National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

The effect of strawberry, Rome beauty apple, and their combination on the level of low-density lipoprotein cholesterol of Type 2 diabetes mellitus patients

Niken Yuliwati[1], Budiyanti Wiboworini[2], Vitri Widyaningsih[3]

[1]Department of Nutrition Science, Sebelas Maret University, Surakarta, Central Java, Indonesia, [2]Department of Nutrition, Faculty of Medicine, Sebelas Maret University, Surakarta, Central Java, Indonesia, [3]Department of Public Health, Faculty of Medicine, Sebelas Maret University, Surakarta, Central Java, Indonesia

Correspondence to: Niken Yuliwati, E-mail: nikenyuliwati03@gmail.com

Received: October 06, 2020; **Accepted:** October 24, 2020

ABSTRACT

Background: Diabetes mellitus (DM) is a chronic metabolic disease with an increasing prevalence over the world. **Aim and Objective:** This research aimed to analyze the effect of strawberries, Rome beauty apples, and their combination on the low-density lipoprotein cholesterol (LDL-C) levels of Type 2 DM patients. **Materials and Methods:** This study was experimental research with randomized pre- and post-test group design. The subjects were 44 patients with Type 2 DM divided into four groups, namely, K (control, no treatment), P1 (200 g/day strawberry), P2 (300 g/day Rome beauty apple), and P3 (combination of 100 g/day strawberries and 150 g/day Rome beauty apple) for 14 days. **Results:** The results showed that the LDL-C level in DM patients was markedly high in all groups before the treatment. Treatment with only strawberry, Rome beauty apple and its combination significantly decreased the level of LDL-C compared to the control group. Furthermore, treatment with 300 g/day of Rome beauty apple exhibited a high decrease in LDL-C level compared to other treatment groups. **Conclusion:** These findings suggested that strawberries, Rome beauty apples, and their combinations could be used as promising functional food for DM therapy by lowering LDL-C levels.

KEY WORDS: Strawberry; Rome Beauty Apple; Diabetes Mellitus

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease with an increasing prevalence over the world. DM and its complications cause significant morbidity and mortality.[1] There were 425 million people around the world diagnosed with DM in 2017 and 4 million deaths due to DM.[2]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2020.10.10267202024102020	

DM Type 2 is characterized by chronic hyperglycemia. Chronic hyperglycemia causes oxidative stress and the pathogenesis of DM complications.[3] The increasing levels of free radicals cause an increase of lipid peroxidation and make low-density lipoprotein cholesterol (LDL-C) easily oxidized and lead to form cell damage.[4] There is a positive correlation between low-density lipoprotein oxidation and LDL-C concentration. The low antioxidant level was contributed to the increasing low-density lipoprotein oxidation in DM patients.[5] DM Type 2 patients indicated by small dense LDL-C particles which are very atherogenic, easily oxidized, and lead to complications.[6] Lowering LDL-C levels are an important prevention strategy in preventing DM complications.[7] LDL-C levels are recommended as the primary target for lipid-lowering therapy. Control of blood

glucose and LDL-C levels is an essential part of DM Type 2 management.[8]

The current therapy of DM Type 2 is the use of insulin and oral antidiabetic drugs. These drugs have several adverse effects due to long-term administration, including kidney and liver damage and gastrointestinal disorder such as anorexia, nausea, stomach discomfort, and diarrhea.[9] The use of the drug should be considered to determine the intolerable side effects, drug ineffectiveness, and high cost of treatment.[10] The incidence of diabetes was increased globally and encouraged exploration of potential complementary medicine.[11] The use of functional foods and their bioactive compounds prevents the progression of DM Type 2 by reducing hyperglycemia, hyperlipidemia, insulin resistance, and oxidative stress.[12]

Apples contain several bioactive compounds such as quercetin and water-soluble fiber (pectin) which has been proved as potent natural antioxidants, antidiabetic effect, and reducing lipid metabolism.[13] Strawberries contain anthocyanins which have several biological effects such as increasing antioxidants, reducing oxidative stress, protecting cells from oxidative damage, and inhibiting the oxidation reaction of LDL-C.[14] Therefore, the present study aimed to analyze the effect of strawberries, Rome beauty apples, and their combination on the (LDL-C) levels of Type 2 DM patients.

MATERIALS AND METHODS

Study Design

This study is experimental research with pretest-posttest control-group design.

Study Population

DM Type 2 patients at Kratonan, Ngoresan, Sangkrah, and Banyuanyar Public Health Centers in Surakarta City from February to March 2020 were recruited as the research subjects.

Randomization and Intervention

The subjects who met the inclusion criteria at the four public health centers were randomly selected, which resulted in 44 people assigned into four groups, namely, Group K (control group, no treatment), P1 (treated with 200 g/day of strawberries), P2 (treated with 300 g/day of Rome beauty apples), and P3 (treated with combined 100 g/day of strawberries and 150 g/day of Rome beauty apples). The inclusion criteria were male and female DM Type 2 patients, aged 40–55 years, taking oral antidiabetic drugs, being able to consume fresh fruit, and being able to communicate well. The fruits were delivered to the respondents home twice a day (morning and afternoon) for 14 days.

Data Analysis

The differences before and after the intervention/treatment were analyzed using a paired *t*-test. The analysis of differences in the effect of giving strawberries, Rome beauty apples, and their combinations was carried out using a one-way ANOVA test. Bonferroni posthoc test was used to analyze the most different intervention between strawberry, Rome beauty apple, and combination groups ($P < 0.05$).

Ethics Approval

The study was approved by the Health Research Ethics Commission of Dr. Moewardi No. 087/I/HREC/2020 on January 16, 2020.

RESULTS

Table 1 showed that the distribution of the subjects between the control, strawberry, Rome beauty apples, and combination groups was based on the characteristics of age, gender, education, occupation, nutritional status, physical activity, and oral anti-diabetes. There was no significant difference ($P > 0.05$) in all groups. Therefore, it was indicated that all subjects are homogeneous.

Table 2 showed that all groups exhibited a decrease in LDL-C levels after the intervention. The lowest decrease of LCL-C was found in the control group and the highest decrease of LCL-C was found in Rome beauty apple group (P2). Based on the paired *t*-test, the average decrease in LDL-C levels of the strawberry, Rome beauty apple, and combination groups was significant ($P < 0.05$), but in the control group, it was not significant ($P < 0.05$). The results showed that before the intervention, there was no significant difference ($P = 0.056$) between the control, strawberry, Rome beauty apple, and combination groups. It was indicated that randomization has been achieved as intended.

The results showed that the LDL-C level in DM patients was markedly high in all groups before the treatment. Treatment with only strawberry, Rome beauty apple, and its combination significantly decreased the level of LDL-C compared to the control group [Table 2]. Furthermore, treatment with 300 g/day of Rome beauty apple exhibited a high decrease in LDL-C level compared to other treatment groups.

The results of the Bonferroni *post hoc* test in Table 3 showed that the decrease in LDL-C levels of the Rome beauty apple group is more significant than of the control group ($P = 0.072$).

DISCUSSION

The results showed that the administration of 200 g/day of strawberries for 14 days significantly ($P < 0.05$) reduced LDL-C levels (20.27 mg/dL). The decrease in LDL-C levels

Table 1: Characteristics of subjects

Characteristics	Group		Intervention						*P*
	K (*n*=11)		P1 (*n*=11)		P2 (*n*=11)		P3 (*n*=11)		
	n	%	*n*	%	*n*	%	*n*	%	
Age (years)									
40–45	1	9.1	1	9.1	3	27.3	3	27.3	0.54
46–50	3	27.3	4	36.4	1	9.1	4	36.4	
51–55	7	63.6	6	54.5	7	63.6	4	36.4	
Gender									
Female	4	36.4	1	9.1	2	18.2	3	27.3	0.46
Male	7	63.6	10	90.9	9	81.8	8	72.7	
BMI									
Normal	5	45.5	7	63.6	6	54.5	6	54.5	0.932
Overweight	1	9.1	1	9.1	2	18.2	2	18.2	
Obesity I	5	45.5	3	27.3	3	27.3	3	27.3	
Physical activity									
Low	11	100	10	100	9	81.8	11	100	0.269
Moderate	-	-	1	-	2	18.2	0	-	
Oral anti diabetes (OAD)									
Metformin	5	45.5	8	72.7	10	90.9	8	72.7	0.13
Metformin +Glimepiride	6	54.5	3	27.3	1	9.1	3	27.3	

K = Control, P1 = Strawberry, P2 = Rome beauty apples, P3 = Combination

Table 2: LDL-C levels in all groups treatment before and after the intervention

Group	Mean±SD		Mean±SD Decrease LDL-C	*P*[a]
	Before intervention	After intervention		
	mg/dl	mg/dl	mg/dl	
K	126.36±17.654	120.27±12.150	6.09±11.666	0.114
P1	121.55±16.114	101.27±9.155	20.27±12.784	<0.001*
P2	139.45±18.408	115.45±19.674	24.00±13.461	<0.001*
P3	136.91±15.821	115.91±19.434	21.00±15.02	0.001*
P[b]	0.056	0.041*	<0.014*	

*Significant differences, [a]*P*<0.05) paired *t*-test, [b]*P*<0.05) One-way ANOVA

Table 3: Comparison of the mean difference in LDL-C levels

Group	*P*
	After intervention
K and P1	0.099
K and P2	0.018*
K and P3	0.072
P1 and P2	1.000
P1 and P3	1.000
P2 and P3	1.000

*Significant differences. [a]*P*<0.05) Bonferroni *post hoc* test

might be caused by the anthocyanin content in strawberries, which served as antioxidant enzymes activity inducer.[15] The anthocyanins reduce free fatty acid (FFA) levels and lipolysis in adipose tissue.[16] Anthocyanins improve endothelial dysfunction and increase mitochondrial function. Therefore, it could improve glycemic response and lipid profile, suppress lipogenesis, and increase lipolysis through decreasing fat accumulation in the liver, increasing the activity of peroxisome proliferator-activated receptor-gamma (PPAR-γ) in skeletal muscle and tissue.[17] Anthocyanins can increase the oxidation of fatty acids in the liver, inhibit cholesterol synthesis by hepatic cells, and increase insulin sensitivity. Increased insulin sensitivity will increase the lipoprotein lipase enzyme and reduce FFAs, inhibit cholesteryl ester transfer protein (CETP) activity, inhibit the 3-hydroxy-3-methyl-glutaryl coenzyme (HMGCoA), increase the number of LDL-C receptors, and reduce cholesterol concentrations in the liver and plasma so that LDL-C decreases.[18] The results of this study in line with a previous study which proved that administration of strawberries for 4 weeks in diabetic rats could reduce LDL-C levels with an average decrease of 81.77 mg/dL ± 5.29.[9]

In this study, the administration of Rome beauty apples significantly reduced LDL-C levels ($P < 0.05$) by 24.00 mg/dL. The quercetin content in apples has a hypolipidemic effect, which leads to an increase in the level of phosphorylation, prevents increased hepatic glycogen synthesis, and increases glucose metabolism, thereby improving glucose and lipid metabolism in DM.[19] Quercetin prevents oxidative stress and lipid peroxidation by protecting and enhancing mitochondrial function, providing a protective effect against cholesterol-induced pancreatic cell dysfunction for glycemic control and preventing lipid deposition and overproduction of reactive oxygen species.[20] Quercetin has a potential activity to improve glucose and lipid metabolism in DM by decreasing SIRT1 expression and serine/threonine phosphorylation signaling pathways, regulating the expression of an enzyme involved in lipid metabolism, sterol regulatory element-binding protein (SREBP)2 protein, and activating adenosine monophosphate-activated protein kinase (AMPK).[21] Apple polyphenols reduce LDL-C levels through cholesterol catabolism in the liver, the secretion of cholesterol lipoproteins containing apoB, and CETP activity.[22] This study is in line with that on the effect of giving Anna apples on reducing LDL-C levels in DM rats. The results showed that 15 ml/kg of apple juice reduced the mean LDL-C level by 43.27 ± 1.80 mg/dL and 1 g/kgBW/day of apple skin extract reduced the mean LDL-C level by 66.03 ± 3.00 mg/dL with $P < 0.05$.[23]

The level of LDL-C in Rome beauty apple group was lower than the other groups because the quercetin and fiber contents in Rome beauty apple were higher than strawberries and the combination group. Furthermore, Rome beauty apple peels were high in pectin. During the ripening process, the protopectin in the apple peels is formed and converted into water-soluble pectin. The fiber in apples is a good composition compared to other fruits because it contains other active compounds which strongly bound to the fiber, including quercetin. The quercetin in apples can reach the large intestine and serve as a substrate for human intestinal bacteria. Flavonoids are usually absorbed at a low level in the intestines, but apple pectin has been demonstrated to increase the absorption of quercetin. The absorption rate of polyphenols depends on the concentration of apple pectin. The antioxidant activity of apple peels was higher than apple pulp.[24]

The polyphenols content of apple exhibited a cholesterol-lowering activity with the same mechanisms as atorvastatin and simvastatin through HMG-CoA reductase inhibition.[25] Apple extract inhibited cholesterol synthesis by increasing mitochondrial respiration, glycolysis, lipolysis, and β oxidation of fatty acids, citric, and acetyl-CoA.[26]

Apple pectin is a highly fermentable substrate by human intestinal bacteria that produce short-chain fatty acids (SCFA). SCFA production provides a hypocholesterolemic effect by decreasing the activity of (CETP), reducing the cholesteryl ester in very-low-density lipoprotein (VLDL) particles which are transferred to LDL-C.[27] SCFA suppresses cholesterol synthesis in the liver and intestine by decreasing the expression of SREBP1c, fatty acid synthase, acetyl-CoA carboxylase, and PPAR-σ.[28]

Fiber could bind with cholesterol, fat, and bile acids, and also excrete through the large intestine in the form of feces. Water-soluble fiber reduces blood glucose levels, LDL-C levels, and insulin resistance in DM Type 2.[29] Based on Table 3, there was a significant difference in the average decrease in LDL-C levels between the control group and the Rome beauty apple group ($P < 0.05$). It was indicated that the administration of 300 g/day Rome beauty apples for 14 days was effectively reduced LDL-C levels in DM Type 2 patients.

In this study, the administration of 150 g/day of Rome beauty apples for 14 days significantly reduced LDL-C levels ($P < 0.05$) with a mean decrease of 21.00 mg/dL. The combination of strawberries and Rome beauty apples (P3) could not provide a synergistic effect in reducing LDL-C levels. It might be due to the concentration ratio of each extract in combination. The increase or decrease in the concentration of the combination greatly affects the antioxidant interaction and changes the interaction effect. The combination of tomato and purple sweet potato at the ratio of 1/10 and 3/10 showed a synergistic effect, while the ratio of 7/10 and 9/10 showed an antagonistic effect.[30]

CONCLUSION

The LDL-C level in DM patients was markedly high in all groups before the treatment. Treatment with only strawberry, Rome beauty apple, and its combination significantly decreased the level of LDL-C compared to the control group. Furthermore, treatment with 300 g/day of Rome beauty apple exhibited a high decrease in LDL-C level compared to other treatment groups. These findings suggested that strawberries, Rome beauty apples, and their combinations could be used as promising functional food for DM therapy by lowering LDL-C levels.

ACKNOWLEDGMENT

The author expresses his gratitude to the Head of the Surakarta City Health Office and the Head of the Kratonan, Ngoresan, Sangkrah, and Banyuanyar Public Health Centers, who have given permission to conduct the study.

REFERENCES

1. Rajasurya V, Gunasekaran K, Surani S. Interstitial lung disease and diabetes. World J Diabetes 2020;11:351-7.
2. International Diabetes Federation. Diabetes Atlas. 8th ed. Belgium: International Diabetes Federation; 2017.
3. Papatheodorou K, Banach M, Edmonds M, Papanas N,

Papazoglou D. Complications of diabetes. J Diabetes Res 2015;2015:189525.
4. Fonseca L, Paredes S, Ramos H, Oliveira JC, Palma I. Apolipoprotein B and non-high-density lipoprotein cholesterol reveal a high atherogenicity in individuals with Type 2 diabetes and controlled low-density lipoprotein-cholesterol. Lipids Health Dis 2020;19:127.
5. Eldin EE, Almarzouki A, Assiri AM, Elsheikh OM, Mohamed BE, Babakr AT. Oxidized low density lipoprotein and total antioxidant capacity in Type-2 diabetic and impaired glucose tolerance Saudi men. Diabetol Metab Syndr 2014;6:94.
6. Linna M, Ahotupa M, Löppönen MK, Irjala K, Vasankari T. Circulating oxidised LDL lipids, when proportioned to HDL-C, emerged as a risk factor of all-cause mortality in a population-based survival study. Age Ageing 2012;42:110-3.
7. Tiainen S, Kiviniemi A, Hautala A, Huikuri H, Ukkola O, Tokola K, *et al*. Effects of a two-year home-based exercise training program on oxidized LDL and HDL lipids in coronary artery disease patients with and without Type-2 diabetes. Antioxidants (Basel) 2018;7:144.
8. Nichols GA, Joshua-Gotlib S, Parasuraman S. Independent contribution of A1C, systolic blood pressure, and LDL cholesterol control to risk of cardiovascular disease hospitalizations in Type 2 diabetes: An observational cohort study. J Gen Intern Med 2013;28:691-7.
9. Mandave P, Khadke S, Karandikar M, Pandit V, Ranjekar P, Kuvalekar A, *et al*. Antidiabetic, lipid normalizing, and nephroprotective actions of the strawberry: A potent supplementary fruit. Int J Mol Sci 2017;18:124.
10. Pandey A, Tripathi P, Pandey RD, Srivatava R, Goswami S. Alternative therapies useful in the management of diabetes: A systematic review. J Pharm Bioallied Sci 2011;3:504-12.
11. Dehdashtian E, Pourhanifeh MH, Hemati K, Mehrzadi S, Hosseinzadeh A. Therapeutic application of nutraceuticals in diabetic nephropathy: Current evidence and future implications. Diabetes Metab Res Rev 2020;2020:3336.
12. Mirmiran P, Bahadoran Z, Azizi F. Functional foods-based diet as a novel dietary approach for management of Type 2 diabetes and its complications: A review. World J Diabetes 2014;5:267-81.
13. Tri PN, Do TO, Nguyen TA. Smart Nanocontainers. Cambridge: Elsevier; 2020.
14. Różańska D, Regulska-Ilow B. The significance of anthocyanins in the prevention and treatment of Type 2 diabetes. Adv Clin Exp Med 2018;27:135-42.
15. Forbez-Hernandez TY, Gasparrini M, Afrin S, Bompadre S, Mezzetti B, Quiles JL, *et al*. The healthy effects of strawberry polyphenols: Which strategy behind antioxidant capacity? Crit Rev Food Sci Nutr 2016;56:S46-59.
16. Belwal T, Nabavi SF, Nabavi SM, Habtemariam S. Dietary anthocyanins and insulin resistance: When food becomes a medicine. Nutrients 2017;9:1111.
17. Giampieri F, Forbes-Hernandez TY, Gasparrini M, Afrin S, Cianciosi D, Reboredo-Rodriguez P, *et al*. The healthy effects of strawberry bioactive compounds on molecular pathways related to chronic diseases. Ann N Y Acad Sci 2017;1398:62-71.
18. Basu A. Role of berry bioactive compounds on lipids and lipoproteins in diabetes and metabolic syndrome. Nutrients 2019;11:1983.
19. Peng J, Li Q, Li K, Zhu L, Lin X, Lin X, *et al*. Quercetin improves glucose and lipid metabolism of diabetic rats: Involvement of Akt signaling and SIRT1. J Diabetes Res 2017;2017:3417306.
20. Carrasco-Pozo C, Tan KN, Reyes-Farias M, De La Jara N, Ngo T, Garzia-Diaz DF, *et al*. The deleterious effect of cholesterol and protection by quercetin on mitochondrial bioenergetics of pancreatic β-cells, glycemic control and inflammation: *In vitro* and *in vivo* studies. Redox Biol 2016;9:229-43.
21. Jayachandran M, Zhang T, Wu Z, Liu Y, Xu B. Isoquercetin regulates SREBP-1C via AMPK pathway in skeletal muscle to exert antihyperlipidemic and anti-inflammatory effects in STZ induced diabetic rats. Mol Biol Rep 2019;47:593-602.
22. Koutsos A, Tuohy KM, Lovegrove JA. Apples and cardiovascular health--is the gut microbiota a core consideration? Nutrients 2015;7:3959-98.
23. Fathy SM, Drees EA. Protective effects of Egyptian cloudy apple juice and apple peel extract on lipid peroxidation, antioxidant enzymes and inflammatory status in diabetic rat pancreas. BMC Complement Altern Med 2016;16:8.
24. Efimtseva EA, Chelpanova TI. Apples as a source of soluble and insoluble dietary fibers: Effect of dietary fibers on appetite. Hum Physiol 2020;46:224-34.
25. Stirpe M, Palermo V, Bianchi MM, Silvestri R, Falcone C, Tenore G, *et al*. Annurca apple (*M. pumila* Miller cv Annurca) extracts act against stress and ageing in *S. cerevisiae* yeast cells. BMC Complement Altern Med 2017;17:200.
26. Sunagawa T, Ohta Y, Sami M, Kanda T, Osada K. Hypocholesterolemic effect of dietary apple polyphenol is associated with alterations in hepatic gene expression related to cholesterol metabolism in rats. Int J Life Sci Med Res 2013;3:50-8.
27. Soliman GA. Dietary fiber, atherosclerosis, and cardiovascular disease. Nutrients 2019;11:1155.
28. Jiao AR, Diao H, Yu B, He J, Yu J, Zheng P, *et al*. Oral administration of short chain fatty acids could attenuate fat deposition of pigs. PLoS One 2018;13:e0196867.
29. Chen C, Zeng Y, Xu J, Zheng H, Liu J, Fan R, *et al*. Therapeutic effects of soluble dietary fiber consumption on Type 2 diabetes mellitus. Exp Ther Med 2016;12:1232-42.
30. Jiang HW, Li HY, Yu CW, Yang TT, Hu JN, Liu R, *et al*. The evaluation of antioxidant interactions among 4 common vegetables using isobolographic analysis. J Food Sci 2015;80:C1162-9.

How to cite this article: Yuliwati N, Wiboworini B, Widyaningsih V. The effect of strawberry, Rome beauty apple, and their combination on the level of low-density lipoprotein cholesterol of Type 2 diabetes mellitus patients. Natl J Physiol Pharm Pharmacol 2020;10(12):1105-1109.

Source of Support: Nil, **Conflicts of Interest:** None declared.