Eurasian Journal of Veterinary Sciences

www.eurasianjvetsci.org

RESEARCH ARTICLE

Evaluation of antihyperlipidemic effect of rosemary oil in streptozotocin-induced diabetic rats

Deniz Uluisik*, Ercan Keskin

Selcuk Univercity, Veterinary Faculty, Department of Physiology, Konya, Türkiye

Received: 02.01.2024 , Accepted: 21.02.2024

*denizfedai@selcuk.edu.tr

Streptozotosin ile diyabet oluşturulan ratlarda rosemary yağının antihiperlipidemik etkisinin değerlendirilmesi

Eurasian J Vet Sci, 2024, 40, 1, 10-15
DOI: 10.15312/EurasianJVetSci.2024.420

Öz

Amaç: Bu çalışmada streptozotosin ile diyabet oluşturulan ratlarda lipit profil üzerine rosemary yağının potansiyel etkileri incelenmiştir.

Gereç ve Yöntem: Çalışmada otuz iki adet yetişkin erkek Wistar Albino rat kullanıldı. Çalışma grupları; kontrol grubu (C, n=6), rosemary grubu (R, n=6), diyabet grubu (STZ, n=10) ve diyabet+rosemary grubu (STZ+R, n=10) olarak oluşturuldu. Rosemary yağı alan gruplara üç hafta süreyle günlük 200 mg/kg oral dozunda rosemary yağı uygulandı. Diyabet iki gün üst üste günlük tek doz olarak 0.1 M sitrat bufferda (pH 4.5) 40 mg/kg dozunda subkutan streptozotosin enjeksiyonu ile oluşturuldu. Üç haftanın sonunda, tüm hayvanlardan alınan kan örneklerinde lipit parametreleri değerlendirildi.

Bulgular: Bu çalışmada, diyabet grubunda kontrol grubuyla karşılaştırıldığında plazma trigliserit, total kolesterol ve LDL-kolesterol seviyeleri önemli ölçüde yükselirken, plazma HDL-kolesterol seviyeleri de önemli ölçüde azaldı. Bununla birlikte, rosemary yağının streptozotosin ile indüklenen diyabetik ratlara uygulanması ile plazma trigliserit, total kolesterol ve LDL-kolesterol seviyelerinde önemli bir azalma gözlenirken, plazma HDL-kolesterolünde belirgin bir artış gözlendi.

Öneri: Mevcut bulgular sonucunda rosemary yağının antihiperlipidemik özelliklere sahip olabileceği ve diyabet tedavisinde bitkisel ilaç olarak kullanılabileceği sonucuna varılmıştır.

Anahtar kelimeler: Diyabet, lipit profil, rat, rosemary

Abstract

Aim: In this study, the potential effects of rosemary oil on the lipid profile in streptozotocin-induced diabetic rats were examined.

Materials and Methods: In this study, thirty-two adult male Wistar Albino rats were used. Working groups were consisted as follows: control group (C, n=6), rosemary group (R, n=6), diabetes group (STZ, n=10) and diabetes+rosemary group (STZ+R, n=10). The rosemary oil was administered at oral dosage of 200 mg/kg daily for duration of three weeks in the groups receiving rosemary oil. Diabetes was performed by subcutaneous injections of streptozotocin at dosage of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) for two consecutive days as a single daily dose. At the end of three weeks, blood samples collected from the all animals were assessed lipid parameters.

Results: In this study, plasma levels of triglyceride, total cholesterol, and LDL-cholesterol significantly elevated, alongside plasma HDL-cholesterol levels in diabetes group significantly reduced compared to the control group. However, upon the application of rosemary oil to streptozotocin-induced diabetic rats, a substantial decrease in plasma triglyceride, total cholesterol, and LDL-cholesterol levels was observed, while plasma HDL-cholesterol notably increased.

Conclusion: As a result of the current findings, it is concluded that rosemary oil may have antihiperlipidemic properties and could be used as a phytomedicine for the treatment of diabetes.

Keywords: Diabetes, lipid profile, rats, rosemary

CITE THIS ARTICLE: *Uluisik and Keskin 2024. Evaluation of Antihyperlipidemic Effect of Rosemary Oil in Streptozotocin-induced Diabetic Rats Eurasian J Vet Sci, 40, 1, 10-15*

Introduction

Diabetes mellitus is a metabolic disorder in which individuals experience heightened blood glucose levels due to either insufficient production or resistance of insulin which is a hormone pivotal in regulating glucose levels by facilitating cellular glucose uptake and restraining hepatic glucose production (Edgerton et al 2017, Keskin and Uluisik 2017, Khan et al 2019). It is acknowledged as among the most widespread non-communicable disease on global scale. In addition, the diabetes is characterized by multifaceted complications, especially those that exert an impact on the cardiovascular system (Zakir et al 2023). The primary cause of morbidity and mortality in diabetes results from vascular complications affecting both the macrovascular system, which includes cardiovascular disease, and the microvascular system, which includes diabetic kidney disease, diabetic neuropathy, retinopathy (Morrish et al 2001, Cole and Florez 2020). Various cardiovascular risk factors, including glucose intolerance, insulin resistance and irregular lipid profile, significantly contribute to the development of atherosclerosis in diabetes (Howard 1999, Fryirs et al 2009, von Eckardstein and Sibler 2011, Chakraborty et al 2020).

Today, the utilization of medicinal plants is enhancement worldwide and clinical studies and safety evaluations are needed. The outcomes derived from these investigations can serve as pivotal guidelines for the development of subsequent pharmaceutical formulations (Tahmasebi et al 2019). Besides existing therapeutic choices with certain limitations in diabetes, like hypoglycemic drugs and insulin therapy, there has also been considerable focus on employing traditional plant-based medicines. These alternatives aim to regulate hyperglycemia and dyslipidemia and also preventing complications caused by diabetes. Furthermore, plant-based medicine has demonstrates favorable effects with minimal or no complications in clinical trials, presenting a relatively cost-effective alternative compared to other pharmaceutical interventions (Shabani et al 2019).

One of the botanical remedies employed for this objective is Rosmarinus officinalis. *Rosmarinus officinalis L.*, a member of Lamiaceae family, is characterized as an aromatic plant with dark green leaves, whitish-blue flower and upright stems. The chemical composition of rosemary exhibits variability among different extracts, but its analysis shows phenolic acids, phenolic triterpenes and diterpenes as the most relevant active components. With regard to phenolic compounds, rosmarinic acid, carnosol and carnosic acid have been suggested to have therapeutic effects, such as antiviral, anti-inflammatory, antioxidant and antibacterial activities (de Oliveira et al 2019, Farkhondeh et al 2019, Ahmed and Babakir-Mina 2020, Gonçalves et al 2022). Numerous studies conducted in both hyperlipidemic and diabetic animal models, as well as in human have consistently demonstrated that supplementation with rosemary, carnosol, and carnosic acid leads to improvements in total cholesterol, LDL, HDL and triglyceride levels (Belmouhoub et al 2017, Eissa et al 2017, Samarghandian et al 2017, Farkhondeh et al 2019).

In this investigation, the effectiveness of rosemary oil on lipid profile in streptozotocin-induced diabetic rats was evaluated.

Material and Methods

Ethical Statement

The experimental procedures were conducted in accordance with the ethical standards and guidelines approved by the Ethics Committee of Selçuk University Experimental Medicine Research and Application Center (Decision no: 2021-61).

Animals and Experimental Design

Thirty-two adult male Wistar Albino rats were housed under standard conditions. All animals were allowed ad libitum access to standard feed and drinking water. Following randomization, working groups were consisted as follows:

Control group (C, n=6): The control group animals did not undergo any specific treatment.

Rosemary group (R, n=6): Animals in the rosemary group were administered orally with 200 mg/kg of rosemary oil (Softem, Aksu Vital, Turkey) daily for duration of three weeks. Rosemary oil application was performed via a pipette at 11:00 am everyday.

Diabetes group (STZ, n=10): Diabetes was performed by subcutaneous injections of streptozotocin (SigmaAldrich, St. Louis, MO, USA) at dosage of 40 mg/kg in 0.1 M citrate buffer (pH 4.5) for two consecutive days as a single daily dose in diabetes group animals.

Diabetes+rosemary group (STZ+R, n=10): In the diabetes+rosemary group, diabetes was induced similarly at the study's onset, followed by oral administration of 200 mg/kg rosemary oil daily for three weeks in these animals.

Six hours subsequent to the administration of streptozotocin, rats were orally given a 5% dextrose solution for duration of three days to prevent sudden hypoglycemia. Confirmation of diabetes was established by measuring blood glucose levels using glucometer strips (PlusMED Accuro, Taiwan) via the tail vein one week following the streptozotocin injections. The animals exhibiting exceeding 250 mg/dl blood glucose levels were considered as diabetic and subsequently included in the experimental procedures. Finally, blood samples were collected from hearts of all animals for the determination of triglyceride, total cholesterol, LDL-cholesterol, and HDL-cholesterol levels. Triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol levels were determined using Abbott kits through the Abbott-C8000 autoanalyzer.

Statistics analysis

The statistical analysis of the study's data at its conclusion was carried out using the SPSS 20.00 software package. Analytical methods were employed to assess variables for normal distribution, and the results were presented in terms of mean and standard deviations for all variables. One-way ANOVA test was utilized to compare groups. To ensure variance homogeneity, statistical significance was set at a threshold of 0.05. Additionally, Duncan's Multiple Range test was employed in the analysis of variance. These statistical techniques were chosen to robustly examine and determine the significance of differences between the groups under investigation.

Results

In the study, the effects of 200 mg/kg rosemary oil administration on lipid profile are shown in Table 1.

Discussion

Diabetes mellitus represents a significant global health challenge and it is estimated that its prevalence will exceed 300 million in 2025 (Assiri et al 2017, Rahimi-Madiseh et al 2017, Sarfraz et al 2017). Furthermore, hyperglycemia impairs the endogenous antioxidant defense mechanisms by triggering the formation of free radicals. As seen from the elevation of LDL-cholesterol and triglyceride levels while concurrently diminishing HDL-cholesterol, oxidative stress has been linked to adverse lipid profile alterations in animal models or individuals affected by metabolic syndrome (Kowalska and Olejnik 2016, Qu et al 2018).

Cardiovascular diseases stand as prominent causes of mortality in developed nations. Within diabetes mellitus, several factors significantly elevate the risk of cardiovascular complications. Irregularities in the lipid profile and high cholesterol levels are among these factors. Numerous studies have indicated notable increases in triglyceride, total cholesterol, and LDL-cholesterol levels, accompanied by decreased HDL-cholesterol levels in diabetic rats compared to control groups (Al-Jamal and Alqadi 2011, Alnahdi 2012, Qu et al 2018). Streptozotocin-induced diabetes has been associated with a substantial increase in fasting blood glucose and glycosylated hemoglobin (HbA1c) levels alongside alterations in lipid profiles, including cholesterol, LDL-cholesterol, and VLDL-cholesterol (Soliman 2013). It has also been reported in studies that alloxan-induced diabetes significantly increases total cholesterol, triglyceride and LDL-cholesterol levels while significantly decrease HDL-cholesterol levels compared to the control group (Gabr 2016, Selmi et al 2017). Consistent with the above studies, in our study, plasma triglyceride, total cholesterol and LDL-cholesterol levels significantly increased and plasma HDL-cholesterol level significantly decreased compared to the control group in streptozotocin-induced diabetic rats (Table 1, $p<0.05$). Diabetic dyslipidemia identified in our study may results from increased amount of fatty acids entering the liver and impaired hepatic clearance of lipoproteins.

With the application of rosemary oil to diabetic rats, plasma triglyceride, total cholesterol and LDL-cholesterol levels were significantly decreased and plasma HDL-cholesterol level was significantly increased (Table 1, $p<0,05$) compared to the values in the diabetes group. The findings, which we obtained in our study on lipid profile, are parallel to studies conducted in the same direction (Al-Jamal and Alqadi 2011, Alnahdi 2012, Belmouhoub et al 2017). Increased of circulating free fatty acids levels are known to elevate hepatic triglyceride production, subsequently leading to the formation of atherogenic small and dense LDL-cholesterol. Studies have demonstrated the potential benefits of rosemary and its primary constituents in ameliorating streptozotocin-induced diabetes and associated complications. Al-Jamal and Alqadi (2011) have reported that rosemary plant's aqueous extract has shown promising effects such as increase in HDL-cholesterol levels and decrease in plasma glucose, fasting plasma glucose, triglyceride, total cholesterol, and LDL-cholesterol levels in diabetic rats induced by streptozotocin. Other studies stated that rosemary aqueous extract

Table 1. Effects of 200 mg/kg rosemary oil on lipid parameters in 40 mg/kg streptozotocin-induced diabetic rats (Mean±SE).

Groups	Triglyceride (mg/dl)	Total Cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	HDL-cholesterol (mg/dl)
C	78,20±6,90^{b}	92,86±3,07^{c}	54,50±3,07^{b}	48,28±3,99^{a}
R	74,62±4,54^{b}	90,34±2,69^{c}	51,83±3,16^{b}	49,06±3,24^{a}
STZ	137,05±8,06^{a}	146,08±3,71^{a}	87,10±4,39^{a}	33,41±1,87^{b}
STZ+R	94,18±3,50^{b}	121,32±4,93^{b}	62,30±3,46^{b}	52,84±2,00^{a}

a-c Different superscripts in the same column indicate that the difference between the mean values is significant ($p<0.05$). C: control group, R: rosemary group, STZ: diabetes group, STZ+R: diabetes+rosemary group.

improved levels of fasting plasma glucose, LDL-cholesterol, total cholesterol, triglyceride and HDL-cholesterol in diabetic animals (Alnahdi 2012, Emam 2012). Dried rosemary leaves have been reported to reduce glycosylated hemoglobin, fasting plasma glucose, triglyceride, total cholesterol and LDL-cholesterol levels in diabetic rats. Thus, it is suggested that rosemary application positively modulates lipoprotein metabolism (Soliman 2013). It has been stated that rosemary n-butanol fraction reduced LDL-cholesterol and total cholesterol levels in streptozotocin-induced diabetic animals (Belmouhoub et al 2017). Intraperitoneal injection of carnosol in diabetic rats has been suggested to decrease LDL-cholesterol, triglyceride and total cholesterol levels while increasing HDL-cholesterol level (Samarghandian et al 2017). These lipid-regulating effects attributed to rosemary and its bioactive constituents are thought to be associated with the suppression of both lipid biosynthesis and intestinal absorption (Farkhondeh et al 2019).

Rosemary and its constituents have demonstrated to be the ability to elicit hypolipidemic effects by activating specific signaling pathways, notably such as PPAR-γ (peroxisome proliferator-activated receptors). Studies indicate that this nuclear receptor protein serve as modulating glucose metabolism and transport by regulating the transcription of enzymes and proteins responsible for cellular uptake of glucose and fatty acids (Scazzocchio et al 2011). The anti-inflammatory properties exhibited by rosemary and its compounds have been related to their effects on dyslipidemia. Moreover, it has been suggested that these compounds improve dyslipidemia by stimulating Phase 2 enzymes. It has been stated that these enzymes associated with glutathione metabolism via the activation of the transcription factor Nrf2 (nuclear factor-like 2). Nrf2 functions in regulating Phase 2 enzymes expression (Takahashi et al 2009).

Rosemary and its active compounds play a role in modulating both lipolysis and lipid synthesis. These compounds have been shown the ability to inhibit the function of diacylglycerol acyltransferase (DGAT1) and the synthesis of intracellular triglyceride in human hepatocyte HepG2 cells. DGAT1 and DGAT2 are pivotal enzymes responsible for triglyceride synthesis and are considered significant therapeutic targets in pharmacological research (Cui et al 2012). In studies conducted in vitro, it has been demonstrated that carnosic acid effectively protects human hepatoma cell lines from lipid accumulation induced by palmitate (Reis et al 2009). The suppression of DGAT1 function has been proposed as a principal therapeutic strategy for hyperlipidemia treatment. It has also been reported that carnosic acid and carnosol application inhibits differentiation process of 3T3-L1 preadipocytes into mature adipocytes by enhancing the antioxidant ingredient and by reducing the generation of ROS in these cells (Takahashi et al 2009). It has also been stated that another possible mechanism by which rosemary extract and carnosic acid inhibit 3T3-L1 adipocyte differentiation may be PPAR-γ blockade (Gaya et al 2013). It has also been reported that treatment with carnosic acid reduced triglyceride level and intracellular lipid accumulation in 3T3-L1 adipocytes (Park and Sung 2015b). Carnosic acid has been noted to modulate adipogenesis through the PPARγ/SREBP1 pathway (Park and Sung 2015a, Park and Sung 2015b, Farkhondeh et al 2019).

The increase detected in rats with diabetes in plasma triglyceride and total cholesterol levels is consistent with Maiti et al (2005) and Yadav et al (2008). It has been stated that dried rosemary leaf powder led to an important decrease in total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglyceride levels and an increase in HDL-cholesterol in diabetic rats. It has been reported that this decrease may be due to dried rosemary leaf powder being able to modulate fatty acids oxidation rate in the liver and to reduce triglyceride biosynthesis rate in rats. Rosmarinic acid or carnosic acid demonstrated a dose-dependent inhibition of LDL oxidation, as documented by Fuhrman et al (2000). It has been noted that this reduction maight be because of the renewal of pancreatic β-cells and strengthening of insulin secretion from surviving β-cells stimulated by dried rosemary leaf powder. The enhancement in insulin and the resulting reduction in glucose levels might contribute to inhibiting lipid peroxidation and regulating lipolytic hormones, as suggested by Iweala and Oludare (2011). Alnahdi (2012) reported important improvement in triglyceride, HDL-cholesterol, VLDL-cholesterol, LDL-cholesterol, total cholesterol levels, which it was determined to evaluate antihyperlipidemic activities of this extract.

Conclusion

The current findings reveal the antihyperlipidemic effects of rosemary oil against streptozotocin-induced diabetes. This study shows that this effect of rosemary oil has the potential for use in the management of diabetes mellitus. Futher, comprehensive and detailed biochemical studies should be performed to identify the exact mechanisms of rosemary oil antihiperlipidemic effects.

Conflict of Interest

Authors declare that there are no conflicts of interest related to the publication of this article

Funding

This research was supported by Selcuk University Scientific Research Projects Coordinatorship (Project Number: 21202134).

References

Ahmed HM, Babakir-Mina M, 2020. Investigation of rosemary herbal extracts (Rosmarinus officinalis) and their potential effects on immunity. Phytother Res, 34(8), 1829-1837. https://doi.org/10.1002/ptr.6648.

Al-Jamal AR, Alqadi T, 2011. Effects of rosemary (Rosmarinus officinalis) on lipid profile of diabetic rats. Jordan J Biol Sci, 4(4), 199-204. Corpus ID: 20971156. https://doi.org/10.5897/AJPS11.138.

Alnahdi HS, 2012. Effect of rosmarinus officinalis extract on some cardiac enzymes of streptozotocin-induced diabetic rats. J Health Sci, 2(4), 33-37. https://doi.org/10.5923/j.health.20120204.03.

Assiri AMA, El-Beeh ME, Amin AH, Ramadan MF, 2017. Ameliorative impact of Morus alba leaves' aqueous extract against embryonic ophthalmic tissue malformation in streptozotocin-induced diabetic rats. Biomed Pharmacother, 95, 1072-1081. https://doi.org/10.1016/j.biopha.2017.09.013.

Belmouhoub M, Chebout I, Iguer-ouada M, 2017. Antidiabetic and anti-hypercholesterolemic effects of flavonoid-rich fractions of Rosmarinus officinalis in streptozotocin-induced diabetes in mice. Phytothérapie, 16(4), 204-210. https://doi.org/10.3166/phyto-2018-0054.

Chakraborty M, Singh P, Dsouza JMP, Pethusamy K, et al., 2020. Fasting and postprandial lipid parameters: A comparative evaluation of cardiovascular risk assessment in prediabetes and diabetes. J Family Med Prim Care, 9(1), 287-292. https://doi.org/10.4103/jfmpc.jfmpc_769_19.

Cole JB, Florez JC, 2020. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol, 16(7), 377-390. https://doi.org/10.1038/s41581-020-0278-5.

Cui L, Kim MO, Seo JH, Kim IS, et al., 2012. Abietane diterpenoids of Rosmarinus officinalis and their diacylglycerol acyltransferase-inhibitory activity. Food Chem, 132(4), 1775-1780. https://doi.org/10.1016/j.foodchem.2011.11.138.

de Oliveira JR, Camargo SEA, de Oliveira LD, 2019. Rosmarinus officinalis L. (rosemary) as therapeutic and prophylactic agent. J Biomed Sci, 26(1), 5. https://doi.org/10.1186/s12929-019-0499-8.

Edgerton DS, Kraft G, Smith M, Farmer B, et al., 2017. Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. JCI Insight, 2(6), e91863. https://doi.org/10.1172/jci.insight.91863.

Eissa FA, Choudhry H, Abdulaal WH, Baothman OA, et al., 2017. Possible hypocholesterolemic effect of ginger and rosemary oils in rats. Afr J Tradit Complement Altern Med, 14(4), 188-200. https://doi.org/10.21010/ajtcam.v14i4.22.

Emam MA, 2012. Comparative evaluation of anti-diabetic activity of Rosmarinus officinailis L. and Chamomile recutita in streptozotocin induced diabetic rats. Agric Biol J North America, 3(6), 247-252. https://doi.org/10.5251/abjna.2012.3.6.247.252.

Farkhondeh T, Samarghandian S, Pourbagher-Shahri AM, 2019. Hypolipidemic effects of Rosmarinus officinalis L. J Cell Physiol, 234(9), 14680-14688. https://doi.org/10.1002/jcp.28221.

Fryirs M, Barter PJ, Rye KA, 2009. Cholesterol metabolism and pancreatic beta-cell function. Curr Opin Lipidol, 20(3), 159-164. https://doi.org/10.1097/MOL.0b013e32832ac180.

Fuhrman B, Volkova N, Rosenblat M, Aviram M, 2000. Lycopene synergistically inhibits LDL oxidation in combination with vitamin E, glabridin, rosmarinic acid, carnosic acid, or garlic. Antioxid Redox Signal, 2(3), 491-506. https://doi.org/10.1089/15230860050192279.

Gabr NM, 2016. Effects of the aqueous extract of rosemarinus officinalis l. (rosemary) leaves on lipid profile of diabetic adult male albino rats. Al-Azhar Med J, 45(1), 185-194. https://doi.org/10.12816/0026284.

Gaya M, Repetto V, Toneatto J, Anesini C, et al., 2013. Antiadipogenic effect of carnosic acid, a natural compound present in Rosmarinus officinalis, is exerted through the C/EBPs and PPARgamma pathways at the onset of the differentiation program. Biochim Biophys Acta, 1830(6), 3796-3806. https://doi.org/10.1016/j.bbagen.2013.03.021.

Gonçalves C, Fernandes D, Silva I, Mateus V, 2022. Potential Anti-Inflammatory Effect of Rosmarinus officinalis in Preclinical In Vivo Models of Inflammation. Molecules, 27(3), 609. https://doi.org/10.3390/molecules27030609.

Howard BV, 1999. Insulin resistance and lipid metabolism. Am J Cardiol, 84(1A), 28J-32J. https://doi.org/10.1016/s0002-9149(99)00355-0.

Iweala EJ, Oludare FD, 2011. Hypoglycemic effect, biochemical and histological changes of Sspondias mombin linn, and Painari polyandra benth. Seeds Ethanolic extracts in alloxan induced diabetic rats. J Pharma Toxic, 6(2), 101-112. https://doi.org/10.3923/jpt.2011.101.112.

Keskin E and Uluisik D, 2017. Hematological effects of Coenzyme Q10 in streptozotocin-induced diabetic rats. Eurasian J Vet Sci, 33(3), 167-171. https://doi.org/10.15312/EurasianJVetSci.2017.154.

Khan RMM, Chua ZJY, Tan JC, Yang Y, et al., 2019. From Pre-Diabetes to Diabetes: Diagnosis, Treatments and Translational Research. Medicina (Kaunas), 55(9), 546. https://doi.org/10.3390/medicina55090546.

Kowalska K, Olejnik A, 2016. Beneficial effects of cranberry in the prevention of obesity and related complications: Metabolic syndrome and diabetes-A review. J Funct Foods, 20, 171–181. https://doi.org/10.1016/j.jff.2015.11.001.

Maiti R, Das UK, Ghosh D, 2005. Attenuation of hyperglycemia in STZ induced diabetic rats by aqueous extract of seed of Tamarindus Indica. Biol Pharm Bull, 28(7), 1172-1176. https://doi.org/10.1248/bpb.28.1172.

Morrish NJ, Wang SL, Stevens LK, Fuller JH, et al., 2001. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia, 44(Suppl 2), S14-21. https://doi.org/10.1007/pl00002934.

Park MY, Sung MK, 2015a. Carnosic acid attenuates obesity induced glucose intolerance and hepatic fat accumulation by modulating genes of lipid metabolism in C57BL/6J-ob/ob mice. J Sci Food Agric, 95(4), 828-835. https://doi.org/10.1002/jsfa.6973.

Park MY, Sung MK, 2015b. Carnosic acid inhibits lipid accumulation in 3T3-L1 adipocytes through attenuation of fatty acid desaturation. J Cancer Prev, 20(1), 41-49. https://doi.org/10.15430/JCP.2015.20.1.41.

Qu J, Huang J, Zhao D, Du B, et al., 2018. Protective effect of rosmarinic acid and carnosic acid against streptozotocin-induced oxidation, glycation, inflammation and microbiota imbalance in diabetic rats. Food Funct, 9(2), 851-860. https://doi.org/10.1039/c7fo01508a.

Rahimi-Madiseh M, Heidarian E, Kheiri S, Rafieian-Kopaei M, 2017. Effect of hydroalcoholic Allium ampeloprasum extract on oxidative stress, diabetes mellitus and dyslipidemia in alloxan-induced diabetic rats. Biomed Pharmacother, 86, 363-367. https://doi.org/10.1016/j.biopha.2016.12.028.

Reis P, Holmberg K, Watzke H, Leser ME, et al., 2009. Lipases at interfaces: a review. Adv Colloid Interface Sci, 147-148, 237-250. https://doi.org/10.1016/j.cis.2008.06.001.

Samarghandian S, Borji A, Farkhondeh T, 2017. Evaluation of antidiabetic activity of carnosol (phenolic diterpene in rosemary) in streptozotocin-induced diabetic rats. Cardiovasc Hematol Disord Drug Targets, 17(1), 11-17. https://doi.org/10.2174/1871529X16666161229154910.

Sarfraz M, Khaliq T, Khan JA, Aslam B, 2017. Effect of aqueous extract of black pepper and ajwa seed on liver enzymes in alloxaninduced diabetic Wister albino rats. Saudi Pharm J, 25(4), 449-452. https://doi.org/10.1016/j.jsps.2017.04.004.

Scazzocchio B, Varì R, Filesi C, D'Archivio M, et al., 2011. Cyanidin-3-O-β-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARγ activity in human omental adipocytes. Diabetes, 60(9), 2234-2244. https://doi.org/10.2337/db10-1461.

Selmi S, Rtibi K, Grami D, Sebai H, et al., 2017. Rosemary (Rosmarinus officinalis) essential oil components exhibit anti-hyperglycemic, anti-hyperlipidemic and antioxidant effects in experimental diabetes. Pathophysiology, 24(4), 297-303. https://doi.org/10.1016/j.pathophys.2017.08.002.

Shabani E, Sayemiri K, Mohammadpour M, 2019. The effect of garlic on lipid profile and glucose parameters in diabetic patients: A systematic review and meta-analysis. Prim Care Diabetes, 13(1), 28-42. https://doi.org/10.1016/j.pcd.2018.07.007.

Soliman GZA, 2013. Effect of Rosmarinus officinalis on lipid profile of streptozotocin-induced diabetic rats. Egyptian J Hosp Med, 53(1), 809-815. https://doi.org/10.12816/0001643.

Tahmasebi L, Zakerkish M, Golfakhrabadi F, Namjoyan F, 2019. Randomised clinical trial of Berberis vulgaris root extract on glycemic and lipid parameters in type 2 diabetes mellitus patients. Eur J Integrat Med, 32, 100998. https://doi.org/10.1016/j.eujim.2019.100998.

Takahashi T, Tabuchi T, Tamaki Y, Kosaka K, et al., 2009. Carnosic acid and carnosol inhibit adipocyte differentiation in mouse 3T3-L1 cells through induction of phase2 enzymes and activation of glutathione metabolism. Biochem Biophys Res Commun, 382(3), 549-554. https://doi.org/10.1016/j.bbrc.2009.03.059.

von Eckardstein A, Sibler RA, 2011. Possible contributions of lipoproteins and cholesterol to the pathogenesis of diabetes mellitus type 2. Curr Opin Lipidol, 22(1), 26-32. https://doi.org/10.1097/MOL.0b013e3283412279.

Yadav JP, Saini S, Kalia AN, Dangi AS, 2008. Hypoglycemic and hypolipidemic activity of Ethanolic extract of Salvadora oleoides in normal and alloxan-induced diabetic rats. Ind J Pharmacol, 40(1), 23-27. https://doi.org/10.4103/0253-7613.40485.

Zakir M, Ahuja N, Surksha MA, Sachdev R, et al., 2023. Cardiovascular Complications of Diabetes: From Microvascular to Macrovascular Pathways. Cureus, 15(9), e45835. https://doi.org/10.7759/cureus.45835.

Author Contributions

Motivation / Concept: DU, EK; Design: DU, EK; Control/Supervision: DU, EK; Data Collection and / or Processing: DU, EK; Analysis and / or Interpretation: DU, EK; Literature Review: DU, EK; Writing the Article: DU, EK; Critical Review: DU, EK

Ethical Approval

Ethics Committee of Selçuk University Experimental Medicine Research and Application Center 22.11.2021, 2021/61 Number Ethics Committee Decision.