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The Effect of Curcumin on Some Plasma Cytokine Levels in Experimentally-Induced Diabetic Rats

Diyabet Oluşturulan Ratlarda Kurkuminin Bazı Plazma Sitokin Düzeyleri Üzerine Etkisi

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This study was presented as orally in 5. International Eurasian Congress on Natural Nutrition and Healthy Life, 2-6 October 2019, Ankara, Turkey.

ABSTRACT Objective: The aim of this study was to determine the effect of curcumin on some plasma cytokines and insulin levels in diabetes mellitus, which has negative effects on many acute and chronic systems in humans and animals. **Material and Methods:** In the study, thirty adult male Wistar albino rats with similar live weights were used. The subjects used in the study were divided into four groups including Control (K), Diabetes (D), Curcumin (C), and Diabetes+Curcumin (DC). At the end of the experiment, interleukin-6 (IL-6), IL-10, insulin, tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) levels in the blood samples taken from the subjects in the groups were determined. **Results:** IL-6 level was determined to increase significantly in experimentally induced diabetic rats compared to the other three groups ($p<0.05$). The IL-6 level in the C group was found to be similar to that in the K group whereas it was observed that the IL-6 level was significantly lower in the DC group, in which C was supplemented for the experimentally induced diabetic rats, than in the D group, and approached to the levels obtained in the K and C groups ($p<0.05$). The CRP level was significantly higher in the D group compared to the other three groups whereas the insulin level was prominently lower ($p<0.05$). In this study, it was observed that there was a positive and strong relationship between IL-6 and TNF and CRP, and a moderately strong and negative relationship with insulin **Conclusion:** In conclusion, it was seen that curcumin application does not cause a negative impact on healthy rats and that it is beneficial in reducing the negative effects of diabetes in streptozotocin-induced diabetic rats.

Keywords: Diabetes mellitus; cytokine; curcumin; insulin; streptozotocin

ÖZET Amaç: Bu çalışmanın amacı; insan ve hayvanlarda akut ve kronik çok sayıda sistem üzerine olumsuz etkileri olan diabetes mellitusta, kurkumin verilmesinin bazı plazma sitokinleri ve insülin düzeyine etkisinin belirlemektir. **Gereç ve Yöntemler:** Çalışmada, canlı ağırlıkları birbirine yakın 30 adet yetişkin erkek Wistar Albino sıçan kullanıldı. Denemede kullanılan denekler Kontrol (K), Diyabet (D), Kurkumin (C) ve Diyabet+Kurkumin (DC) olmak üzere 4 gruba ayrıldı. Araştırmada, deneme sonunda gruplardaki deneklerden alınan kan örneklerinde interlökin-6 (IL-6), IL-10, insülin, tümör nekroz faktör alfa (TNF-α), C-reaktif protein (CRP) düzeyleri belirlendi. **Bulgular:** IL-6 düzeyinin diyabet oluşturulan sıçanlarda diğer 3 gruba göre önemli ($p<0,05$) oranda arttığı belirlendi. Kurkumin uygulanan grupta belirlenen IL-6 düzeyi kontrole benzerken, diyabet oluşturulduktan sonra C takviyesi yapılan DC grubunda ise IL-6 düzeyinin D grubuna göre önemli oranda düşük olduğu, K ve C gruplarından elde edilen düzeylere ise yaklaştığı gözlendi ($p<0,05$). IL-10 düzeyinin C grubunda D grubuna kıyasla daha yüksek olduğu, D grubuna kurkumin takviyesinden sonra DC grubunda da IL-10 seviyesinin önemli ($p<0,05$) oranda arttığı belirlendi. D grubunda CRP seviyesi diğer 3 gruba göre anlamlı bir şekilde yüksek iken insülin düzeyi ise belirgin bir şekilde düşük olarak belirlendi ($p<0,05$). Bu çalışmada, IL-6 ile TNF ve CRP arasında pozitif ve güçlü bir ilişki olduğu, insülin ile orta derecede güçlü ve negatif bir ilişki olduğu görülmüştür. **Sonuç:** Streptozotosin ile deneysel diyabet oluşturulan sıçanlarda kurkumin uygulaması sağlıklı sıçanlarda olumsuz bir etki oluşturmamasının yanı sıra diyabette de meydana gelen olumsuz etkileri hafifletmesi bakımından yararlı olduğu görülmektedir.

Anahtar Kelimeler: Diabetes mellitus; sitokin; kurkumin; insülin; streptozotosin

Diabetes mellitus (DM) is a chronic and metabolic disease that develops due to complete or partial insufficiency of insulin hormone secreted from beta cells in the pancreas or insulin resistance and that causes impairments in carbohydrate, protein, fat metabolisms.[1] DM is considered epidemic worldwide due to severe acute and chronic complications. According to the World Health Organization (WHO) es-

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timate, about 500 million people will have DM by 2030.[2] It has been reported that genetic and environmental factors have great importance in the development and complications of DM.[3] Among the environmental factors, obesity, especially abdominal fat accumulation, is a prominent and frequently seen factor in individuals with diabetes. It has been reported that it affects the inflammatory response of various genes and gene sites, and that cytokines with genetic susceptibility play a role in this response.[3,4]

Cytokines are natural and adaptive immunity regulators that allow immune system cells to communicate at short range. Cytokines are secreted by the cells of the immune system and, similar to those in interferons, disrupt cell integrity by causing cellular damage in response to infection.[5] Cytokines are important immune regulators that play a role in the emergence of many problems in DM and the pro-inflammatory factors are synthesized and secreted from adipose tissue in the mechanism of chronic inflammation. DM causes changes in the functions of inflammatory cells and cytokine patterns, impairment in the matrix cycle, chronic infection, and many acute and chronic complications. Infection, neuropathy, and major degenerative changes, which may lead to morbidity, disability, and hospitalization, occur in patients.[6,7] In the development of these degenerative changes in diabetes, pro-inflammatory/anti-inflammatory cytokines produced by the cells of the defense mechanism of the host against microorganisms and antigens are very important. Inflammatory mechanisms have been reported to cause diabetes, insulin resistance, and increased free fatty acid levels.[8] IL-6 level is correlated directly with obesity, glucose intolerance, and insulin resistance. Plasma IL-6 level is an important determinant in DM. In addition, IL-6 is an important regulator and stimulus of C-reactive protein (CRP) synthesis.[8] Tumor necrosis factor (TNF) has pro-inflammatory properties and is indirectly involved in insulin resistance pathogenesis and obesity.[6-9]

Curcumin is a yellow compound isolated from the *Curcuma longa* plant, which is a member of the Zingiberaceae family and commonly used in Asian countries.[10] It has many features such as anti-inflammatory, anti-diabetic, anti-coagulant, anti-carcinogenic, anti-mutagenic, anti-bacterial, anti-viral, and antioxidant.[1,11] It has been reported that it limits the expression and signaling of TNF alpha (TNF-α), reduces insulin resistance, and has an anti-diabetic effect in patients with type-II diabetes.[12] The essential oils found in curcumin have anti-inflammatory effects. In the studies, it has been reported that curcumin leads to an anti-inflammatory effect by activating the B cell (NF-kb) pathway and It is effective in the inhibition of cytokines, which we know as pro-inflammatory, such as TNF-α and CRP.[13]

In light of this information, the purpose of this experimental study was to determine the effect of curcumin on certain plasma cytokine levels in experimentally-induced diabetic rats.

MATERIAL AND METHODS

STUDY ANIMALS

In this study, animal rights were protected in line with the Guidelines for the Care and Use of Laboratory Animals, and a work document and ethics committee approval were obtained. Approval was obtained from Selçuk University Experimental Medicine Research and Application Center Experimental Animals Ethics Committee on 21.03.2017 with the number of decision 2017-11. The study was conducted in accordance with the Helsinki Declaration principles. We used 30 healthy, 350±10 g 4-month-old male rats. The experimental animals were divided into four groups as control (K), DM (D), Curcumin (C) and DM+Curcumin (DC). A single dose of 60 mg/kg streptozotocin (STZ) (Streptozotocin, Sigma S0130-1G, China) dissolved in 0.1M citrate buffer (pH 4.5) was administered to the D and DC group through intra-peritoneal injection. Three days after the STZ administration, fasting blood glucose level of the rats was tested from the capillary blood collected from the tail end using glucometry (PlusMED) in order to check whether diabetes formed. Animals with fasting blood sugar levels of 250 mg/dL and above were considered DM. After the formation of diabetes, 50 mg/kg/day curcumin (Sigma C1386-10G, China) was administered by gavage throughout the study. The ex-

periment was pursued for 4 weeks after the formation of diabetes.

BLOOD ANALYSIS

At the end of the working period, blood samples of the subjects in the groups were collected from the heart through cardiac puncture under general anesthesia (Xylazine 10 mg/kg and Ketamine 5 mg/kg anesthesia) into anti-coagulant (ethylenediaminetetraacetic acid) tubes. Rats, of which blood samples were taken, were killed by cervical dislocation while under anesthesia. Collected blood samples were centrifuged, the serum and plasma were separated and stored at -80 ^{o}C until the time of analysis. Insulin, IL-6, IL-10, CRP, and TNF levels in the plasma and serum were determined in the Siemens Centaur XP Immunoassay System using commercial kits (Siemens, USA) according to their protocols.

STATISTICAL EVALUATION

Descriptive statistics are presented with mean, standard deviation values. Shapiro Wilk's test was applied to examine the normality distributions of IL-6, IL-10, insulin, TNF-α, CRP measurements of the study groups. According to the test results, the non-parametric test approach was chosen because the distributions of IL-6 and IL-10, insulin, TNF-α, CRP did not show normal distribution and the number for the group was n=6. In the study, Kruskal Wallis test was used to analyze the difference between IL-6 and IL-10, insulin, TNF-α, CRP measurement values of four different groups, Mann for each pair of groups to identify groups that make the difference. Comparison test of Whitney-U (Bonferroni corrected) test was used. In addition, Sperman correlation was used to examine the relationships between IL-6, IL-10, insulin, TNF-α, CRP measurements. P values less than 0.05 were considered statistically significant in the study. The analyzes were made with the SPSS 25.0 package program.

RESULTS

Findings obtained in the experimental study are presented in Table 1 and Table 2.

In Table 1, it was seen that IL-6 measurement was at different levels according to the study groups. The reason for the difference was that the IL-6 levels of the DC and D groups were higher than the C and K groups ($p=0.01$, $p<0.05$).

It was observed that IL-10 measurement was at different levels according to the study groups. It was observed that the reason for the difference was that the IL-10 levels of the D groups were lower than the C and K groups ($p=0.03$, $p<0.05$).

TABLE 1: The effect of curcumin administration on IL-6 and IL-10 in experimentally-induced diabetic rats.

Measure	K (n=6) X±SD	C (n=6) X±SD	D (n=6) X±SD	DC (n=6) X±SD	p value	Post-hoc
IL-6	35.85±4.59	36.00±3.96	85.35±32.67	61.6±15.65	0.01*	D, DC >K, C
IL-10	56.41±19.00	51.84±21.17	27.07±10.46	42.14±12.22	0.03*	D< K, C

*0.05 Significant difference in level; *K: Control group; C: Curcumin group, D: Diabetes group, DC: Diabetes and curcumin group; IL: Interleukin; SD; Standart deviation.

TABLE 2: The effect of curcumin administration on plasma insulin, TNF-α, and CRP levels in experimentally-induced diabetic rats.

Measure	K (n=6) X±SD	C (n=6) X±SD	D (n=6) X±SD	DC (n=6) X±SD	p value	Post-hoc
TNF	54.85±13.25	52.93±5.88	119.42±48.93	85.47±19.05	0.01	D, DC> K,C
Insulin	1.17±0.42	1.02±0.15	0.69±0.17	0.83±0.16	0.02	D<K,C
CRP	1.02±2.01	0.92±1.30	15.68±8.13	7.17±7.46	0.01	D, DC> K,C

0.05 Significant difference in level; K: Control group; C: Curcumin group, D: Diabetes group, DC: Diabetes and curcumin group; SD; Standart deviation; TNF: Tumor necrosis factor; CRP: C-reactive protein.

In Table 2, it was seen that TNF measurement was at different levels according to the study groups. The reason for the difference was that the levels of TNF in the DC and D groups were higher than the C and K groups ($p=0.01$, $p<0.05$).

It was observed that the insulin measurement was at different levels according to the study groups. It was observed that the reason for the difference was that the insulin levels of the D groups were lower than the C and K groups ($p=0.02$, $p<0.05$).

In the study, it was observed that CRP measurement according to the groups was at different levels according to the groups. The reason for the difference was that the CRP levels of the DC and D groups were higher than the C and K groups ($p=0.01$, $p<0.05$).

It was observed in Table 3 that there was no relationship between IL-6 and IL-10 levels ($p=0.08$). It was observed that there was a positive and strong relationship between IL-6 and TNF and CRP ($p=0.01$), and a moderately strong and negative relationship with insulin ($p=0.04$). It was observed that there was a negative and moderately strong relationship between IL-10 and TNF and CRP ($p=0.01$), and there was no relationship between insulin levels ($p=0.13$). It was observed that there was a negative and strong relationship between TNF and insulin ($p=0.01$), a positive and strong relationship between TNF and CRP ($p=0.01$), and a negative and strong relationship between TNF and CRP ($p=0.01$)

DISCUSSION

According to the World Health Organization (WHO) data, approximately 4 billion people first try to overcome their problems through herbal medicines when they encounter health problems and 80% of the world's population and 95% of the African population use treatment methods based on medicinal plants.[14] Recent studies on curcumin have shown that curcumin modulates many growth factors, enzymes, and cytokines. It has been reported that, in particular, it is highly effective in the pathogenesis of the inflammatory process as well reducing the number of pancreatic cells involved in antidiabetics and hypoglycemia.[15]

In the study, it was seen that TNF measurement was at different levels according to the study groups. The reason for the difference was that the levels of TNF in the DC and D groups were higher than the C and K groups ($p=0.01$). Besides, it was found that CRP, IL-6, TNF-α levels of group D increased significantly compared to other groups (K, C, and DC) ($p<0.05$). In addition, IL-10 and insulin levels in the animals in the D group were significantly lower than the other groups. When the data obtained from the C group were examined, they were found to be similar to those in the K group in terms of the parameters generally examined. Moreover, when the data obtained from the group (DC) in which curcumin was administered after D formation group were examined, it was found to be significantly lower than that in the D group ($p<0.05$) but still higher than those in the K and C groups. However, in terms of

TABLE 3: Relationship between IL-6 and IL-10, insulin, TNF-α, CRP levels.

Measure		IL-6	IL-10	TNF	Insulin	CRP
IL-6	r value	1				
	p value					
IL-10	r value	-0.37	1			
	p value	0.08				
TNF	r value	0.67	-0.52	1		
	p value	0.01	0.01			
Insulin	r value	-0.47	0.32	-0.65	1	
	p value	0.04	0.13	0.01		
CRP	r value	0.66	-0.41	0.62	-0.69	1
	p value	0.01	0.04	0.05	0.01	

IL: Interleukin; TNF: Tumor necrosis factor; CRP: C-reactive protein.

the other parameters (TNF-α, CRP, IL-10, and insulin), the values obtained from the DC group were found to be significantly different from that obtained from the D group whereas it was similar to the values measured in K and C groups.

In many studies conducted in recent years, chronic inflammation has been reported to play an important role in the development of type 2 diabetes.[16] Proinflammatory cytokines such as TNF-α, IL-1, and IL-10 are secreted from adipose tissue and it is thought that there is a close correlation between body fat mass and these inflammatory cytokines. Obesity, in other words, increased subcutaneous adipose tissue is a risk factor for DM and is caused by leptin release and increased fatty acids. Leptin release is directly proportional to adipose tissue. It stimulates the production of IL-6 and TNF-α, activates nuclear factor kappa B (NF-Kb), which is one of the key members of inflammation, thus leads to the increase of IL-6 and TNF-α.[17]

In this study, it was observed that there was a positive and strong relationship between IL-6 and TNF and CRP, and a moderately strong and negative relationship with insulin. Similar collation has been reported in constructions.[35] Carey et al. reported that there was no such correlation in their study.[36]

It has been reported that plasma IL-6 has a predictive characteristic for the development of diabetes and that there is a very strong, prominent, and reverse correlation between IL-6 level and insulin sensitivity.[8] In the study conducted by Vestra et al. with diabetic patients, it was reported that CRP and IL-6 levels increased in cases who developed nephropathy.[18] Demir et al. determined a significant increase in IL-6 and TNF-α levels in experimentally-induced diabetic rat models.[17] In a study conducted on experimentally induced diabetic dog models, an increase in IL-6 levels was determined in the experimental group compared to healthy dogs.[19] In the study conducted by Yalcınkaya et al. with diabetic patients, the correlation between IL-6, TNF-α, CRP levels as well insulin resistance and DM was examined and it was found that IL-6, TNF-α, CRP levels increased in diabetic individuals.[7] It is stated that these pro-inflammatory cytokines also increase the production of TNF-α in microvascular and neural tissues, leading to an increase in microvascular permeability and to damage in hypercoagulability and nerves, thus causes diabetic polyneuropathy.[9]

Soetikno et al. conducted a study on rats with diabetic nephropathy and applied 100 mg/kg curcumin treatment daily for 8 weeks. As a result, they found that hyperglycemia developed at the end of the experiment caused nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha and NF-κB activation, increased pro-inflammatory cytokines, and macrophage infiltration. They reported that curcumin treatment reduced macrophage infiltration.[20] The inflammation process, which is considered to be one of the main factors involved in diabetes pathogenesis, has been emphasized in the studies investigating the relationship between diabetes and curcumin and the beneficial effect of curcumin on diabetes has been explained with its positive contribution in the inflammation process and its ability to accelerate the immune system.[21] In this study, the changes occurred in pro-inflammatory cytokines in STZ-induced diabetic rats showed that diabetes caused significant inflammation-based problems in the liver, pancreas, and other tissues. In fact, it has been suggested that pro-inflammatory cytokines suppress insulin transduction and cause insulin resistance in the liver, skeletal muscle, and other tissues by.[22]

It has been reported that curcumin affects the activation of liver enzymes involved in fat metabolism, glycolysis, gluconeogenesis.[23] Seo et al. observed that curcumin supplementation reduced glucose intolerance in a diabetic rat model that developed obesity at the same time with insulin resistance.[23] In some studies, it has been found that concomitant administration of curcumin with vitamin C and yogurt reduces blood sugar and HbA1c levels, in particular.[24,25] Moreover, insulin resistance may cause excessive CRP release and this is attributed to the effect of insulin on hepatic acute phase protein synthesis. It is known that the CRP level increases during chronic inflammation process in diabetes. In metabolic syndrome, the reason for the increase in CRP level has been associated with the production of cytokines from adipose tissue.[26] In the present study, it was observed that CRP measurement according to the groups was at different

levels according to the groups. The reason for the difference was that the CRP levels of the DC and D groups were higher than the C and K group ($p<0.05$).

Curcumin is an indigenous anti-inflammatory component, can stimulate the expression and also production of IL-10, can increase the effect on multiple tissues. It has been reported that curcumin modulates the IL-10 secretion in in-vitro and preclinical models.[27] It was observed that IL-10 measurement was at different levels according to the study groups. It was observed that the reason for the difference was that the IL-10 levels of the D groups were lower than the C and K groups. This finding supports the idea that curcumin modulates the immune system. Li et al. reported that oral administration of curcumin (15 mg/kg, 30 mg/kg, 60 mg/kg) increased insulin receptor activity by stimulating insulin resistance in rats.[28] In another study, curcumin administration to rats has been reported to improve blood-cell activities and insulin release, lower blood sugar and HbA1c levels.[29]

In this study, as in the above-mentioned studies, the fact that the data obtained from the C group were similar to the those in the K group or that there was no significant difference suggests that curcumin is reliable for homeostatic mechanisms of inflammation. It shows that curcumin has an immuno-modulatory effect rather than an immuno-suppressive effect in terms of the diabetic condition.

Many of the experimental studies report that curcumin can be used as a positive option for the management of DM and insulin resistance.[30,31] In fact, in a study, it was found that curcumin reduces insulin resistance, increases the uptake of glucose in muscles, and reduces plasma glucose level.[32] In experimentally-induced mouse and rat models with insulin resistance and DM, Curcumin has been reported to increase its sensitivity by increasing insulin stimulation.[32,33] Chougale et al. determined that curcumin reduces hyperglycemia and prevents weight loss.[34] In accordance with all this information, it was seen that curcumin administration plays an effective role in regulating insulin level. These findings obtained from the study supports this view. In line with these results, the positive effect of curcumin may mediate in insulin resistance and diabetes through protein homeostasis regulation.[35]

In this study, it was observed that there was a pos-itive and strong relationship between IL-6 and TNF and CRP, and a moderately strong and negative relationship with insulin. Similar collation has been reported in con-structions.[36] Carey et al. reported that there was no such correlation in their study.[37]

CONCLUSION

In conclusion, in this study, curcumin was preferred since it is a natural product and effective in STZ-induced diabetic rats in terms of cytokines. It was remarkable that it had a positive effect on insulin, IL-6-10, CRP and also TNF-α levels in diabetic patients and did not cause a negative effect on rats in the C group. According to the results of the study, it was observed that there was no relationship between IL-6 and IL-10 levels, there was a positive and strong relationship between TNF and CRP, there was a negative and moderately strong relationship between IL-10 and TNF and CRP, but there was no relationship between insulin levels. In direction of this information obtained from the study, it was concluded that inflammation-targeted therapy may be a new treatment option in terms of the follow-up of DM and its complications.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nurcan Dönmez, Ülkü Saygılı;* ***Design:*** *Nurcan Dönmez;* ***Control/Supervision:*** *Ülkü Saygılı, Nurcan Dönmez;* ***Data Collection and/or Processing:*** *Ülkü Saygılı;* ***Analysis and/or Interpretation:*** *Ülkü Saygılı;* ***Literature Review:*** *Ülkü Saygılı;* ***Writing the Article:*** *Ülkü Saygılı;* ***Critical Review:*** *Nurcan Dönmez;* ***References and Fundings:*** *Nurcan Dönmez;* ***Materials:*** *Ülkü Saygılı, Nurcan Dönmez.*

REFERENCES

1. Mancia SR, Trujillo J, Chaverri JP. Utility of curcumin for the treatment of diabetes mellitus: Evidence from preclinical and clinical studies. Journal of Nutrition & Intermediary Metabolism 2018;14:29-41. [Link]
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4-14. [Crossref] [PubMed]
3. Cruz NG, Sousa LP, Sousa MO, Pietrani NT, Fernandes AP, Gomes KB. The linkage between inflammation and Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2013;99(2):85-92. [Crossref] [PubMed]
4. Liu T, Yang W, Pang S, Yu S, Yan B. Functional genetic variants within the SIRT2 gene promoter in type 2 diabetes mellitus. Diabetes Res Clin Pract. 2018;137:200-7. [Crossref] [PubMed]
5. Conlon KC, Miljkovic MD, Waldmann TA. Cytokines in the Treatment of Cancer. J Interferon Cytokine Res. 2019;39(1):6-21. [Crossref] [PubMed] [PMC]
6. Li J, Liu B, Cai M, Lin X, Lou S. Glucose metabolic alterations in hippocampus of diabetes mellitus rats and the regulation of aerobic exercise. Behav Brain Res. 2019;364:447-56. [Crossref] [PubMed]
7. Yalçınkaya Z, Turan H, Demir H. [Relationship with cytokine of patients diabetes]. Uluslararası Bilimsel Araştırmalar Dergisi. 2017;449-51. [Link]
8. Emral R. [Adiponectin and other cytokines: medical education]. Turkey Clinics Journal of Medical Sciences. 2006;26(4):409-20. [Link]
9. Yarım GF, Kazak F. [Cytokine response in metabolic syndrome and its components]. Journal of Harran University Faculty of Veterinary Medicine 2016;5(1):90-9. [Link]
10. Yalçın AS, Yılmaz AM, Altundağ EM, Koçtürk S. [Anti-cancer effects of curcumin, quercetin and tea catechins]. Marmara Pharmaceutical Journal. 2016;21:19-29. [Crossref]
11. Belviranli M, Okudan N, Nurullahoğlu Atalık KE. Effects of curcumin supplementation on oxidant / antioxidant status of heart tissue in elderly rats. Journal of General Medicine. 2012;22(2):61-6. [Link]
12. Ghosh S, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. Food Chem Toxicol. 2015;83:111-24. [Crossref] [PubMed]
13. Maithilikarpagaselvi N, Sridhar MG, Swaminathan RP, Zachariah B. Curcumin prevents inflammatory response, oxidative stress and insulin resistance in high fructose fed male Wistar rats: Potential role of serine kinases. Chem Biol Interact. 2016;244:187-94. [Crossref] [PubMed]
14. Faydaoğlu E, Sürücüoğlu M. [History of the use of medical and aromatic plants and their economic importance]. Journal of Faculty of Forestry. 2011;11(1):52-67. [Link]
15. Shehzad A, Ha T, Subhan F, Lee YS. New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases. Eur J Nutr. 2011;50(3):151-61. [Crossref] [PubMed]
16. Senatorski G, Paczek L, Kropiewnicka E, Bartłomiejczyk I. [Cytokines in noninvasive diagnostics of diabetic nephropathy progression]. Pol Merkur Lekarski. 2002;13 Suppl 1:28-32. Polish. [PubMed]
17. Demir EA, Öz M, Alp Mİ, Gergerlioğlu HS. Levels of IL-6 and TNF-α in diabetic rats: effect of quercetin. Ibn Sina Journal of Medical Sciences. 2015;1(2):27-31.
18. Dalla Vestra M, Mussap M, Gallina P, Bruseghin M, Cernigoi AM, Saller A, et al. Acute-phase markers of inflammation and glomerular structure in patients with type 2 diabetes. J Am Soc Nephrol. 2005;16 Suppl 1:S78-82. [Crossref] [PubMed]
19. Kim AY, Kim HS, Kang JH, Yang MP. Serum adipokine concentrations in dogs with diabetes mellitus: a pilot study. J Vet Sci. 2015;16(3):333-40. [Crossref] [PubMed] [PMC]
20. Soetikno V, Sari FR, Veeraveedu PT, Thandavarayan RA, Harima M, Sukumaran V, et al. Curcumin ameliorates macrophage infiltration by inhibiting NF-κB activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. Nutr Metab (Lond). 2011;8(1):35. [PubMed] [PMC]
21. Zhang DW, Fu M, Gao SH, Liu JL. Curcumin and diabetes: a systematic review. Evid Based Complement Alternat Med. 2013;2013:636053. [PubMed] [PMC]
22. Kılıçlı MF, Acıbucu F. [Chronic induction, insulin resistance and diabetes]. Turkey Klinikleri J Pharmacol-Special Topics. 2015;3(3): 30-5. [Link]
23. Seo KI, Choi MS, Jung UJ, Kim HJ, Yeo J, Jeon SM, et al. Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. Mol Nutr Food Res. 2008;52(9):995-1004. [Crossref] [PubMed]
24. Patumraj S, Wongeakin N, Sridulyakul P, Jariyapongskul A, Futrakul N, Bunnag S. Combined effects of curcumin and vitamin C to protect endothelial dysfunction in the iris tissue of STZ-induced diabetic rats. Clin Hemorheol Microcirc. 2006;35(4):481-9. [PubMed]
25. Gutierres VO, Pinheiro CM, Assis RP, Vendramini RC, Pepato MT, Brunetti IL. Curcumin-supplemented yoghurt improves physiological and biochemical markers of experimental diabetes. Br J Nutr. 2012;108(3):440-8. [PubMed]
26. İslamoğlu Y, Koplay M, Sunay S, Açıkel M. [Obesity and metabolic syndrome]. Tıp Araştırmaları Dergisi. 2008;6(3):168-74. [Link]
27. El-Moselhy MA, Taye A, Sharkawi SS, El-Sisi SF, Ahmed AF. The antihyperglycemic effect of curcumin in high fat diet fed rats. Role of TNF-α and free fatty acids. Food Chem Toxicol. 2011;49(5):1129-40. [Crossref] [PubMed]
28. Li JM, Li YC, Kong LD, Hu QH. Curcumin inhibits hepatic protein-tyrosine phosphatase 1B and prevents hypertriglyceridemia and hepatic steatosis in fructose-fed rats. Hepatology. 2010;51(5):1555-66. [Crossref] [PubMed]
29. Naijil G, Anju TR, Jayanarayanan S, Paulose CS. Curcumin pretreatment mediates antidiabetogenesis via functional regulation of adrenergic receptor subtypes in the pancreas of multiple low-dose streptozotocin-induced diabetic rats. Nutr Res. 2015;35(9):823-33. [Crossref] [PubMed]
30. Kang C, Kim E. Synergistic effect of curcumin and insulin on muscle cell glucose metabolism. Food Chem Toxicol. 2010;48(8-9):2366-73. [PubMed]
31. Wickenberg J, Ingemansson SL, Hlebowicz J. Effects of Curcuma longa (turmeric) on postprandial plasma glucose and insulin in healthy subjects. Nutr J. 2010;9:43. [Crossref] [PubMed] [PMC]
32. Na LX, Zhang YL, Li Y, Liu LY, Li R, Kong T, et al. Curcumin improves insulin resistance in skeletal muscle of rats. Nutr Metab Cardiovasc Dis. 2011;21(7):526-33. [Crossref] [PubMed]
33. Song Z, Wang H, Zhu L, Han M, Gao Y, Du Y, et al. Curcumin improves high glucose-induced INS-1 cell insulin resistance via activation of insulin signaling. Food Funct. 2015;6(2):461-9. [Crossref] [PubMed]

34. Chougala MB, Bhaskar JJ, Rajan MG, Salimath PV. Effect of curcumin and quercetin on lysosomal enzyme activities in streptozotocin-induced diabetic rats. Clin Nutr. 2012;31(5):749-55. [Crossref] [PubMed]

35. Rashid K, Sil PC. Curcumin enhances recovery of pancreatic islets from cellular stress induced inflammation and apoptosis in diabetic rats. Toxicol Appl Pharmacol. 2015;282(3):297-310. [Crossref] [PubMed]

36. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001;280(5): E745-51. [Crossref] [PubMed]

37. Carey AL, Bruce CR, Sacchetti M, Anderson MJ, Olsen DB, Saltin B, et al. Interleukin-6 and tumor necrosis factor-alpha are not increased in patients with Type 2 diabetes: evidence that plasma interleukin-6 is related to fat mass and not insulin responsiveness. Diabetologia. 2004;47(6):1029-37. [Crossref] [PubMed]