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Annals of Biological Research, 2012, 3 (5):2486-2490
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0976-1233
CODEN (USA): ABRNBW

Anti-obesity and anti-hyperlipidemic effect of *Citrullus colocynthis* oil in the offspring of obese rats

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ABSTRACT

This study aims to test the effect of colocynth oil extracted from seeds of Citrullus colocynthis (medicinal plant known for their various therapeutic properties) on the offspring of rats Wistar obese. Three groups of male Wistar rats were established (n = 6): group 1 (control group) containing the offspring of control mothers receiving a diet iso-caloric (4% sunflower oil), group 2 containing the offspring of mothers obese receiving a high-calorie diet (32% sunflower oil) and Group 3 containing the offspring of obese mothers receiving a high-calorie diet based on a mixture of 28% sunflower oil + 4% oil of colocynth. After 8 weeks of diet, the offspring were sacrificed. Blood and organs were harvested. Weight, blood glucose, cholesterol, and triglycerides were measured. Our results showed a significant decrease in body weight in offspring of obese mothers fed a diet of colocynth oil, compared to obese rats, but remain almost parallel to that of controls. Furthermore, the glucose values remain within physiological limits in group 1 and 3 while those of group 2 increased significantly. On lipid markers, we scored a significant increase of triglycerides in obese rats compared with controls. The same result was found for cholesterol. For rats receiving oil of colocynth, these values remain in the standards. This study suggests that colocynth oil has a lowering effect on weight control, lipid profile and glucose in offspring of obese rats.

Keywords: Obesity; Offspring; Animal model; Citrullus colocynthis oil; Sunflower oil; Lipid parameters.

INTRODUCTION

Obesity rates in our society are at an all-time high, proportionately affecting reproductive-age women.Obesity in pregnancy is associated with a high frequency of adverse pregnancy outcomes, having both perinatal and long-term implications for mother and her offspring **[1]**. The impact of obesity in pregnancy on offspring risk of obesity requires further research. Moreover, nutrition guidance regarding appropriate pregnancy weight gain has not evolved to address the obesity epidemic **[2]**.

Obese mothers are more likely to have obese children **[3]**. Childhood obesity is a major public health problem associated with significant comorbidities and is notoriously difficult to reverse. Specifically, the rate of obesity in middle-class preschool-age children has dramatically increased during the past 22 years **[4]**, and recent longitudinal studies indicate that once children that age are obese, the risk of remaining obese in adulthood is doubled **[5]**. Accordingly, researchers have theorized that intervention to prevent obesity must occur early in life **[6, 7]**. Such intervention requires identifying infants atrisk for obesity before these children become overweight.

Factors present in the fetal-neonatal period that have been correlated to later obesity risk include: large birth weight, maternal diabetes mellitus (including gestational diabetes mellitus), excessive gestational weight gain, maternal smoking, and obesity in pregnancy **[3, 8-11]**.

Citrullus colocynthis (L.) Schrad. (Cucurbitaceae), commonly known as « bitter-apple »,« colocynth », or « wild-gourd », is a tropical plant that grows abundantly in many place in theworld **[12]**.

Originally from Tropical Asia and Africa, it is now widely distributed in the Saharo-Arabian phytogeographic region in Africa and the Mediteranean region. InAlgeria, *C.colocynthis* occurs in many places from the north to the hot desert it's known as« Handal », « Hdejj » « Tijjeltl », « Tabarka » or « Tifersite **»**. The fruits are widely usedmedicinally as an anti-inflammatory, purgative in constipation, anti-rheumatic and anti-diabeticin Mediterranean countries **[13, 14]**.

The seeds of *C.colocynthis* have been subjected to a rangeof pharmacological, phytochemical and nutritional investigations in recent years. It has been shown to contain 17% of a fixed oil with high proportion of unsaturated fatty acids, mainlylinoleic acid (60-70%), oleic acid (11.7-15%) and a very low n-3 poly-unsaturated FA level(0.5%). It is also rich in antioxidant (eg. tocopherol, polyphenol and plant sterol) **[13, 15]**.

This study was conducted to evaluate the effect of Colocynthoil on weight change and lipid parameters in the offspring of obese rats.

MATERIALS AND METHODS

Plant materials

C. colocynthis fruits were collected from Mechria (western Algeria), divided in half and theseeds removed by hand. Mature black seeds were selected, dried and they were powderedmechanically. The lipid fraction was extracted with petroleum ether (40-60°c) in a soxhletapparatus for two hours by the Natural products laboratory in Tlemcen, Algeria. The solvent wasevaporated and the lipid fraction was weighed. Oil content in seeds was 17%.
Sunflower oil is commercial local products (Fleurial plus, Cevital, Algeria). Oils fatty acids compositions were analyzed by gaze chromatography and are shown in Table1.

Table 1: Percentage composition of the main fatty acids of dietary oils

Fatty acids (g/100g)	*Sun flower oil*	*Colocynthis oil*
SFA	10	15
MUFA	30	7,8
18:2(n-6)	54	76,4
20:4(n-6)	5,8	0,3
Total n-6	59,8	76,7
Total n-3	0,2	0,5
Total PUFA	60	77,2
P/ S	06	5,14
n-6/n-3	299	153,7

SFA: Satured fatty acids, MUFA: Monounsatured fatty acids, PUFA: Poyunsatured fatty acids

Experimental animal

The experimental protocol was approved by the Animal Care and Use Committee of theUniversity of Tlemcen. Animals were placed in stainless-steel cages and maintained under controlled conditions; 12-h light and 12-h dark cycle, and a constant temperature of 22±3°c. Food and water were freely available in the home cages.

Animals were divided into three groups (6 rats per cage): control group containing the offspring of control mothers fed the control diet,group 2 containing the offspring of obese mothers fed the hyper fat diet (32% oil sunflower), and Group 3 containing the offspring of obese mothers fed the test diet (28% oil sunflower + 4% colocynth oil).

After 8 weeks of diet,the offspring were sacrificed, all the rats were given a lethal intraperitoneal dose of hydro-chloral 10% (300µl/100g bw). Blood was immediately collected from the abdominal aorta. Plasma obtained by low speed (2000 rpm) centrifugation for biochemical analysis. Blood glucose was determined with the glucometer type (Acku check Active, Roche, Mannheim, Germany). Totalcholesterol, triacylglycerol, LDL-Cholesterol, and HDL-Cholesterol concentrations, assayswere done by enzymatic kits (Biosystem, Barcelona, Spain).

Diets

Three different diets were prepared:
Diet1: 16% casein and 4% sunflower oil (control group)
Diet 2: 16% casein and 32% sunflower oil (obese group)
Diet 3:16% casein,28% sunflower oiland 4% Colocynth oil

The composition of each diet is presented in Table2.

Table 2: Composition of the study diets.

Constituents (g/100g diet)	*Group 1:Standard diet 4 % SO*	*Group 2:Obese HFD 32% SO*	*Group 3: 28 % SO+4 % CO*
Casein	16	16	16
Methionine	0,3	0,3	0,3
Starch	60,7	28,7	28,7
Saccharose	05	05	05
Cellulose	05	05	05
Mineral mix	07,37	07,37	07,37
Vitamin mix	02	02	02
Oil	04	32	04
Total	100	100	100
Energetic values Kcal/100g)	317,88	557	557

So: sunflower oil; HFD: High fat diet, Co: Colocynth oil.
Mineral mix composition (g/100 g of dry diet): Ca2+, 4; K+, 2.4; Na+, 1.6; Mg2+, 0.4 Fe2+, 0.12; trace elements: manganese, 0.032; copper, 0.05; zinc, 0.018.
Vitamin mix composition (mg/kg of dry diet): retinol, 1.8; cholicalciferol, 0.019; thiamine, 6; riboflavin, 4.5; pantothenic acid, 21; inositol, 5; ascorbic acid, 240; α-tocopherol, 51; nicotinic acid, 30; folic acid, 1.5; biotin, 0.09.

Statistical analysis: All values are expressed as mean± standard error (SEM). Independent Student's test was applied to analyze the significance of differences between mean values and critical P-values were considered to be significant at 0.05.

RESULTS AND DISCUSSION

Effects of dietary oils on body weights

The weight evolution followed for two months experimental varied significantly according to the diets. A weight gain observed since the first week, between offspring of control rats receiving an isocaloric diet and offspring of obese rats receiving high-fat diet is equal at 75,2 % and this is due to the high fat nature of the food thus promoting weight gain and installing obesity (figure 1).The persistence of obesity and metabolic disorders in offspring of obese mothers suggests an epigenetic programming following an adverse intrauterine environment**[16]**.

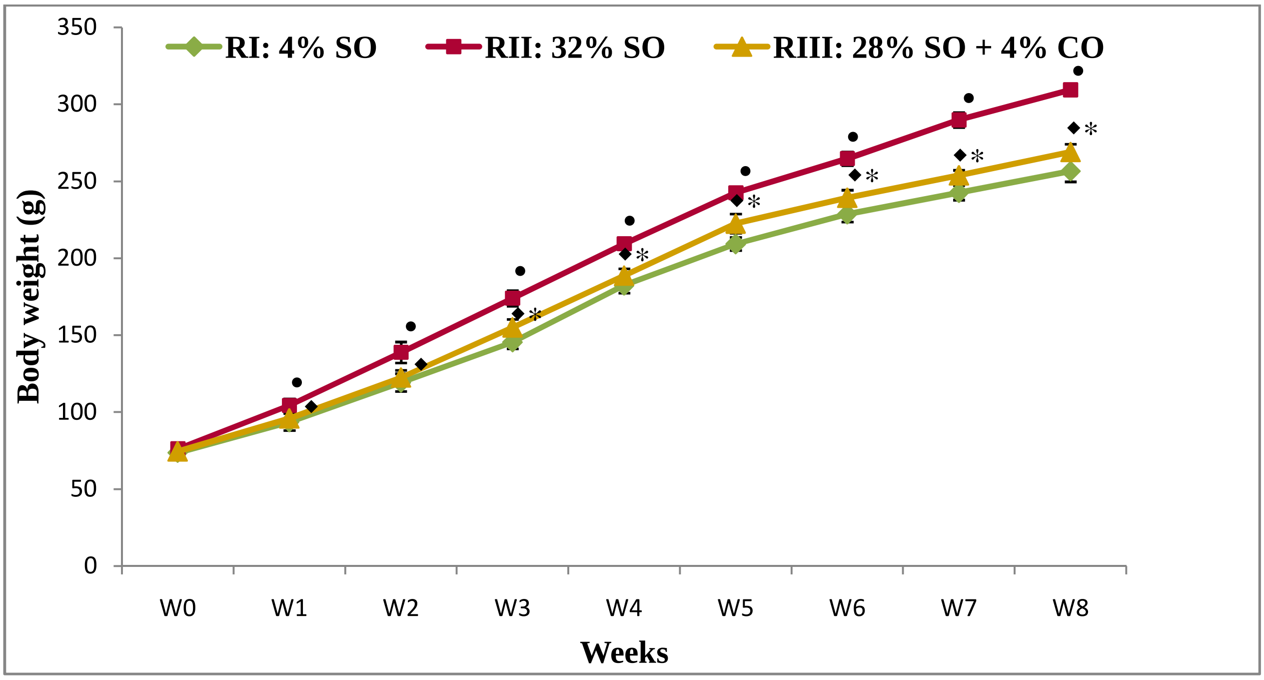

Fig 1: Body weight (g) in rats subjected to different diets during the two months of experimentation.
*So: sunflower oil, Co: Colocynth oil. Values are means ±SEM, n = 6 per group. • P< 0.05 compared to RI (4% SO) RII (32% SO); ♦ P< 0.05 compared to RII (32% SO) RIII (28% SO + 4% CO); * P< 0.05 compared to RI (4% SO) RIII (28% SO + 4% CO).*

However,body weight decreases gradually in rats receiving a high fat diet containing 4% of Colocynth oil.This significant decrease with a correction factor of 43% is due to the fact that this oil is very rich in polyunsaturated fatty acids 77, 2% that have the ability to modulate gene expression and increase energy expenditure by activating hepatic β-oxidation **[17, 18, 19]**. The amount of fat digested by group 3 treated by Colocynth oil remains high and the lipid released shows that this group compared to the others is significantly lower.

Effects of dietary oils on lipid parameters

Regarding biochemical parameters, we note that the offspring of obese rats presented increased serum levels of triglycerides and glucose in total cholesterol compared with controls (table 3).Hypertriglyceridemia and hypercholesterolemia are probably due to increased synthesis and secretion of lipoproteins as a result of fetal hyperinsulinemia and hepatic hyperlipogenese**[20]**.

Obese rats also show an increase in LDL-C and lower HDL-C. This is due to an excessive secretion of hepatic lipoproteins or defect elimination of LDL**[21]**.

Table 3: Effect of C. colocynthis fixed oil on lipid parameters

Parameter (unit)	*Group 1:Standard diet 4 % SO*	*Group 2:Obese HFD 32% SO*	*Group 3: 28 % SO+4 % CO*
Glycaemia (g/l)	**0,98±0,03**	**1,25±0,06•**	**0,8±0,05♦**
Triglycerides (g/l)	**0,51±0,07**	**0,85±0,12•**	**0,45±0,08♦**
Cholesterol (g/l)	**0,63±0,11**	**0,85±0,20•**	**0,59±0,08♦**
LDL-C (g/l)	**0,21±0,02**	**0,49±0,13•**	**0,30±0,04♦**
HDL-C (g/l)	**0,40±0,09**	**0,31±0,03•**	**0,39±0,01♦**

*So: sunflower oil, Co: Colocynth oil, LDL-C: Low Density lipoprotein, HDL-C: high density lipoprotein. Values are means ±SEM, n = 6 per group. • P< 0.05 compared to RI (4% SO) RII (32% SO); ♦ P< 0.05 compared to RII (32% SO) RIII (28% SO + 4% CO); * P< 0.05 compared to RI (4% SO) RIII (28% SO + 4% CO).*

Our results show an decrease in blood glucose in offspring of obese mothers fed a diet of colocynth oil, compared to obese rats and also with control rats. Blood levels of triglycerides and cholesterol also decreased in the group fed with oil of colocynth compared with the other samples (table 3).

We also note an increase in LDL-C in the offspring of obese rats and rats treated with oil of colocynth compared with control rats.However, the plasma levels of HDL-C are increased in control rats and rats treated with oil of colocynth compared to obese rats (table 3).

These effects can be explained by the presence of some inhibitory factors of digestibility in colocynth oil decreasing intestinal absorption of lipids and thereby promoting there fecal elimination. Other explanations of reduction of body weight are also possible, like a toxic effect. Moreover the mean levels of plasma lipids remained relatively low in rats fed diets with colocynth oil, which is rich in minor components such as hydrocarbons, mainly squalenes, α-tocopherol and phytosterols **[15]**. Many and various studies have shown that these substances exert beneficial effects **[22]**. This effect could be due also to the inhibition of intestinal absorption of lipids by this oil.

In conclusion, administration of colocynth oil causes a decrease in body weight and significant lipid-lowering effect in offspring of obese rats. This study suggests that this oil has a remedial and regulating effect on obesity and more depth analysis were up at our laboratory.

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