Special Issue:
Emerging and Re-emerging Animal Health Challenges in Low and Middle-Income Countries

Ameliorative Pathological Aspect of Pumpkin Seed Oil and Rousovastatin on Lipid Profile and Glucose Level in Rats

Abbas A. Khudhair[1*], Mohammed A. Qathee[2], Muhsin S.G. Almozie'l[3], Kassim F. Abdulkarem[4]

[1]Department of Clinical Laboratory Science, College of Pharmacy, University of Basrah, Iraq; [2]Department of Animal Production Techniques, Technical Agricultural College of Mosul, Northern Technical University, Iraq; [3]Department of Pharmacology and Toxicology, College of Pharmacy, University of Basrah, Iraq; [4]Dentistry Department, University College of Alkunooze, Basrah, Iraq.

Abstract | Dyslipidemia is a condition characterized by an abnormal cholesterol and triglyceride metabolism. Here we aim to evaluate pumpkin and rousovastatin for their effect on lipid profile and glucose level in laboratory rats. For this purpose, thirty female rats were used after induction of hyperlipidemia through cholesterol administration, divided in to five groups and treated with different concentrations of pumpkin and rousovastatin. Pumpkin group (treated with 200mg/kg), rousovastatin group (treated with 20mg/kg) and comb group (treated with 20mg/kg rousovastatin and 200mg/kg pumpkin seed oil). Pumpkin and rousovastatin groups showed a significant decrease *($p<0.05$)* in total cholesterol, triglyceride, LDL-C, VLDL-C and glucose level, while there is a significant increase *($p<0.05$)* in HDL-C when compared to positive control. However, rousovastatin caused a significant increase *($p<0.05$)* in AST, ALT and creatinine level when compared to control group. Histopathological examination reveals varying degrees of fatty degeneration, vascular congestion along with infiltration of inflammatory cells in comparison to pumpkin and negative control. Renal tissue showed atrophy of some glomeruli along with infiltration of inflammatory cell with tubular degeneration in rosuovastatin group, while pumpkin group is similar to normal control kidney tissue. Taken together, pumpkin seed oil offers a protective effect by lowering lipid and glucose concentration. In addition to hypolipidemic effect of rousovastatin, it affected glucose level positively but should be used with a lower dose to avoid their adverse effect on biochemical parameters.

Keywords | Dyslipidemia, Pumpkin, Alanine aminotransferase, Aspartate aminotransferase, Rousovastatin

Received | July 02, 2024; **Accepted** | September 29, 2024; **Published** | November 20, 2024
***Correspondence** | Abbas A. Khudhair, Department of Clinical Laboratory Science, College of Pharmacy, University of Basrah, Iraq; **Email:** Abbas.razzaq@uobasrah.edu.iq
Citation | Khudhair AA, Qathee MA, Almozie'l MSG, Abdulkarem KF (2024). Ameliorative pathological aspect of pumpkin seed oil and rousovastatin on lipid profile and glucose level in rats. J. Anim. Health Prod. 12(s1): 127-132.
DOI | http://dx.doi.org/10.17582/journal.jahp/2024/12.s1.127.132
ISSN (Online) | 2308-2801

Copyright: 2024 by the authors. Licensee ResearchersLinks Ltd, England, UK.
This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

INTRODUCTION

Pumpkin is a natural nutritional product that widely used around the world (Montesano et al., 2018), having a multiple components including tocopherols, sterol and carotenoids having a special role on reducing lipid, cholesterol, glucose level, in addition to their antioxidant properties because their higher content of antioxidant compounds (Morrison et al., 2015; Dyshlyuk et al., 2017). Several research stated the role of pumpkin as lipid lowering agent from decreasing the fat level in several tissues including liver, intestine and blood to their homeostatic state (Ramadan et al., 2011; Mallick et al., 2016), in addition some study showed hypoglycemic effect

of pumpkin in induced diabetic rat (Abd-Elnoor, 2019).

Hyperlipidemia and diabetes are considered the main causes of cardiovascular disturbances, characterized by abnormal metabolism of cholesterol and glucose (Liu et al., 2022). Statin or lipid lowering drug is the most effective agent used for the treatment of dyslipidemia (Gupta et al., 2020). These compounds, exert their beneficial role by inhibiting HMG Co-A reductase enzyme which is the catalytic enzyme for cholesterol synthesis in the body and considered the rate limiting step for development of dyslipidemia (Razali et al., 2018). Rosuvastatin is used for the treatment of cholesterol and triglyceride level elevation (Xilifu et al., 2022).

Szendroedi et al. (2009) and Bellia et al. (2012), reported an association between statin and glucose level control. Owing to the adverse effect of simvastatin and atorvastatin on muscle tissue and their obstacle in liver diseases (Al-Malki et al., 2009), it is necessary to be administered carefully and to explore another natural product having a consequence similar to statin effect. This study is designed to evaluate hypolipidemic and hypoglycemic effect of pumpkin and/or rosuvastatin in experiment rat pre-fed with high cholesterol diet. Moreover, we aim to assess their histopathological effects on liver and kidney parameters of performance.

MATERIALS AND METHODS

Experimental animals

A total of 30 female rats is use in this study with a body weight ranging from (155gm-165gm). These animals bought from the Animal House of Veterinary Medicine College and kept for acclimatization for two weeks in the animal house of Pharmacy College, University of Basrah. Animals were house as six rats per cage, at room temperature 25±2 ºC, and kept on *ad libitum* food and water until the end of adaptation peroids.

Study design

The animals were classified into five groups as shown below:

- The group 1 (G1) was used as non-treated negative control and was kept on standard food and water for 60 days. The other four groups of the study (positive control, pumpkin group, rousovastatin group and combination of both) were kept on hyper-lipidemic diets consisting of standard diet with 0.25 gm cholesterol powder and 3.7ml of coconut oil for each group a long 30 days (Mallick et al., 2016). On the other hands, for another 30 days, these groups also kept on hyper-lipidemic diet and treated with as follows.
- Group 2: Positive control; kept on hyper-lipidemic diet for 1 months.
- Group 3: Treated with pumpkin seed oil 200mg/kg/day for 30 days i.e 0.2ml of pumpkin seed oil (Landeka et al., 2011).
- Group 4: Treated with rousovastatin at the rate of 20mg/kg/day for 30 days.
- Group 5: (combination of both pumpkin and rousovastin) group; treated with 200mg/kg of pumpkin seed oil and 20mg/kg rousovastatin drug for 30 days.

Sample collection

All animals were sacrificed at the end of experiment, blood samples were collected from vena cava for preparation of serum to estimate lipid profile (Fossati and Prencipe,1982; Cc, 1974), glucose level (Trinder, 1969), liver enzymes and creatinine level (Tietz and Andresen, 1986) through using Mindray-PS230 chemistry analyzer. Liver and kidney tissue were collected, preserved in 10% formalin for histopathological study (Luna, 1968) with Genex microscope.

Statistical analysis

Data are presented as (Mean±Standard Deviation), ANOVA were used to detect the relationship among study groups. The P-value of 0.05 was used for significant differences among groups.

RESULTS AND DISCUSSION

Effect of pumpkin and rousovastatin on body weight

The body weight changes among groups are illustrate in the Table 1, we observed no significant differences among groups and through the duration of the study, although there was non-significant increase in body weight within the same study group and throughout study periods.

Table 1: Illustrative effect of pumpkin and rousovastatin on body weight.

Parameters groups	Weight 0	Weight 1	Weight 2
	Mean ± SD		
-VE control	165.8 ± 25.2	217 ± 11.0	224.6 ± 8.2
+VE control	164.6 ± 11.08	230.4 ± 27.9	240.4 ± 28.3
Rousoast	166 ± 18.0	213.6 ± 34.7	225 ± 34.7
Pumpkin	165 ± 20.5	216.4 ± 28.7	231 ± 21.5
RP Comb.	165 ± 21.4	219.4 ± 17.9	234.2 ± 13.1
P-value	1.000	0.858	0.804

Effect of pumpkin and rousovastatin on AST and ALT level

As presented in Table 2, we observed a significant increase ($p<0.05$) in AST and ALT level in all study group (s137, 146, 117.4, 132.4 U/L), (30.2, 38, 31.2 U/L) when compare

with negative control (110 U/L) and (23 U/L) respectively. However, there was non-significant changes in ALT level between combination group and negative control.

Table 2: Effect of pumpkin and rousovastatin on AST and ALT level.

Parameters groups	AST U/L	ALT U/L
	Mean ± SD	
-VE control	110 ± 0.89 d	23 ± 2.55 c
+VE control	137 ± 1.87 b	30.2 ± 2.95 b
Rousoast	146 ± 2.38 a	38 ± 1.58 a
Pumpkin	117.4 ± 4.77 c	24.4 ± 1.14 c
RP Comb.	132.4 ± 2.07 b	31.2 ± 1.64 b
P-value	0.005	0.005

Effect of pumpkin and rousovastatin on creatinine and glucose level

According to Table 3, creatinine level shows a significant increase ($p<0.05$) in rousovastatin group (0.62mg/dl) when compared to negative control (0.52 mg/dl). On the other hands, there was non-significant differences among other groups. Glucose level was significantly decrease ($p<0.05$) in pumpkin, combination group and rousovastatin (226, 228, 230 mg/dl) respectively in comparison to positive control group (240 mg/dl) and did not display any differences among others.

Table 3: Effect of pumpkin and rousovastatin on creatinine and glucose level.

Parameters groups	Creatinine mg/dl	Glucose mg/dl
	Mean ± SD	
-VE control	0.52 ± 0.07 b	217 ± 2.91 c
+VE Control	0.59 ± 0.03 ab	240 ± 3.39 a
Rousoast	0.62 ± 0.03 a	230 ± 3.46 b
Pumpkin	0.57 ± 0.05 ab	226 ± 2.00 b
RP Comb.	0.60 ± 0.02 ab	228 ± 4.35 b
P-value	0.04	0.005

Effect of pumpkin and rousovastatin on cholestrol and triglyceride level

The effect of pumpkin and rousovastatin on cholesterol and triglyceride presented in Table 4. We noticed a significant decrease ($p<0.05$) in both cholesterol and triglyceride level in the treatment groups (73, 69.2, 70.8 mg/dl), (65.4, 60, 45.4 mg/dl) when compared to positive (90.2, 116 mg/dl) and negative control (65, 101 mg/dl) groups, respectively.

Effect of pumpkin and rousovastatin on HDL, LDL and VLDL level

Table 5, exhibit a significant increase ($p<0.05$) in HDL level in the treatment groups (36.3, 37.7, 35 mg/dl) in comparison to positive control (25.3 mg/dl) group. However, there was a significant decrease ($p<0.05$) in LDL (18.6, 19.2, 17.6 mg/dl) and VLDL (13.3, 12, 9.68 mg/dl) concentration in treated groups when compared to positive control group (34, 23.3 mg/dl), respectively.

Table 4: Effect of pumpkin and rousovastatin on cholesterole and triglyceride.

Parameters groups	Cholesterol mg/dl	Triglyceride mg/dl
	Mean ± SD	
-VE control	65 ± 1.87 c	101 ± 4.35 b
+VE control	90.2 ± 3.27 a	116 ± 3.24 a
Rousoast	73 ± 2.55 b	65.4 ± 3.05 c
Pumpkin	69.2 ± 1.92 bc	60 ± 2.91 c
RP Comb.	70.8 ± 3.19 b	45.4 ± 4.66 d
P-value	0.005	0.005

Table 5: Effect of pumpkin and rousovastatin on HDL, LDL and VLDL level.

Parameters groups	HDL-C	LDL-C	VLDL-C
	Mean ± SD		
-VE control	41.2 ± 2.72 a	15.4 ± 1.81 b	18.4 ± 0.14 b
+VE control	25.3 ± 1.64 c	34 ± 2.91 a	23.3 ± 3.15 a
Rousoast	36.3 ± 3.88 a	18.6 ± 1.14 b	13.3 ± 2.13 c
Pumpkin	37.7 ± 3.12 a	19.2 ± 2.28 b	12 ± 1.77 c
RP Comb.	35 ± 1.62 b	17.6 ± 1.14 b	9.68 ± 0.80 c
P-value	0.005	0.005	0.005

Histopathological profiling

For pathological examination, liver tissue with obvious hepatic steatosis changes with various grades of fatty changes and vascular congestion can be notice along with hepatic fatty inflammation that represented in rousovastatin and positive control groups, while a lesser degree of fat droplets accumulation can be observed in the other groups. On the other hands, pumpkin group showed in some section an analogous diagnosis to control group with normal hepatic tissue when compared to other groups (Figure 1). Same dramatic changes in the hepatic tissue of combination group with mild degree of alteration and pathogenesis in renal tissue like in pumpkin group with normal glomeruli and renal tubules (Figure 2). Moreover, renal parenchyma observed with massive areas of inflammatory cells infiltration along renal tissue tubules and atrophy of some glomeruli in rousovastatin and positive control group.

In this study, we found that administration of rousovastatin can be significantly lowering lipid along with pumpkin seed oil consequently to their wide prescription in several health states of animal.

The body weight increment was observed among all study groups may be related the pathway of induction of hyperlipidemia. However, it is non-significant change undoubtedly as observed earlier (Ali, 2015).

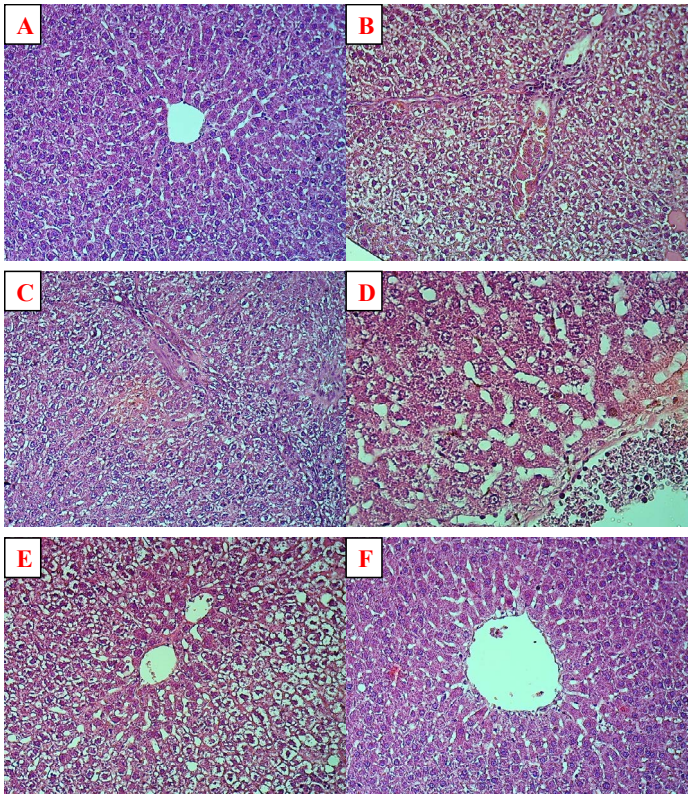

Figure 1: Histopathology of liver tissue. (A) negative control with normal hepatic tissue architecture, X20. (B) positive control showed fatty changes of hepatocytes along with congestion of blood vessels and infiltration of inflammatory cells, X20. (C) and (D) rousovastatin groups showed vacuolation of hepatocyte with fatty changes and congestion of blood vessels with inflammatory cells, X20, X40 respectively. (E) combination group showed accumulation of fat droplets inside the hepatocytes, X20. (F): pumpkin group presented with mild degree of fatty changes and appear normal in other one to some degree with normal architecture, X20.

The level of liver enzymes (AST and ALT) increased significantly in rousovastatin group compared to other study groups. On the contrary, the positive and significant effect of pumpkin seed oil in reduction of liver enzymes aligned to previously reported studies (El-Senousy et al., 2019). The beneficial effect may be related to the high content of antioxidant in pumpkin.

Mallick et al. (2016), reported that administration of different dose of pumpkin seed oil associated with increase in antioxidant state in liver tissue, consequently reduction of the adverse effect of high fat diet. Liver histopathological examination support the above finding in which the hepatocyte treated with rousovastatin and hyperlipidemic group suffered from moderate to severe fatty changes along with infiltration of inflammatory cells and vascular congestion. This damage may be related to oxidative stress produced by high fat diet as proposed by (Humaish et al., 2017), there is a decrease in serum GSH with increase in MDA level as indicator of oxidative damage.

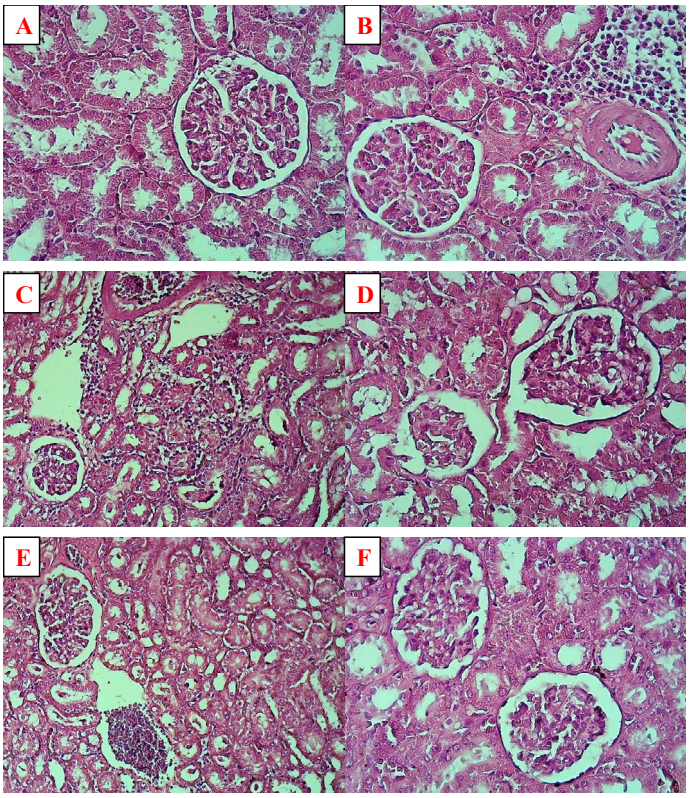

Figure 2: Histopathology of renal tissue. (A) negative control with normal glomeruli and renal tubules, X40. (B) positive control with aggregate of inflammatory cells among renal tubules and vascular congestion, X40. (C) and (D) rousovastatin group with massive infiltration of inflammatory cells in renal tissue along with some degenerative changes of renal tubules and atrophy of glomeruli, X20, X40 respectively. (E) combination group showed congestion and vascular aggregate of inflammatory cells with a lesser degree, X20. (F) pumpkin group showed a normal renal tissue, X40.

Antioxidant effect of pumpkin has been associated with their higher content of phenolic compound, carotenoids and zinc element (Ali, 2015). The damaging effect related to decrease level of serum superoxide dismutase and catalase enzyme in hyperlipidemic groups that play a protective role as antioxidant (Mallick et al., 2016). This finding explains the advantageous pathological result obtained from pumpkin group.

The hypoglycemic effect determined in both pumpkin seed oil and to a less degree in rousovastatin drug, was significantly decreased compared to positive hyperlipidemic group (Sedigheh et al., 2011; Abd-Elnoor, 2019). These

studies highlight that administration of pumpkin has a positive hypoglycemic effect in hyperlipidemic and induced diabetic rat respectively. Because pumpkin seed has a high level of flavonoids especially quercetin, which has a capability to increase release of insulin through elevation of hepatic glucokiase production thus controlling the glucose level (Vessal et al., 2003).

Feng et al. (2006) and Dar et al. (2017), have reported that the main component of pumpkin seed oil in controlling glucose level was unsaturated fatty acid linoleic acid through modulation of pancreatic β-cells.

However, contradisctive resutls were presented by (Xilifu et al., 2022) who have found that rousovastatin increased the fasting blood glucose compared to control group. This may be due to, disrupted β-cells and the islet of langerhans which led to atrophy or being enlarged with fibrosis. This effect may also be related to the elevated uric acid which interferes with progression of hyperglycemia (Hwa et al., 2011).

Insulin resistance has been found to be induced due to rousovastatin drug (Shi et al., 2020). However, other studies have suggested that rousovastatin does not altering insulin sensitivity and cause elevation of glucose and HbA1c level (Bellia et al., 2012). Creatinine level was significantly increased in rousovastatin compared to control group. These results were confirmed by renal pathological investigations representing with destruction of renal tubules associated with infiltration of inflammatory cells and some glomerular atrophy. In contrast, researchers reported that administration of pumpkin seed oil cause a decrease in serum level of urea and creatinine (Elsenousy et al., 2019).

Studies have shown that use of high lipid diet associated with increase of cholesterol, triglyceride and oxidative stress responsible for most adverse effect (Humaish et al., 2017). We observed similar differences and effect in our study. The lipid profile was significantly decreased in all treated groups compared to control groups. These results are parallel agreement with (Farid et al., 2015; Bustan and Jawad, 2017) and are related to inhibition of HMG CoA reductase enzyme with rousovastatin, to presence of polyunsaturated fatty acid including linoleic acid and alpha-linolenic acid (Bhatti et al., 2017). The advantageous hypolipidemic effect produced with pumpkin related to the presence of phytosterol, phenolic compounds and large proportion of fibers that lower blood fat and inhibit absorption of cholesterol (Abd-Elnoor, 2019).

CONCLUSIONS AND RECOMMENDATIONS

Based on the presented finding, the pumpkin seed oil and rousovastatin hold protective effect through managing lipid profile and glucose level. Furthermore, to avoid the negative effect of rousovastatin on biochemical parameters, a lower dose should be used for treatment of dyslipidemia.

ACKNOWLEDGEMENTS

The authors thank their respected college of pharmacy managers for their effort and continuous support for the scientific researches.

NOVELTY STATEMENT

This study is Modern in Basrah city That Ameliorative Pathological Aspect of Pumpkin Seed Oil and Rousovastatin on Lipid Profile and Glucose Level in Rats.

AUTHOR'S CONTRIBUTION

All authors had supervision contribution. The first to fourth author had the major contribution in paper writing, editing, and reviewing, in addition the role of the first and third authors in practical part implementation, the fourth author participate in histopathology assessment and finally corresponding by the first author.

Ethical approval

Animal care was permit according to the local ethical committee at the College of Pharmacy, University of Basrah, (with approval number EC19).

Conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Abd-Elnoor EV (2019). Hypoglycemic and hypolipidemic effects of pumpkin seeds powder and oil on alloxan-induced diabetic in rats. Egypt. J. Food Sci., 47(2): 255-269.

Ali WS (2015). Nutrition with pumpkin (*Cucrbita pepo*) cake as lowering cholesterol in rats. Middle East J. Appl. Sci., 5(1): 10-11.

Al-Malki FH, Ali SH, Abdulbari GA (2009). Role of ezetimibe in combination with statins (*Simvastatin and Atorvastatin*) in controlling dyslipidemia. Iraqi J. Pharm. Sci., 18(1).

Bellia A, Rizza S, Lombardo MF, Donadel G, Fabiano R, Andreadi K, Lauro D (2012). Deterioration of glucose homeostasis in type 2 diabetic patients one year after beginning of statins therapy. *Atherosclerosis*, 223(1): 197-203. https://doi.org/10.1016/j.atherosclerosis.2012.04.015

Bhatti N, Ayaz S, Rehman R (2017). Effect of flaxseed and pumpkin seeds mixture on hypercholesterolemia. Pak. J. Med. Biol. Sci., 1(2): 34-39.

Bustan AA, Jawad AM (2017). The effect of two types of statins (rosuvastatin and atorvastatin) on the fertility of male and female mice. J. Adv. Med. Med. Res., 1: 1992-0849. http://creativecommons.org/licenses/by/4.0, https://doi.org/10.9734/BJMMR/2017/31150

Cc A (1974). Enzymatic determination of total serum cholesterol. Clin. Chem., 20: 470-475. https://doi.org/10.1093/clinchem/20.4.470

Dar AH, Sofi SA, Rafiq S (2017). Pumpkin the functional and therapeutic ingredient: A review. Int. J. Food Sci. Nutr., 2(6): 165-170.

Dyshlyuk L, Babich O, Prosekov A, Ivanova S, Pavsky V, Yang Y (2017). *In vivo* study of medical and biological properties of functional bakery products with the addition of pumpkin flour. Bioact. Carbohyd. Diet. Fibre, 12: 20-24. https://doi.org/10.1016/j.bcdf.2017.09.001

Elsenousy A, Farid A, Fararh K (2019). Effect of pumpkin seed oil on lipid metabolism in experimental hyperlipidemic rats. Benha Vet. Med. J., 36(1): 302-309. https://doi.org/10.21608/bvmj.2019.114449

Farid HEA, El-Sayed SM, Abozid MM (2015). Pumpkin and sunflower seeds attenuate hyperglycemia and protect liver in alloxan-induced diabetic rats. Res. J. Pharma. Biol. Chem. Sci., pp. 1269-1279. http://rjpbcs.com/pdf/2015_6(5)/[178].pdf

Feng DD, Luo Z, Roh SG, Hernandez M, Tawadros N, Keating DJ, Chen C (2006). Reduction in voltage-gated K+ currents in primary cultured rat pancreatic β-cells by linoleic acids. Endocrinology, 147(2): 674-682. https://doi.org/10.1210/en.2005-0225

Fossati P, Prencipe L (1982). Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin. Chem., 28(10): 2077-2080. https://doi.org/10.1093/clinchem/28.10.2077

Gupta M, Blumenthal C, Chatterjee S, Bandyopadhyay D, Jain V, Lavie CJ, Ghosh RK (2020). Novel emerging therapies in atherosclerosis targeting lipid metabolism. Expert. Opin. Investigat. Drugs, 29(6): 611-622. https://doi.org/10.1080/13543784.2020.1764937

Humaish HH, Muslem ZZ, Numaan KT (2017). Comparison the Anti-atherogenic and hypolipidaemic effect of Cod liver oil, pomegranate seed oil and Rosuvastatin in hyperecholestrolemic rats. J. Kerbala Agric. Sci., 4(5): 99-112. https://doi.org/10.59658/jkas.v4i5.696

Hwa KS, Chung DM, Chung YC, Chun HK (2011). Hypouricemic effects of anthocyanin extracts of purple sweet potato on potassium oxonate-induced hyperuricemia in mice. Phytother. Res., 25(9): 1415-1417. https://doi.org/10.1002/ptr.3421

Landeka I, Đikić D, Radišić I, Teparić R, Bačun-Družina V, Rogić D (2011). The effects of olive and pumpkin seed oil on serum lipid concentrations. Croatian J. Food Technol. Biotechnol. Nutr., 6(1/2): 63-68.

Liu Y, Liu C, Kou X, Wang Y, Yu Y, Zhen N, Xue Z (2022). Synergistic hypolipidemic effects and mechanisms of phytochemicals: A review. Foods, 11(18): 2774. https://doi.org/10.3390/foods11182774

Luna LG (1968). Manual of histologic staining methods of the armed forces institute of pathology. In: Manual of histologic staining methods of the Armed Forces Institute of Pathology, pp. xii-258.

Mallick S, Mandal M, Roy S, Pradhan S (2016). Effect of phytosterol extract from sesame seed on experimentally induced hyperlipidemic rats: Dose dependent study. Int. J. Pharma Biol. Sci., 7(1): 370–377.

Montesano D, Blasi F, Simonetti MS, Santini A, Cossignani L (2018). Chemical and nutritional characterization of seed oil from *Cucurbita maxima* L. (var. Berrettina) pumpkin. Foods, 7(3): 30. https://doi.org/10.3390/foods7030030

Morrison MC, Mulder P, Stavro PM, Suárez M, Arola-Arnal A, Van Duyvenvoorde W, Kleemann R (2015). Replacement of dietary saturated fat by PUFA-rich pumpkin seed oil attenuates non-alcoholic fatty liver disease and atherosclerosis development, with additional health effects of virgin over refined oil. PLoS One, 10(9): e0139196. https://doi.org/10.1371/journal.pone.0139196

Ramadan MF, Zayed R, Abozid M, Asker MMS (2011). Apricot and pumpkin oils reduce plasma cholesterol and triacylglycerol concentrations in rats fed a high-fat diet. Grasasy Aceites, 62(4): 443-452. https://doi.org/10.3989/gya.032911

Razali NR, Huri HZ, Ibrahim L, Vethakkan SR, Abdullah BM (2018). Glycemic effects of simvastatin: Where do we stand? Braz. J. Pharma. Sci., 54: e17192. https://doi.org/10.1590/s2175-97902018000117192

Sedigheh A, Jamal MS, Mahbubeh S, Somayeh K, Mahmoud RK, Azadeh A, Fatemeh S (2011). Hypoglycaemic and hypolipidemic effects of pumpkin (*Cucurbita pepo* L.) on alloxan-induced diabetic rats. Afr. J. Pharma. Pharmacol., 5(23): 2620-2626. http://www.academicjournals.org/AJPP/abstracts/abstracts/abstract%202011/22%20December/Sedigheh%20et%20al.htm, https://doi.org/10.5897/AJPP11.635

Shi MY, Bang IH, Han CY, Lee DH, Park BH, Bae EJ (2020). Statin suppresses sirtuin 6 through miR-495, increasing FoxO1-dependent hepatic gluconeogenesis. Theranostics, 10(25): 11416. https://doi.org/10.7150/thno.49770

Szendroedi J, Anderwald C, Krssak M, Bayerle-Eder M, Esterbauer H, Pfeiler G, Roden M (2009). Effects of high-dose simvastatin therapy on glucose metabolism and ectopic lipid deposition in nonobese type 2 diabetic patients. Diabetes Care, 32(2): 209-214. https://doi.org/10.2337/dc08-1123

Tietz NW, Andresen BD (1986). Textbook of clinical chemistry. (No Title).

Trinder P (1969). Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann. Clin. Biochem., 6(1): 24-27. https://doi.org/10.1177/000456326900600108

Vessal M, Hemmati M, Vasei M (2003). Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp. Biochem. Physiol. C: Toxicol. Pharmacol., 135(3): 357-364. https://doi.org/10.1016/S1532-0456(03)00140-6

Xilifu D, Tuerxun Z, Nuermaimaiti B, Aili A, Rehemu N, Sun H, Zhang X (2022). Effects of rosuvastatin on serum glucose and insulin in hyperuricemic rats. BMC Pharmacol. Toxicol., 23(1): 66. https://doi.org/10.1186/s40360-022-00595-1