ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Impact of Curcumin Intake on Gluco- Insulin Homeostasis, Leptin and Adiponectin in Obese Subjects.

Nagwa A. Ismail[1]*, Soha M. Abd El Dayem[1], Emad Salama[1], Shadia Ragab[2], Abeer N.Abd El Baky[1], and Wafaa M. Ezzat[3].

[1]Department of Pediatrics, National Research Centre (NRC), Egypt.
[2]Department of Clinical Pathology, National Research Centre (NRC), Egypt.
[3]Department of Internal Medicine, National Research Centre (NRC), Egypt.

ABSTRACT

Regulation of adipocytokines is linked to inflammation , insulin resistance and obesity complications. Our study investigated the effect of curcumin on serum level of leptin, adiponectin, fasting insulin and blood sugar. A randomized open-label was carried out. The study was divided into trial group (15 obese children and 15 obese adults) receiving curcumin derivative and control group (14 obese children and 14 obese adults) receiving Placebo capsules. Another group of 39 children & 37 adults with normal weight serving as controls for laboratory results. The trial group received one capsule containing 500 mg curcumin for 4 weeks. The control group received one placebo capsule for the same duration. Ingested curcumin resulted in significantly higher fasting serum insulin in both obese children and adults (P =. 014 & .002 respectively) after curcumin intake. A significant reduction in leptin was observed after curcumin supplementation in obese children and adults (P =.014& .000 respectively). Serum adiponectin was increased after curcumin intake. Short-term curcumin supplementation in obese subject could lower plasma leptin level and raising plasma insulin level significantly in obese children and adults. It could have a role in the protection against metabolic disorders related to obesity.

Keywords: obesity, leptin, adiponectin, Curcumin, insulin

ISSN: 0975-8585

INTRODUCTION

Curcumin (CCM) the active ingredient in Turmeric could have a protective role in treatment of obesity and related metabolic disorders [1]. Curcumin, a dietary polyphenol in turmeric affects human preadipocytes mainly in the early stages of differentiation [2]. Fat tissue exerts important endocrine and immune functions through the release of adipocytokines by white adipose tissues. Adipocytokines includes leptin, resistin, plasminogen activator inhibitor type-1 and adiponectin [3]. Adiponectin suppresses the production and secretion of proinflammatory cytokines TNF-α and IL-6 and decreasing the synthesis of monocyte adhesion molecules in endothelial cells [4,5].

Over nutrition, could elevate endoplasmic reticulum stress which activates hypothalamus, and interrupts central insulin/leptin actions [6]. These studies show that regulation of adipocytokines regulate obesity-induced inflammation and insulin resistance. Modification of this pathway could help in the treatment of obesity and its complication.

Leptin is the link between obesity and carcinogenesis, because leptin is increased in obese humans and animals [7, 8], and it stimulates cellular proliferation in many tumor cell lines [9]. leptin stimulates human breast cancer cell proliferation in vitro studies while adiponectin prevent the proliferative actions.

Our aim is to evaluate the impact of curcumin intake on serum level of leptin, adiponectin, fasting insulin and blood sugar.

MATERIAL AND METHODS

A randomized controlled trials, investigating curcumin effect on obesity outcomes, in children, adolescents and young adults without diabetes.

Subjects

The trial was approved by the local ethics committee of National Research Centre (NRC), Egypt. Written informed consent was obtained from adults and parent of each child before enrolment. Twenty nine obese children, defined by BMI >95th percentile for age and sex [10] were enrolment. Also 29 obese adults with BMI >30 were included. Eligibility criteria: age 10-18 years for children and age 20-40 for adults; plus two risk factors: 1st or 2nd degree relative with diabetes, signs or conditions associated with IRS (Acanthosis nigricans; Hypertension; Dyslipidemia; Polycystic ovary syndrome) or metabolic syndrome(a cluster of increased waist circumference, dyslipidemia, impaired glucose metabolism, hypertension). They were enrolled between January and December 2013 at the National Research Centre, Pediatrics and internal medicine Clinics. Exclusion criteria in our study were medical conditions associated with obesity such as, hypothyroidism, Cushing syndrome or Turner syndrome or subjects taking anti- inflammatory drugs or anti-convulsing therapy and contraceptive therapy for the influence on insulin resistance. Another group of 39 children and 37 adults with normal weight serving as controls for laboratory results.

Study drug

All subjects were examined at baseline and after four weeks of ingested curcumin capsules (500 mg tabs, once daily). The extract is standardized to contain a minimum of 95% Curcuminoids: Curcumin, Desmethoxycurcumin, and Bisdemethoxycurcumin. Thus, in our product the full spectrum of Curcumin antioxidant Curcuminoids are extracted from Turmeric (Curcuma longa root) and represented in their natural arrangement for maximum potency.

- Full clinical examination and anthropometric parameters and blood pressure measurements. Measurements of height and body weight were taken by the anthropometric measurements and instruments followed the International Biological Programme (IBP) [11] to calculate body mass index (BMI), where BMI= weight in kg/square height in meters. Blood pressure for each patient was measured according to American Heart Association guidelines weekly three times .All measurements were taken by the same researcher to assure accuracy [12].

- The Laboratory measurements: Fasting venous blood samples were collected on days 1 and 29. Blood samples were collected and centrifuged and separated serum was aliquotted into eppendorf, and stored at −80°C. FBG was assessed by an OLYMPUS AU 400 Chemistry Analyzer, Insulin level and Human Leptin level were estimated by Enzyme immunoassay (ELISA). Adiponectin was measured by ELISA technique using the kit provided from Orgenium Laboratories' Adiponectin (Acrp30) (AviBion Human Adiponectin ELISA, Finland).

Statistical analysis

The standard computer program Statistical Package for the Social Sciences (SPSS) for Windows, release 12.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). Comparison of different variables in various groups was done using Student t test for normal variable. To assess the effect of oral curcumin vs. placebo, the paired sample t test was used to compare means for normally distributed data. P values < 0.05 were considered as statistically significant.

RESULTS

Comparison between obese children & adults and normal weight-matched controls

Twenty nine obese children and 29 obese adults were compared with thirty nine normal weight children and 37 adults with normal weight .The results are shown in Table1. The mean age of the obese children and normal weight controls was 14.70±4.52 and 12.24 ±3.11 years respectively with no statistical significant difference. While in adults it was 37.55±9.93 and 34.35 ±10.75 years respectively with no statistical significant difference. The present work showed that the anthropometric measurements were significantly higher in obese children and adults than in the normal weight controls. Also, the biochemical markers were significantly higher in obese children and adults than in the normal weight controls (table 1).

Table 1: Comparison between normal weight and obese subjects.

	Pediatrics(obese=29&controls=39)			Adults(obese=29&controls=37)			
		Mean	Std. Deviation	Sig. (2-tailed)	Mean	Std. Deviation	Sig. (2-tailed)
AGE years	Obese	14.707	4.52	.089	37.552	9.934	.219
	Controls	12.243	3.11		34.351	10.750	
BMI	Obese	33.9683	6.23	.000	37.7976	6.6399	.000
	Controls	22.1223	2.77		21.3259	2.5519	
DIASTOLIC BP mmHg	Obese	71.90	8.60	.065	79.31	10.67	.054
	Controls	66.00	6.32		74.19	10.44	
SYSTOLIC BP mmHg	Obese	111.55	13.50		123.10	19.88	.133
	Controls	103.00	9.86	.015	116.22	16.85	
WC cm	Obese	97.53	12.04		104.552	14.564	.000
	Controls	72.98	9.33	.000	86.081	14.196	
WHIPR	Obese	.8762	.163	.000	.7300	.1163	.001
	Controls	.8462	.159		.7538	.1559	
HIP C cm	Obese	111.75	123.13	.000	123.138	14.66	.000
	Controls	86.41	104.40		104.405	15.92	
ADIPONECTIN ug/L	Obese	16737.93	5535.37	.020	17346.43	3954.51	.002
	Controls	22256.41	6603.38		34164.86	27154.78	
INSULIN [mU/l]	Obese	6.272	6.03	.488	9.914	5.768	.000
	Controls	6.005	3.79		8.078	3.978	
LEPTIN (ng/mL)	Obese	56.04	25.51	.046	72.24	26.10	.000
	Controls	23.05	32.99		9.10	5.85	
FBG [mg/l]	Obese	89.34	11.00	.899	93.72	15.54	.001
	Controls	87.63	9.81		91.57	7.46	

Results of the trial

A randomized open-label was carried out. The study was divided into trial group (15 obese children and 15 obese adults) receiving curcumin derivative and control group (14 obese children and 14 obese adults)

ISSN: 0975-8585

receiving Placebo capsules. Another group of 39 children & 37 adults with normal weight serving as controls for laboratory results. The trial group received one capsule containing 500 mg curcumin for 4 weeks. The control group received one placebo capsule for the same duration.

Comparison between Curcumin Group and control group (Placebo Group) before starting the study, showed no statistical significant difference between the two groups as shown in table 2.

Table 2: Comparison between basal data of curcumin and placebo groups.

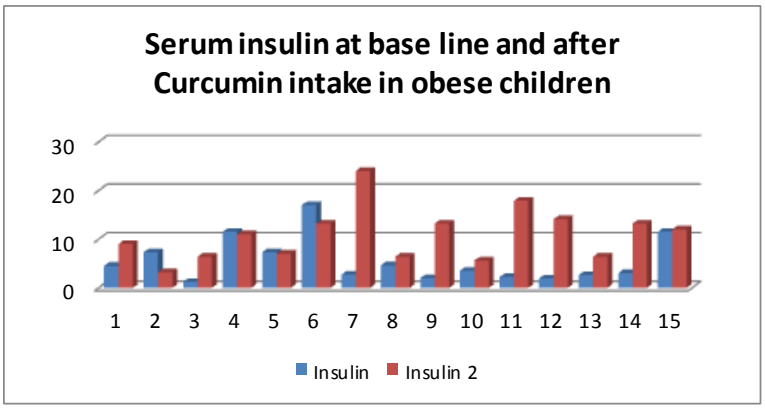
(Pediatrics &Adults)

		Pediatrics Group Statistics			Adults Group Statistics		
		Mean	SD	Sig. (2-tailed)	Mean	SD	Sig. (2-tailed)
Adiponectin ug/L	curcumin Group	16286.67	3885.48	.658	15771.43	3315.56	.123
	placebo Group	17221.43	7017.80		16921.43	4017.88	
INSULIN [mU/l]	curcumin Group	5.520	4.580	.497	9.267	5.071	.138
	placebo Group	7.079	7.389		10.607	6.555	
LEPTIN (ng/mL)	curcumin Group	63.13	20.16	.112	79.07	27.47	.109
	placebo Group	47.17	29.45		64.93	23.30	
FBS [mg/l]	curcumin Group	91.33	9.97	.322	99.07	17.67	.06
	placebo Group	87.21	12.00		88.00	10.74	

Table 3: Paired T-Test Curcumin group (Pediatrics &Adults)

	Pediatrics Paired Samples Statistics (15 cases)			Adults Paired Samples Statistics (15 cases)		
	Mean	Std. Deviation	Sig. (2-tailed)	Mean	Std. Deviation	Sig. (2-tailed)
Adiponectin1	16400.00	4006.34	.633	15771.43	3315.56	.055
Adiponectin2	16771.43	3202.27		18292.86	2857.23	
INSULIN1	5.52	4.58	.014	9.26	5.07	.002
INSULIN2	10.84	5.44		14.06	4.35	
LEPTIN 1	63.13	20.16	.014	79.07	27.47	.000
LEPTIN2	46.68	21.10		57.96	20.629	
FBS 1	91.33	9.97	.390	99.07	17.67	.065
FBS2	88.67	7.13		81.13	31.50	

Table3 and Fig (1-2) show the results of Paired T-Test Curcumin (Pediatrics &Adults). Comparison of samples taken immediately before dosing and at 29 day was performed by paired t test for individual values revealed that the mean fasting blood glucose level before was decreased from that after ingestion of the curcumin in obese children and adults. The mean FBG levels of the obese children before and after curcumin intake were 91.33 ±9.97 & 88.67 ±7.13 [mg/l] respectively, the mean FBG in adults were 99.07 ±17.67 & 81.13 ± 31.50 [mg/l] respectively. Ingested curcumin resulted in significantly higher fasting serum insulin in both obese children and adults (P= .014& .002 respectively) after curcumin intake.



ISSN: 0975-8585

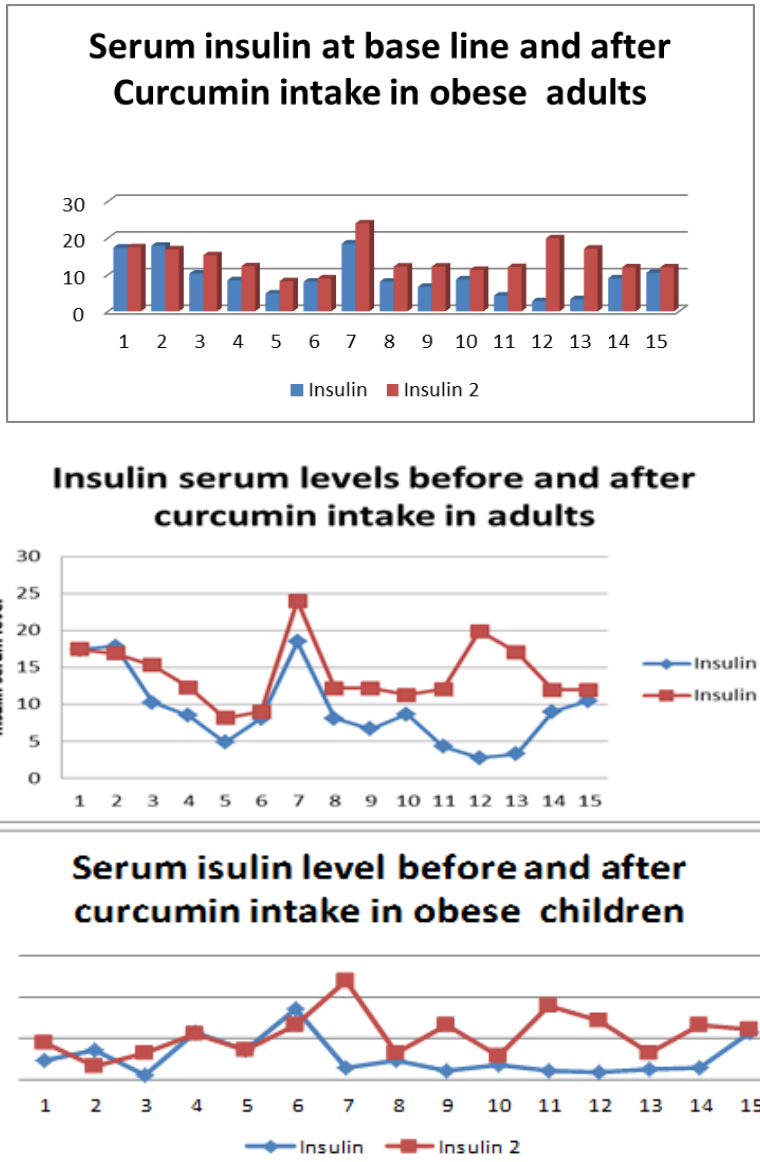


Figure 1: Serum insulin at base line and after Curcumin intake in obese children &adults

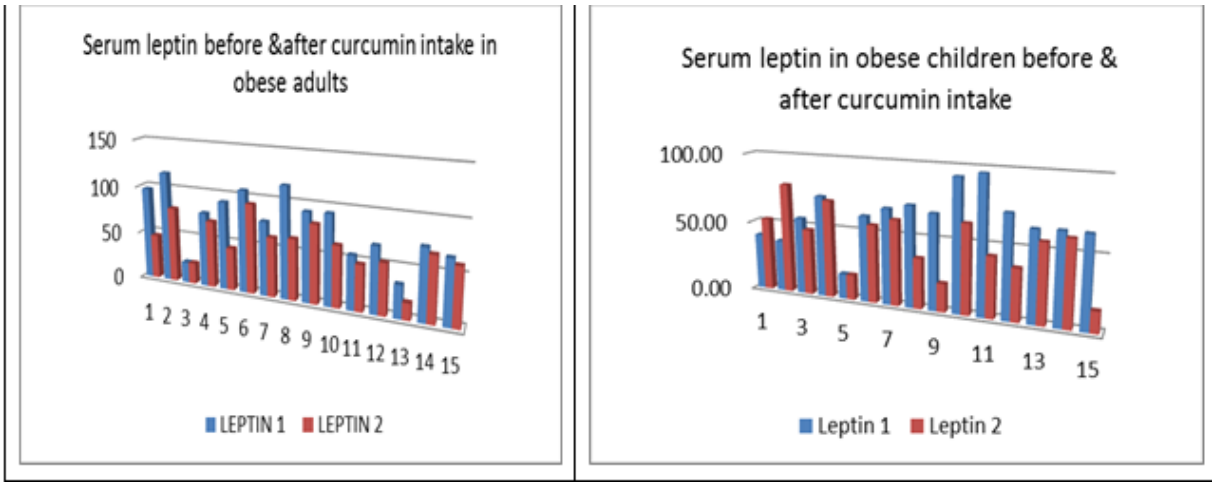


Figure 2: Serum leptin level before and after curcumin intake in obese children and adults

As regards serum leptin there were statistically significantly decrease between samples taken immediately before starting curcumin and at 29 day in obese children and adults(P = .014& .000 respectively). Serum adiponectin was increased in serum levels after curcumin intake. The mean serum levels of the obese children before and after curcumin intake were 16400 ±4006.34 ug/L & 16771.43±3202.27 ug/L respectively, the mean serum adiponectin levels in adults were 15771.43 ±3315.56 ug/L & 18292.86 ±2857.23 ug/L respectively.

Table 4 shows the results of Paired T-Test Placebo group (Pediatrics & Adults). No significant changes were detected after placebo trial neither in obese children nor in obese adults.

Table 4: Paired T-Test Placebo group (Pediatrics & Adults)

	Pediatrics Paired Samples Statistics (14)			Adults Paired Samples Statistics (14)		
	Mean	**SD**	**Sig. (2-tailed)**	**Mean**	**SD**	**Sig. (2-tailed)**
Adiponectin1	17221.43	7017.80	.343	4017.88	1073.82	.883
Adiponectin2	16101.79	5506.80		4059.72	1085.01	
INSULIN 1	7.079	7.38	.680	6.555	1.752	.160
INSULIN2	6.943	7.00		5.472	1.462	
LEPTIN 1	47.17	29.45		23.30	6.23	.086
LEPTIN2	45.483	28.74	.168	23.490	6.278	
FBS1	87.21	12.00	.401	10.74	2.87	.888
FBS2	88.57	10.01		5.69	1.52	

DISCUSSION

Obesity is a major problem in most countries. We aimed to elucidate the effect of the curcumin intake on serum level of leptin, adiponectin, fasting insulin and blood sugar. The results show that the ingestion of one capsule containing 500 mg curcumin with the main meal for 4 weeks increased fasting serum insulin concentration significantly with a non-significant decrease in fasting blood glucose. Our result is in accordance with the results of Wickenberg et al. they reported that the ingestion of curcumin increased serum insulin levels, but did not seem to affect the level of blood glucose in normal adults [13].Abdel Aziz et al., reported that giving curcumin to diabetic rats resulted in significant lower plasma glucose and increased plasma insulin. They explained that by the fact that curcumin in small dose has antidiabetic actions [14]. Seo et.al, reported that curcumin could decrease serum glucose and HbA 1c levels in diabetic mice. Curcumin resulted also in increase glucokinase activity in liver tissue but G6Pase and phosphoenolpyruvate carboxykinase activities were decreased [15].

Our study showed that obese subjects had significantly increased in BMI, waist circumference, hip circumference and waist hip ratio than in controls, in accordance with previous studies [16, 17]. In our study, leptin serum level was significantly higher in obese children and adults compared to controls. This result is in concordance with a study of Adel Salah et al. [18] and Yu-Feng et al. [19]. Kern et al. reported that the level of serum adiponectin was significantly lower among obese in contrast to many of the other adipokines, the levels of which rise in obesity [20].

Oral curcumin had a beneficial effect over placebo for serum leptin. In our study significant decrease in serum leptin level after the 4 weeks of curcumin intake was recorded. Ciardi et.al, reported a dose-dependent decrease in leptin with curcumin [21]. Curcumin could suppress the proinflammatory transcription factor nuclear factor-kappa B in adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells leading to the downregulation of adipokines, including leptin [21].

In obesity leptin is the main cause of oxidative stress; curcumin could decrease the levels of reactive oxygen species and lipid peroxidation in cultured hepatic stellate cells [22] . The expression of adiponectin decreases with increase in the adiposity. Adiponectin mediates insulin-sensitizing effect by binding to its receptors AdipoR1 and AdipoR2, resulting in activation of adenosine monophosphate dependent kinase (AMPK), PPAR-α′ [23- 24].

Oral curcumin seems to have a beneficial effect on serum adiponectin as it increased the mean serum levels ,giving oral curcumin for a longer duration might made this change of statistical significance.

This study had some limitations. First, we did not follow-up our cases to assess the persistence of the drug effect after its cessation. Second, some results as serum adiponectin level might need a longer duration of intake to be well evaluated.

CONCLUSIONS

The curcumin by its dose 500 mg per day could decrease serum glucose level and increase serum insulin level in obese children and adults. Curcumin appears to improve serum adiponectin and downregulates leptin in obese persons. Future studies utilizing curcumin for longer duration are recommended.

ACKNOWLEDGEMENTS

The study was a part of a project supported financially by National Research Centre Egypt, grant no. 9090102

REFERENCES

[1] Aggarwal BB. Annu Rev Nutr , 2010; 30:14.1–14.27
[2] Kim CY, Le TT, Chen C, Cheng JX, Kim KH. J Nutr Biochem, 2011; 22:910-20.
[3] Aggarwal BB. Nat Rev Immunol 2003; 3:745–56
[4] Ajuwon KM, Spurlock ME. Am J Physiol Regul Integr Comp Physiol 2005; 288:R1220–25
[5] Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, et al. Circulation 2000;102:1296–301
[6] Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Cell 2008; 135:61–73.
[7] Maffei M, et al. Nat Med 1995; 1: 1155-1161.
[8] Frederich RC, et al. Nat Med 1995; 1: 1311-1314.
[9] Garofalo, C. and Surmacz, E. J Cell Physiol 2006; 207: 12-22.
[10] Ghalli I, Salah N, Hussien F, Erfan M, El-Ruby M, Mazen I, et al. In: Proceedings of the 1stNational Congress for Egyptian Growth Curves, Cairo University. Cairo Published in Cresceve Ferring Company. Eds: Sartorio, A., J.M.H. Buckler and N. Marazzi, 2002. Egyptian Growth Curves for Infants, Children and Adolescents.
[11] Hiernaux J, Tanner JM. Growth and physique: anthropometry. In: Weiner JS, Lourie JA, eds. Human biology, a guide to field methods. Philadelphia, FA Davis Company, 1969:2–42.
[12] NHBPEP : National High Blood Pressure Education Working Group. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114:555–576.
[13] Wickenberg J, Sandra L I, Joanna H. Nutrition J 2010; 9:43
[14] Abdel Aziz, Mohamed F El-Asmar, Ibrahim N El-Ibrashy,et al. Diabetol Metab Synd 2012; 4:30.
[15] Seo KI, Choi MS, Jung UJ, Kim HJ, Yeo J, Jeon SM, Lee MK. Mol Nutr Food Res 2008; 52(9):995–1004.
[16] Ismail NA, Nahla M. Mansour, Shadia Ragab et al. RJPBCS 2014; 5,6 :646-653
[17] Ismail N A , Shadia Ragab, Soha M. Abd El Dayem et al. Arch Med Sci 2012; 8(5): 826-833
[18] Adel Salah, Mostafa Ragab, Waleed Mansour, Mohammed Taher. Egyptian J Chest Dis Tubercul 2015; 64(3): 529-533.
[19] Yu-Feng Tian, et al. Life Sci 2014; 116(1): 51-58
[20] Kern GB. Di Gregorio, T Lu, et al, Diabetes 2003;52: 1779–1785.
[21] Ciardi C, Jenny M, Tschoner A, Ueberall F, Patsch J, Pedrini M, Ebenbichler C, Fuchs D. Br J Nutr 2011; 1:1-8.
[22] Tang Y, Zheng S, Chen A. Endocrinol 2009; 150:3011–20
[23] Yadav A1, Kataria MA, Saini V, Yadav A. Clin Chim Acta 2013; 417:80-4.
[24] Ohara K, Uchida A, Nagasaka R, Ushio H, Ohshima T. Phytomed 2009; 16:130–37
[25] Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, et al. Circulation 1999; 100:2473–76
[26] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. Nat Med 2001; 7:947–53
[27] Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. J Biol Chem 2003; 278:45021–26
[28] Grossmann ME, Ray A, Dogan S, et al. Cell Res 2008; 18:1154-1156