group.

This presented study was agreed with those of ***Vizzutti et al.*** [21] where they reported that. Histologically, Curcumin has been demonstrated to mitigate steatosis, necrosis and inflammation in the hepatic tissues. In conclusion Curcumin effectively mitigates nonalcoholic fatty liver diseases via its antioxidant and anti-inflammatory actions.

But signs of improvement of liver tissue presented in curcumin group which showed decrease collagen fibers in walls of blood vessels, hepatocytes and sinusoidal spaces nearly too normal.

Also our presented study showed highly decreased PAS stain affinity in liver tissue of obese group and recovery group.

But the results which indicated to the signs of improvement in liver tissue of Curcumin group were accompanied by restored glycogen content in the liver tissue.

These results are in parallel with those recorded by ***Han et al.*** [22] that highly affected glycogen content observed in this study in liver of rats treated with fats may be due to altered insulin levels and insulin sensitivity or insulin resistance due to obesity.

Our results were agreed with those of ***Tiniakos and Kittas*** [23] where they reported that. Macro-vesicular steatosis is explained as abnormalities in the delivery, metabolism, synthesis and export of lipids. However, microvesicular steatosis which is the hallmark of liver diseases is associated with defective beta-oxidation of fatty acids, including mitochondrial abnormality.

Furthermore, cytoplasmic vacuolation were attributed to lipid per-oxidation because of oxidative stress that damage cell membrane as well as membranes of cell organelles leading to increase in their permeability and disturbance of the ions concentrations in the cytoplasm and cell organelles [24]. Ballooned hepatocytes can be attributed to microtubular disruption and severe cell injury [23].

In the present study, the mitochondria in obese group showed morphological disruption where the sizes were increased, the cristae were disrupted, and the matrixes were hypodense compared to Control group, all these changes were consistent with the mitochondria dysfunction which was due to accumulation of lipid vacuoles in the hepatocyte cytoplasm.

Also, the antioxidant ability of curcumin was outlined that the phenolic hydroxyl groups allow curcumin to scavenge free radicals. This ability was observed in both microsomes and chemical testing that curcumin was able to inhibit lipid peroxidation ranged from 82% to 97%.

In additional to anti-obesity effects of curcumin are directly linked with the inhibition of inflammatory and angiogenic biomarkers such as COX-2 and vascular endothelial growth factor (VEGF) ***(Yoysungnoen et al., 2006)***.

Conclusion

There are several stages of NAFLD natural history, ranging from simple steatosis to steatohepatitis (NASH), liver cirrhosis, and finally carcinoma of the liver. The first stage, which is steatosis, is characterized by the presence of lipid inclusion in the liver. In NASH, steatosis is accompanied by inflammatory cells, ballooning of the hepatocytes, and often elevation of liver enzymes. Fibrosis is present when cirrhosis develops and is due to liver cells death. The present study concluded that curcumin has effective role against developing nonalcoholic fatty liver, improving liver enzymes and low body weight. Therefore, administration of curcumin may be beneficial for obese persons having risk factors of developing fatty liver or disturbed liver function.

References

1. Browning JD and Horton JD (2004): Molecular mediators of hepatic steatosis and liver injury. J Clin Invest., 114:147-152.
2. Gholam PM, Flancbaum L, Machan JT, Charney DA, Kotler DP (2007): Nonalcoholic fatty liver disease in severely obese subjects. Am J Gastroenterol., 102: 399-408.
3. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. (2005): Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology., 41:1313–1321.
4. Jadeja RN, Thounaojam MC, Devkar RV, Ramachandran AV (2010): Clerodendron glandulosum Coleb., Verbonaceae, ameliorates high fat diet-induced alteration in lipid and cholesterol metabolism in rats. Braz. J. Pharm., 20(1): 117-123.
5. Khan A, Anthwal V, Ishaq F, Singh RN (2012): Antioxidant and antiatherogenic impacts of Catharanthus roseus and Hibiscus sabdariffa on

Cu++ mediated oxidation kinetics of low density lipoprotein. Der Pharmacia Sinica., 3(4):443-56.
6. Sodipo A, Abdulrahman FI, Sandabe UK, Akinniyij A (2011): Drug therapy for hyperlipidaemia (dyslipidaemia). J. Appl. Pharmaceut. Sci., 1 (6): 1-6.
7. Shin SK, Ha TY, McGregor RA, Choi MS (2011). Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. MolNutr Food Res., 55(12):1829-40.
8. Sivaelango G, Kumaran PS, Kumaravel P, Revathi P, Jaswan A (2012): Antihyperlipidaemic activity of Spermacoce hispida ethanolic extract in triton WR-1339 induced hyperlipidaemic rats. J. Appl. Pharmaceut. Sci., 2 (2): 95-98.
9. Öner-İyidoğan Y, Koçak H, Seyidhanoğlu M, Gürdöl F, Gülçubuk A, Yildirim F, Çevik A, Uysal M (2013): Curcumin prevents liver fat accumulation and serum fetuin-A increase in rats fed a high-fat diet. J Physiol Biochem., 69(4):677-86.
10. Um MY, Hwang KH, Ahn J, Ha TY (2013): Curcumin attenuates diet-induced hepatic steatosis by activating AMP-activated protein kinase. Basic Clin. Pharmacol. Toxicol., 113: 152–157.
11. Zeng C, Zhong P, Zhao Y, Kanchana K, Zhang Y, Khan ZA, Chakrabarti S, Wu L, Wang J, Liang G (2015): Curcumin protects hearts from FFA-induced injury by activating Nrf2 and inactivating NF-κB both in vitro and in vivo. J Mol Cell Cardiol., 79:1-12.
12. Walaa AK and Saad A (2014): Noeman impact of chicory-supplemented diet on HMG-coareductase, acetyl-coa carboxylase, visfatin andanti-oxidant status in triton wr-1339-inducedhyperlipidemia Medical Biochemistry Department, Faculty of Medicine, Tanta University, El-Geish Street, Tanta, El-Gharbia, Egypt Journal of Food Biochemistry, 1745-4514.
13. Yuanyuan W, Minghua J, Lina Z, Suhua L, Jiayu Z, Yongzhi S, Chunyu C, Jian Q (2015): Effect of a combination of calorie-restriction therapy and Lingguizhugan decoction on levels of fasting blood lipid and inflammatory cytokines in a high-fat diet induced hyperlipidemia rat model. J Tradit Chin Med., 35(2):218-21.
14. Ahn J, Lee H, Kim S and Ha T (2010): Curcumin-induced suppression of adipogenic differentiation is accompanied by activation of Wnt/β-catenin signaling. American Journal of Physiology-Cell Physiology, 298: C1510-C1516.
15. McGill A (2014): Causes of metabolic syndrome and obesity-related co-morbidities part 1. A composite unifying theory review of human-specific co-adaptations to brain energy consumption. Archives of Public Health, 72: 30.
16. Elisa F, Shelby S and Samuel K (2010): Obesity and Nonalcoholic Fatty Liver Disease: Biochemical, Metabolic and Clinical Implications1Center for Human Nutrition and Atkins Center of Excellence in Obesity Medicine, Published in final edited form as: Hepatology, 51(2): 679–689.
17. Adams LA, Lymp JF, St Sauver J (2005): The natural history of nonalcoholic fatty liver disease: A population- based cohort study. Gastroenterology, 129: 113–121.
18. Mahtab MA, Fazle Akbar SM (2013): Non-alcoholic Fatty Liver Disease: A Review. Journal of Gastroenterology and Hepatology Research, 2(3):439–44.
19. Tilg H and Moschen AR (2010): Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology, 52: 1836-1846.
20. Giridhar Kanuri and Ina Bergheim (2013): In vitro and in vivo models of non-alcoholic Fatty liver disease (NAFLD) Department of Nutritional Sciences, SD Model Systems of Molecular Nutrition, Friedrich-Schiller-University, Dornburger Str. 25-29, D-07743 Jena, Germany Int. J. Mol. Sci., 14: 11963-11980.
21. Vizzutti F, Provenzano A, Galastri S, Milani S, Delogu W, Novo E, Caligiuri A, Zamara E, Arena U, Laffi G, Parola M, Pinzani M, Marra F (2009): Curcumin limits the fibrogenic evolution of experimental steatohepatitis. Lab Invest., 90(1):104–15.
22. Han SH, Quon MJ, Kim J A and Koh KK (2007): Adiponectin and cardiovascular disease: response to therapeutic interventions. J. Am. Coll. Cardiol., 49: 531-538.
23. Tiniakos DG and Kittas CH (2005): Pathology of nonalcoholic fatty liver disease. Annals of Gastroenterology, 18(2):148–59.
24. Emanuel R and Chap L (2001): Cell injury Essential pathology. 3rdedition Lippincot Williams & Wilkins, p: 1.
25. Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H, Patumraj S (2006): Effects of curcumin on tumor angiogenesis and biomarkers, COX-2 and VEGF, in hepatocellular carcinoma cell-implanted nude mice. Clin Hemorheol Microcirc., 34(1–2):109–115.

8/7/2018