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The Potential Prophylactic Effect of Orange Peel Administration on Fatty Liver and Hyperlipidemia in an Animal Model of Diet Induced Obesity

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CITRUS is an economically important fruit for Egypt. However, its peels generated by the juice industry are one of the major sources of agricultural wastes. Fermentation of those wastes causes many economic and environmental problems. Therefore, it is worthwhile to investigate ways to make use of this citrus waste. The present study aimed to assess the prophylactic role of orange peel on obesity, fatty liver changes and serum lipids profile in an experimental obesity model. Forty male albino mice were divided into four groups and fed respectively a chow normal diet (control group), normal diet supplemented with 5% w/w orange peel (ND+OP), high-fat diet (HF),and HF diet supplemented with 5% w/w orange peel (HF+OP) for 12 weeks . The animals were sacrificed at the 12th week of the experiment, the body weight, back and epididymal fat weights, also serum lipid profiles were measured. Liver specimens were subjected to histopathological examination. Results showed that: 1. Orange peel administration in mice fed high fat diet significantly reduced the total weight gain, epididymal and back fat weights as compared to HF control group. 2. Serum lipid concentrations were also significantly improved in the HF+ OP group than HF control group.3. Histopathological examination of liver specimens showed marked improvement of the fatty changes observed in high fat diet group.

These results suggest that orange peel administration could ameliorate obesity and related metabolic disorders in HF diet-induced obesity in mice.

Key words: Obesity,Orange peel, Hypelipidemia, Fatty liver

Introduction

Obesity is a social health problem and is associated with numerous risk factors such as hyperlipidemia, type 2 diabetes mellitus and hypertension. Reducing body fat is a major health goal throughout the world and identifying functional foods that can help to reduce body fat and meet other health needs has been the subject of numerous studies (Ginter and Simko, 2008).

Citrus fruits are amongest the most important fruit crops worldwide and are rich in nutrients and bioactive compounds. Citrus fruits contain not only basic nutrient compounds such as vitamins, minerals, pectins and dietary fibers, but also ample bioactive compounds including flavonoids, carotenoids, limonoids and coumarins(Kawaii *et al.*, 1999s and Kanaze *et al.,* 2008).

Recently, the study of bioactive compounds has become the focus in both epidemiology and food science (Ginter and Simko, 2008). Citrus fruits have been reported to exhibit important bioactivities, including antioxidant, anti-inflammatory, anti-obesity, anti-cardiovascular and antitumor abilities (Daniels, 2006 , Dhanavade *et al.*, 2011, Duda-Chodak & Tarko, 2007 and Enterazi *et al.*, 2009).

In recent years, the study on the use of citrus fruits in the prevention and treatment of obesity and its related metabolic diseases has attracted increasing attention (Huang *et al*., 2009). It was reported that citrus peel extract regulated the lipid and triglyceride accumulation in 3T3-L1 adipocytes (Jung *et al.,* 2006).

Previously, in an animal experiment, Bok

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(1999) have found that tangerine peel extracts reduced the plasma and hepatic cholesterol levels of rats. The immature citrus peel extract was also reported to have anti-obesity effect by increasing β-oxidation and lipolysis in the adipose tissue of HF diet-induced obesity mice (Khan *et al.*, 2010). In addition, in another study, lemon peels, lemon pectin were found to have a hypocholesterolemic effects in in hybrid F1B hamsters (Terpstra *et al.*, 2002).

In this study, whether long-term supplementation of orange peel (OP) would have a role in the prevention and treatment of obesity and its related metabolic diseases was investigated. Mice fed with HF diet and supplemented with OP were evaluated for body weight gain, serum lipid levels and the fatty changes of the liver cells have been also studied histologically.

Materials and Methods

Orange peel preparation

Fresh Orange peels were washed with water and cut into small pieces and dried at room temperature. The dried peels were grounded to fine powder and incorporated into the diet of experimental animals in a ratio of 5 gm%w/w.

Animals and diets

Forty male albino (C57BL/6J) mice aged 4 weeks, 1620-g weight, were purchased from the animal house in the Research Institute of Ophthalmology. The animals were maintained on a pellet diet (Research Diets, New Brunswick, NJ, USA) for 1 week, and then randomly divided into four groups, each consisting of ten mice: normal diet (ND) group, normal diet containing orange peel (5gm%w/w) (ND+OP) group, high fat diet (HF) model group, and a model group fed a high fat diet containing orange peel (5gm%w/w) (HF+OP). The compositions of the experimental diets are shown in Table 1. The animals were housed in a temperature-controlled environment with a 12-hours light/dark cycle. The animals were given free access to food and water during the entire experimental period. The food intake and body weights were measured at the beginning and at the 8th week of the experiment.

TABLE 1. Composition of experimental diets (AIN-93 modified diet for rodents)

Ingredients (g)	Normal diet (1)	High fat diet (2)
	ND	HF
Casein,lactic(g)	200	200
L-systine(g)	3	3
Corn starch(g)	315	-
Maltodextrin(g)	35	125
Sucrose(g)	350	68.8
cellulose(g)	50	50
Lard(g)	20	245
Mineral mix(g)	10	10
Dicalcium phosphate(g)	13	13
Calcium carbonate(g)	5.5	5.5
Potassium citrate(g)	16.5	16.5
Vitamin mix(g)	10	10
Kcal/(kg)	4057	4057

AIN: American Institute of Nutrition
1) AIN-93 Modified diet with 4% fat content by weight (10% of calories are fat).
2) AIN-93 Modified high fat diet with 35% fat content by weight (60% of calories are fat).
ND: Normal diet, HF: High fat diet.

Collection of serum and tissue samples

Food was removed 12 hours before sacrificing. Blood samples were collected from each mouse by orbital puncture and incubated on ice water for 1 hour. Serum was separated from the blood by centrifugation at 3000 rpm for 15 minutes at 4℃ and kept at -80℃ until analyzed. . The back fat, and epididymal fat were removed, rinsed with a phosphate-buffered saline solution, wiped with a paper towel, and then weighed quickly .Values of serum total cholesterol (TC), triglycerides (TG) and HDL-cholesterol were measured by commercial kits provided by (Boehringer Mannheim, Germany

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Histopathological examination of the liver

The liver specimens were fixed in 10% neutral buffered formalin (NBF) for 12 h at 4oC. Then liver specimens were selected, embedded in paraffin, and cut horizontally into sections of 5µ thickness. The sections were stained with Hematoxylin and Eosin (H&E). Sections were examined by light microscopy to assess the degree of fatty changes in liver cells.

Statistical analysis

The data were analyzed by one-way ANOVA using Statistical Package for Social Science (SPSS) version 16.0.1 program, and the differences among groups were assessed using Duncan's multiple range test. Statistical differences were considered significant at $p<0.05$.

Results

Weight gain and food intake are shown in Table 2 ; there were no significant differences in the initial body weights among the tested groups. After 12 weeks, control group (ND+OP) showed no significant changes in the final body weight, food and energy intake as compared to (ND) group. Inducing obesity in albino mice (HF group) resulted in a significant increase in the final body weight and energy intake as compared to (ND) group ($p< 0.5$). It is to be noted that the food intake is apparently decreased in grams in spite of the increase in the energy intake, which could be explained by the fact that each gram of fat yields nine calories. The high fat diet is containing 60% of its calories derived from fat (lard) whereas the normal diet contains only 10% fat. The weight gain, food and energy intakes in the HF+OP group were still significantly different from control, yet they were improved to be significantly lower than the HF group ($p< 0.5$).

Adipose tissue mass in mice

Control group (ND+OPE) (Table 3) showed no significant changes in epididymal and back fat weights as compared to (ND) group. Inducing obesity in obesity model mice (HF group) resulted in a significant increase in the epididymal and back fat ($p<0.05$) as compared to (ND) group. Although the mean increases in epididymal and back fat in HF+OPE group were still significantly higher than normal control (ND) ($p<0.05$); yet, they were improved to be significantly lower than (HF) group $p<0.05$.

Serum lipid levels (Table 5)

Control group (ND+OP) showed no significant changes in serum total cholesterol, HDL cholesterol (TC) and triglycerides (TG) as compared to (ND). Inducing obesity in HF group resulted in a significant difference in serum total, HDL cholesterol or triglycerides from normal diet (ND) group ($p<0.05$). After orange peel administration in the HF+OP group TG mean level was still significantly higher than (ND) group, but it still was improved to be significantly lower than the (HF) group ($p<0.05$). In addition, mean serum total cholesterol showed a significant decrease ($p<0.05$) than HF group with no significant difference from control group (ND). Moreover, HDL-cholesterol was significantly improved to be higher in the HF+OP group as compared to both control (ND) and obesity model groups (HF) ($p<0.05$).

TABLE 2. Body weight and food intake in mice fed experimental diets for 12 weeks

Groups	Group1 ND	Group2 ND+OP	Group3 HF	Group4 HF+OP
Initial weight(g)Mean±SD				
P1		1.20±18.35	.1±17.59	1.35±17.34
P2	1.60±18.35	1.000	36	747.
			1.000	1.000
Final weight(g)Mean±SD				
P1				1.38±28.22.75
P2	1.26±23.12	1.44±23.11	.1±35.58	000.
		1.000	000. 32	000.
Weight gain (g) Mean±SD				
P1				1.95±10.88
P2	1.97±4.92	1.5±4.86.78	2.12±17.96	000.
		1.000	000.	000.
Foodintake(g/day)Mean±SD				
P1				0.31±1.38
P2	0.0.29±2.16	0.26±2.02	0.22±1.88	000.
		1.000	000.	000.
Energy intake(kcal/day) Mean±SD				
P1				0.86±9.60
P2	0.79±8.50	0.76±8.22	1.1±10.14	000.
		1.000	001.	000.

Values are expressed as Mean ± SD of 10 rats per group

ND: Normal diet, ND+OP: Normal diet+ orange peel, ND+ HF: High fat diet, HF+OP: High fat diet + orange peel.

Values are considered significantly different at $p<0.05$.

P1 compare groups (2, 3 &4) to (1), P2 compare group (4) to (3).

Histopathological results

Histological evaluation of liver specimens in both ND and ND+OP groups demonstrated a normal hepatic architecture with no alteration in the relationship between central veins and portal tracts and the hepatocytes are normal (Fig.1). Whereas, in the high fat diet group, liver sections showed a diffuse fatty vacuoles filling the cytoplasm of liver cells. In the majority of liver cells the vacuoles are small and numerous. In other cells they are larger and in some a single vacuole replaces much of the cell cytoplasm and compresses the hepatocyte nucleus to one side. The fatty changes are particularly prominent at the periphery of the lobules around the portal tracts (Fig. 2 (a, b, c). Administration of orange peel in diet dramatically decreased lipid accumulation to a background level and largely diminished the deposition of fatty vacuoles within hepatocytes (Fig. 3).

TABLE 3. Epididymal fat weight (g)

groups	ND	ND+OP	HF	HF+OP
Mean±SD	0.0816±0.50	0707±0.40	0.3018±2.00	0.1524±1.49
P1		1.000	0.000	0.000
P2				0.000

TABLE 4. back fat weight (g)

groups	ND	ND+OP	HF	HF+OP
Mean±SD	0.0730±0.59	0.0816±0.50	0.3348±2.59	0.1155±1.70
P1		1.000	0.000	0.000
P2				0.000

TABLE 5. Lipid concentrations in serum (mg/dl)

Groups	Group1 ND	Group2 ND+OP	Group3 HF	Group4 HF+OP
Triglyceride P1 P2	55.31±3.26	53.60.07±3.49 1.00	95.16±2.49 0.000	78.12±4.17 0 .000 0 .000
Total cholesterol P1 P2	138.28±3.05	131.97±7.88 1.00	180.22±2 0 .000	159.75±17.09 0.051 0.000
HDL cholesterol P1 P2	74.42±3.71	75.40±2.57 0.074	56.22±2.24 0.000	84.18±2.13 0.000 0.000

Values are expressed as mean ± SD of 10 rats per group
ND: Normal diet, ND+OP, Normal diet+ orange peel, HF: High fat diet, HF+OP: High fat diet plus orange peel.
Values are considered significantly different at $p<0.05$.
P1 compare groups (2, 3& 4) to (1), P2 compare group (4) to (3).

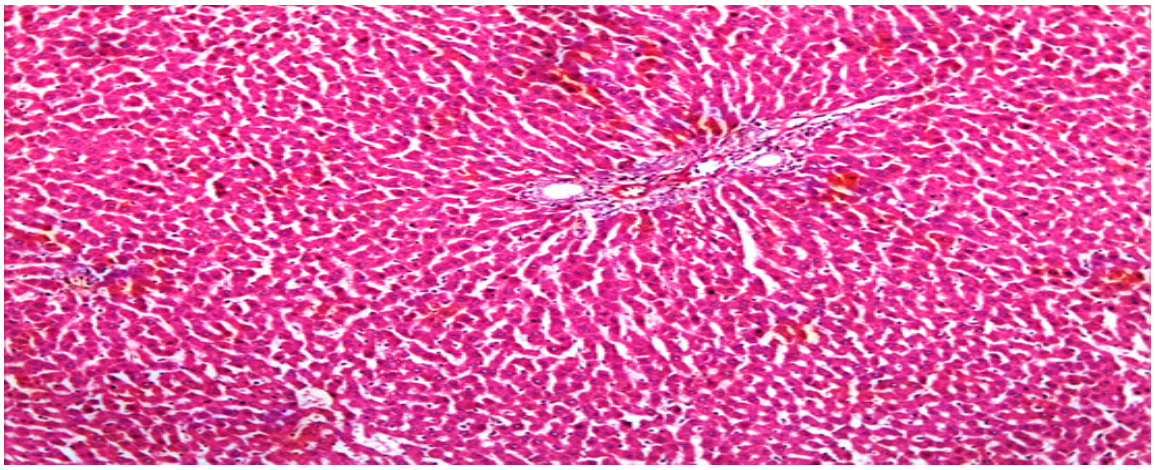

Fig.1. Photomicrographs of normal liver showing the normal hepatocytes and normal lobuleswith the central vein. (H&E) x 100.

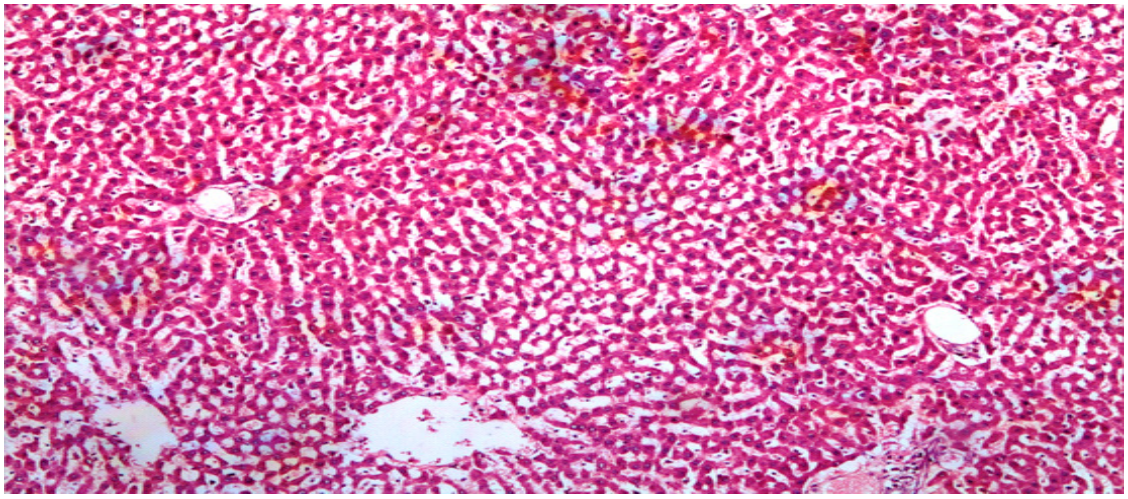

Fig. 2a.Photomicrograph of Fatty liver. The lipid accumulates in the hepatocytes as clear vacuoles showing the appearance of swollen ballooned hepatocytes (stars). (H & E x100)

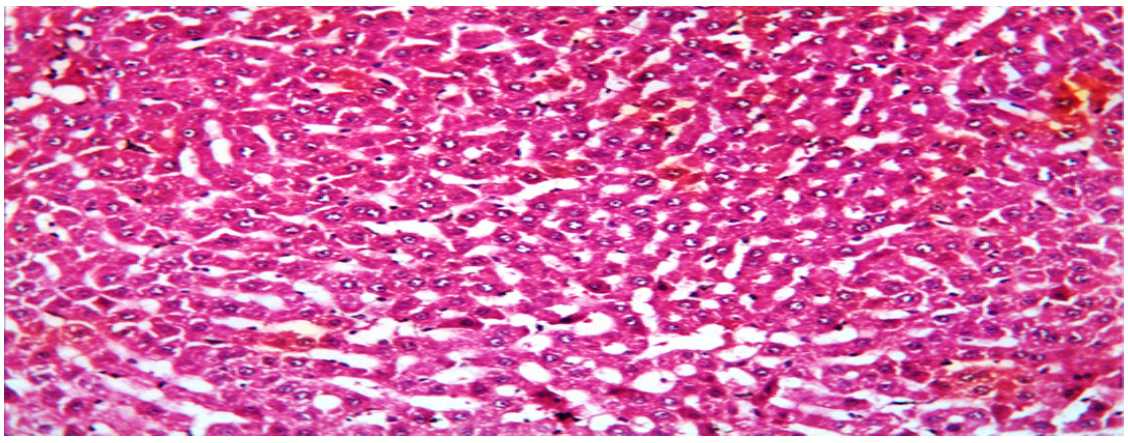

Fig. 2 b. Photomicrograph of fatty liver(H & E x 200)

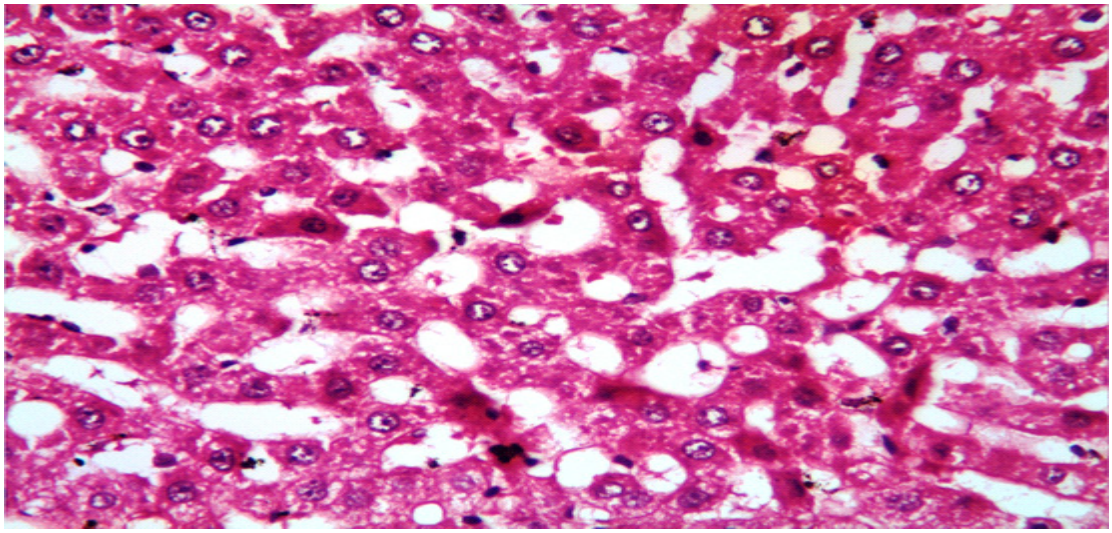

Fig.2 C. photomicrograph of fatty liver (H & E x 400)

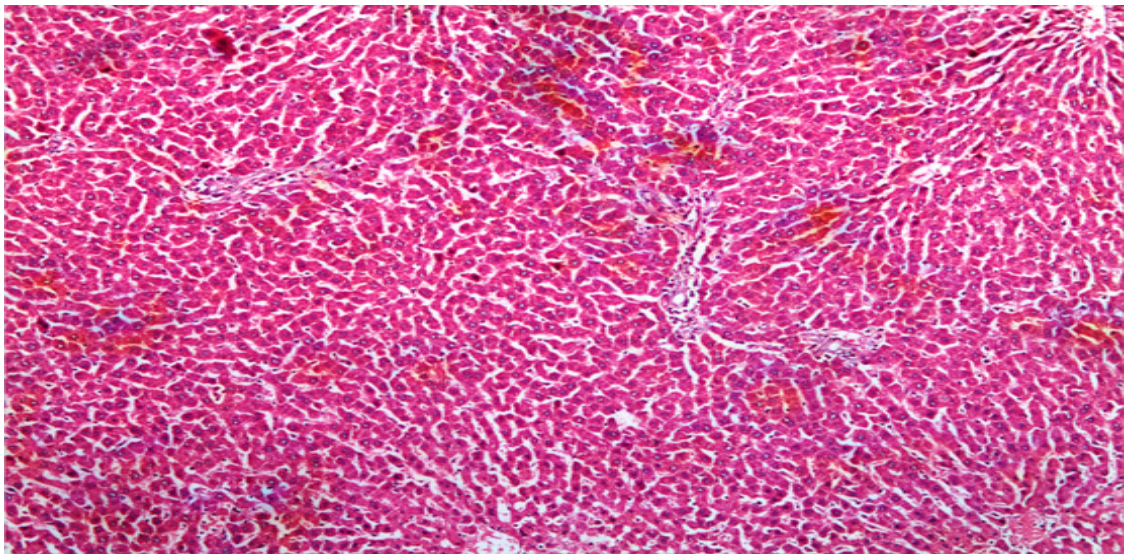

Fig. 3. liver photomicrograph in group taking high fat diet with orange peel (H & E x 100)

Discussion

The present study aimed to assess the anti-obesity effects of orange peel supplemented diet, as well as its effect on related metabolic disorders in an experimental obesity model in albino mice.

The relatively high concentrations of flavanones in orange peels have focused attention on the potential healthful effects of these citrus flavonoids. The extracts of orange peel have been studied recently for its anti-obesity effects, due to its rich functional ingredients (Ginter and Simko, 2008).

Many studies have measured the flavonoid contents of several methanolic extract fractions of orange peel. HPLC analysis confirmed the presence of polymethoxylated flavones, O-glycosylated flavones, C-glycosylated flavones, O-glycosylated flavonols, O-glycosylated flavanones and phenolic acids along with their ester derivatives(Kawaii *et al.*, 1999 and Kanaze *et al.,* 2008). Hesperidin and naringin were found to be the major flavonoid glycosides found in the orange peel (Jung, 2004))

High-fat diets (HF) have been used widely and accepted in nutritional experiments as a good strategy to induce overweight conditions and fat deposition in animals (Aoki, 2007). In this study, HF feeding for 12 weeks resulted in obesity, which was associated with a significant increase in body weights and fat mass with the development of hyperlipidemia and fatty changes in the liver. Although initial body weights of mice did not differ among the groups, the mean final weights in the groups were significantly lower in HF+OP (High fat diet plus orange peel) than that in the high-fat diet (HF) group. In addition, the mean food intake and energy intake were also significantly decreased as compared to the HF group.

Moreover, concomitantly, epididymal and back fat pad depositions were significantly lower in the HF+OP group as compared to the HF group. The drop in fat mass indicated that the weight loss is mainly due to fat loss.

The isoflavones of orange peel may induce weight loss by stimulation of β - 3 cell receptors, thus eliciting thermogenesis, leading to increased lipolysis and metabolic rate (Preuss *et al*, 2002). It has also been determined that isoflavones reduce cortisol levels. Cortisol is a stress hormone, higher levels of which have been linked to weight gain. (Talbot, 2009).

In accordance to the present study, Lim *et al.* (2014) have found that orange peel isoflavones prevented obesity induced by ovariectomy with a high-fat diet, in part by modulating gene expression related to lipid metabolism. That was supported by Zhang *et al.* (2009) who reported that isoflavone could reduce obesity by decreasing food intake, possibly by (1) reducing ghrelin and neuropeptide Y (NPY) levels, thereby decreasing food intake, and (2) increasing cholecystokinin (CCK) and peptide YY (PYY) levels, which can induce satiety by irritating the vagal center.

In the present work, inducing obesity in HF group resulted in a significant difference in serum total cholesterol (TC), HDL cholesterol and triglycerides (TG) from normal diet (ND) group. After orange peel administration to the HF+OP group, serum lipid profiles were significantly improved.

These findings are generally consistent with previous published reports which showed an association between the intake of orange peel containing isoflavones and changes in lipid concentrations in humans (Gabriele and Angela, 1991).

In this work, it was observed that orange peel produced minimal lipid lowering effect on the normal animal group. Therefore, it is suggested that initial serum cholesterol concentrations had a powerful effect on the changes in lipid concentrations. As found in the previous report of Jing *et al.*, (2013), the beneficial effects of orange peel on lipid profiles are more marked in subjects with hypercholesterolemia. That gave an explanation to the variability in lipid lowering effects of orange peel in different groups of the present work.

To understand the mechanism of action of isoflavones on serum lipids, Medjakovic *et al.*, (2010) have reported that orange peel isoflavones may regulate cholesterol homeostasis in hepatic G2 cells (hepatoma cultured cell line arrested in G2 stage

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Also, the work of Hyang-Sook (2006) showed that orange peel isoflavones may affect hepatic and adipose tissue lipase enzyme activity. Following studies have also suggested that they up-regulate LDL receptor and induce gene expression of several enzymes and proteins important in lipid metabolism(Fukuchi *et al.*, 2008, Ezekwesili-Ofili and Gwacham, 2015

The mechanisms by which cholesterol and triglycerides were reduced could be due to interaction of orange peel pectins with bile acids thus preventing reabsorption of the bile acid, and therefore, cholesterol or by inhibition of β HMG CoA reductase and acyl CoA cholesterol acyl transferase (ACAT), thereby preventing de novo synthesis, or by increased lipase activity (Bok, 1999). Hesperidin and naringin, have been reported to decrease plasma and hepatic cholesterol and triacylglycerol by inhibiting these hepatic enzymes in experimental animals (Kim, 2003 and Lee, 2003).It was reported that citrus naringin reduced serum lipids through up-regulating the expression of *PPARγ (*peroxisome proliferator-activated receptors*γ*) and down-regulating the expression of LXRs (liver X receptor) in the liver tissue of type 2 diabetic rats (Lee *et al.*, 2003).

That was confirmed by recent evidences suggesting that citrus flavonoids (hesperidin and naringin) play their roles through the (PPARs) pathway (Cho *et al.*, 2011). It is well known that PPAR is the nuclear receptor transcription

factor that regulates the carbohydrate and lipid metabolism of tissues and cells. There are three isoforms in the PPAR family, PPARα, PPARγ and PPARδ/β, among which PPARγ mainly regulates adipocyte differentiation, lipogenesis and glucose metabolism (Evans *et al.,* 2004).

Therefore, the inhibitory effects of citrus polymethoxylated flavonoids on adipogenesis and adiposity have been partially attributed to up regulation of the *(PPARα* and *PPARγ*) expression levels both in cell and animal models (Goldwasser *et al.*, 2010 and Cho *et al.*, 2011).

In the present study, the marked liver cells fat deposition observed in the HF group was markedly ameliorated by orange peel administration in HF+OP group. That was supported and explained by the recent work of Lu *et al.,* (2013) who reported that orange peel isoflavones supplementation inhibited adiposity in non-alcoholic fatty liver disease (NAFLD) by the up-regulation of genes involved in fatty acid β-oxidation and the antiadipogeneis, and augmented antisteatohepatiticleptin and adiponectin mRNA levels, whereas it reduced the mRNA and concentrations of steatotic tumor necrosis factor α and ghrelin. It was concluded that isoflavones might alleviate (NAFLD) through the direct regulation of hepatic de novo lipogenesis, and the indirect control of adiposity and adipocytokines by the alteration of adipocyte metabolism (Sharma *et al.*, 2011 and Kim *et al.*, 2012).

In conclusion, the results of the present work suggested that orange peel agricultural wastes could be used as a functional food to ameliorate obesity and related metabolic disorders in experimental animals. Further studies should be carried out for confirmation and finding other possible applications for orange peel agricultural wastes.

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التأثير الوقائي المحتمل لتناول قشر البرتقال على السمنة وتراكم دهون الكبد في نموذج حيواني تجريبي للسمنة الناتجة عن النظام الغذائي عالي الدهون

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الحمضيات تعتبرمن الثمار الهامة اقتصاديا لمصر. ومع ذلك، القشور الناتجة عن صناعة عصيرها تعتبر من المصادر الرئيسية للنفايات الزراعية. تخمر هذه النفايات يسبب العديد من المشاكل الاقتصادية والبيئية. لذلك فإنه من المفيد بحث سبل للاستفادة من هذه النفايات الحمضية. هدفت هذه الدراسة إلى تقييم الدور الوقائي لقشر البرتقال على السمنة، و تقليل حدوث الكبد الدهني ونسبةالدهون في الدم في نموذج السمنة التجريبية في حيوانات التجارب . تم تقسيمأربعون من الفئران البيضاء الذكور إلى أربع مجموعات .وتمت تغذيتها على التوالي على ١- النظام الغذائي العادي للفئران (المجموعة الضابطة) ٢-النظام الغذائي العادي مخلوط مع ٥٪ من الوزن قشر البرتقال٣-نظام غذائي عالي الدهون٤- نظام غذائي عالي الدهونمخلوط مع ٥٪ من الوزن قشر البرتقال .استمرت التجربة لمدة ١٢ أسبوعا. وتم التضحية بالحيوانات في الأسبوع ال١٢ من التجربة وتم وزن الجسم ووزن دهون الظهر ودهون النسيج البربخي، كما تم قياس نسب الدهون في الدم. كما اخذت عينات من الكبد للفحص بالميكروسكوب الضوئي. وأظهرت النتائج ما يلي: ١. اعطاء قشر البرتقال للفئران التي غذيت بنظام غذائي عالي الدهون قلل بشكل كبير زيادة الوزن الكلي واوزان الدهون في الجسم بالمقارنة مع المجموعة التي لم تعالج.٢-لوحظ ايضا تحسن ملحوظ في تركيز دهون الدم في المجموعة المعالجة.٣-كماأظهر فحص الأنسجة من عينات الكبد تحسنا ملحوظا فيالتغيرات الدهنية بالمقارن بالتغيرات الملحوظة في المجموعة ذات الغذاء عالي الدهون.

وتشير هذه النتائج إلى أن يمكن الاستفادة من قشر البرتقال كمكمل غذائي لتخفيف السمنة واضطرابات التمثيل الغذائي المتصلة بها.