https://doi.org/10.29309/TPMJ/2022.29.06.6879

The Professional Medical Journal
www.theprofesional.com
2022, Volume, 29 Issue, 06

ORIGINAL ARTICLE

Anti hyperlipidemic effect of Oxyresveratrol and Zinc complex versus simvastatin on Total Cholesterol in Hyperlipidemic rat Model.

Aqsa Tazarrat[1], Farhana Ayub[2], Bushra Rehman[3], Wajahat Ullah Khan[4], Salma Salim[5], Sidra Ashfaq[6]

Article Citation: Tazarrat A, Ayub F, Rehman B, Khan Wajahat Ullah, Salim S, Ashfaq S. Anti hyperlipidemic effect of Oxyresveratrol and Zinc complex versus simvastatin on Total Cholesterol in Hyperlipidemic rat Model. Professional Med J 2022; 29(6):740-744. https://doi.org/10.29309/TPMJ/2022.29.06.6879

ABSTRACT… Objective: To determine the Anti hyperlipidemic effect of Oxyresveratrol and Zinc complex on Total Cholesterol in Hyperlipidemic rat Model. **Study Design:** Experimental study. **Setting:** Islamic International Medical College Rawalpindi. **Period:** Sep 2020 to Sep 2021. **Material & Methods:** In our study on high fat diet fed hyperlipidemic rats comparison of this standard drug with a novel compound oxyresveratrol was done. Forty rats were randomly divided into 4 groups, Group I was used as NC (Negative Control), group II Positive Control (PC), group III (OXY-Zn complex) and group IV SIM respectively. Groups III and IV were given orally 10 mg/kg body wt. OXY-Zn and SIM respectively. Terminal sampling was performed on day 57 for estimation of total cholesterol. **Results:** OXY-Zn complex showed significantly better control over total cholesterol compared with SIM. Total cholesterol of OXY treated group showed $p < 0.001$ like SIM treated group ($p < 0.001$). **Conclusion:** Our results showed that OXY-Zn complex is better than simvastatin because of its significantly positive effect on total cholesterol when compared with SIM.

Key words: Atherosclerosis, High Fat Diet, Oxyresveratrol, Simvastatin, Total Cholesterol.

INTRODUCTION

Hyperlipidemias are a group of diseases marked by abnormally increased levels of lipids in the blood.[1] In hyperlipidemia there is an raised level of plasma lipids such as cholesterol, triglycerides and phospholipids.[2] This increasing level may occur due to either genetic defect or because of diet or drugs. It is most common type of dyslipidemia and may cause atherosclerosis and cardiac diseases. Atherosclerosis leads to coronary artery disease, a leading cause of death across the globe.[3] WHO report reveals CVD as the cause of 12 million deaths around the world annually. Research on hypolipidemic agents in controlling TC and TG levels is being conducted on since centuries using artificial and natural sources.[4] Rats are being used as model for hyperlipidemic testing.[2] According to research estimations 17.3 million deaths annually are due to cardiovascular disease and this level may increase to 23.6 million next 10 years.[1] CHD has highest mortality rate in China and all over the world.[5] This global increase in the prevalence of hyperlipidemia is due to unhealthy eating habits, obesity and sedentary lifestyle. Third report of the National Cholesterol Education program reported south Asian are more likely to develop CHD at a young age in the absence of established risk factors.[6]

Diet modification, regular physical activity, smoking cessation, and weight reduction should be tried as initial treatment, especially in mild cases of hyperlipidemia and in persons without CHD or CHD risk equivalent and ≤2 risk factors. Clinically, many lipid lowering drugs including atorvastatin, fibrates, statins, nicotinic acid and probucol have been used for treating hyperlipidemia. However, since these drugs are expensive and have potential side effects.[1] In the past few decades, herbal medicine has become a topic of global importance, making an impact

1. MBBS, M.Phil, Demonstrator Biochemistry, Mohi-ud-din Islamic Medical College.
2. MBBS, M.Phil, PhD, CHPE, Professor, Poonch Medical College Rawlakot.
3. MBBS, M.Phil, Demonstrator, Foundation University.
4. MBBS, M.Phil, CHPE, Assistant Professor Biochemistry, Mohi-ud-din Islamic Medical College.
5. MBBS, M.Phil, Demostrator Pharmacology, Mohi-ud-din Islamic Medical College.
6. MBBS, M.Phil, Senior Lecturer Biochemistry, Rawal Institute of Health Sciences.

Correspondence Address:
Dr. Aqsa Tazarrat
Department of Biochemistry
Mohi-ud-din Islamic Medical College.
draqsatazarrat@gmail.com

Article received on: 09/11/2021
Accepted for publication: 13/01/2022

on both world health and international trade.[7] Medicinal plants have always been regarded as a healthy source of life for all people due to its rich therapeutic capabilities and being 100% natural.[1] Zinc (Zn) is an essential micronutrient that is integral to the activity of various metalloenzyme required for cellular functions. Zn acts as an anti-inflammatory, anti-atherogenic and antioxidant by protecting against various oxidative stresses.[8]

Mulberry (Morus alba L.) leaves have long been used in medicine for treatment of diabetes, hypertension, obesity, fever, and liver damage. They are rich in various functional components, such as 1-deoxynojirimycin (1-DNJ), γ-amino-butyric acid (GABA), flavonoids, stilbenes, and 2-arylbenzofurans (moracins, MCs), which have anti-hyperglycemic, anti-hypertensive, anti-hyperlipidemic, anti-aging, and antioxidant activities.[9] Oxyresveratrol found in mulberry twigs and fruits. It has an antihyperlipidemic effects and anti-obese actions.[10] (OXY) is an aglycone derivative of MUL. M. alba is tremendously used in traditional medicine, as a cough suppressant, anti-asthmatic, antibiotic, and anticancer agent.[11] Oxyresveratrol (OXY) lowers serum cholesterol through the inhibition of key enzymes (HMG-CoA reductase and squalene synthase) involved in the cholesterol biosynthesis.[3]

Since hyperlipidemia poses a major risk factor for Atherosclerotic Cardiovascular Disease. Lowering the levels of lipids in blood can remarkably reduce the incidence of CVD. Recently researchers are focusing on developing more treatment options by identifying active ingredients of food extracts. Consequently there is an increasing interest in the role of nutritional supplements like zinc with potential hypolipidemic activities in the treatment and reduction of risk for metabolic disorders. Statins have been used for the treatment of hyperlipidemias but many unwanted effects have been reported. To combat the limitations of this standard drug, better treatment options have always been a challenge for the chemist. There is an imminent need to develop a drug with similar or better efficacy with more safety or a less toxic profile.[7]

MATERIAL & METHODS

This experimental study, with a duration six months, was conducted at the Department of Biochemistry, Multidisciplinary research laboratory of Islamic International Medical College Rawalpindi (IIMC), in mutual collaboration with Animal house at NIH, Islamabad from September 2020 to September 2021. Research was started after the official approval of synopsis by accredited Ethical Review Committee of Islamic International Medical College (Riphah/IRC/20/238).

The animal house of the National Institute of Health in Islamabad provided a total of 40 adult male rats weighing 300-350 grams. The animals were retained in well-ventilated metallic cages in Room no: 13 with eight rats per cage. Photoperiod was controlled at constant 12-h light and dark cycle with maintenance of relative humidity (50 ± 5%) and a controlled temperature of 20–25°C, under the standard laboratory conditions. They were fed a normal standard diet and a high fat diet provided at the National Institutes of Health, along with standard food pellets made in accordance with recommendations accepted by the Universities Federation for Animal Welfare. They got free access to tap water via inverted bottles with a capacity of 200ml that were attached to the tops of the cages. The National Institute of Health in Islamabad provided the rodent chow, which was purchased and authorized. To ensure the normal growth and behavior, acclimatization was allowed 1 week before the intervention.

Research grade simvastatin, were obtained from SIGMA-ALDRICH Germany whereas Oxyresveratrol and zinc complex was prepared at Riphah Institute of Pharmaceutical Sciences, Islamabad.

Preparation of Drugs

Simvastatin 20 mg/kg/day was given orally once daily for four weeks.[12] Oxyresveratrol 5mg was given orally once daily for 4 weeks.[13] Zinc complex 10 mg/kg/day was given orally once daily for four weeks.[14]

Group I was named as NC for negative control and throughout the trial of 56 days it was provided

with normal standardized rodent chow (approved and purchased from National Institute of Health Islamabad). Group II labeled PC (positive control) was given high fat diet (HFD) all along the experiment. HFD, constituted of 25% fats, 25% sucrose and 50% standardized Rodent chow, was prepared at NIH. Group III received HFD for first 28 days and then treated with OXY + Zn and fed with standardized rodent chow from day 29 to day 56 i.e. the last day of experiment. Group IV received HFD for first 28 days and then treated with simvastatin and fed with standardized rodent chow from day 29 till day 56.

At day 56, experiment was completed. The biochemical essay measurement was done via intracardiac sampling on Day 0 and Day 29. Terminal sampling was done via cardiac puncture on Day 57. Simple random sampling was done. Sample tubes were placed in the centrifuge and were run at 2500rpm for 10 min. Thus serum was separated at the top of serum separating tube containing the sample. Serum samples thus obtained were stored with the help of micropipette of 1000 microL for biochemical analysis.

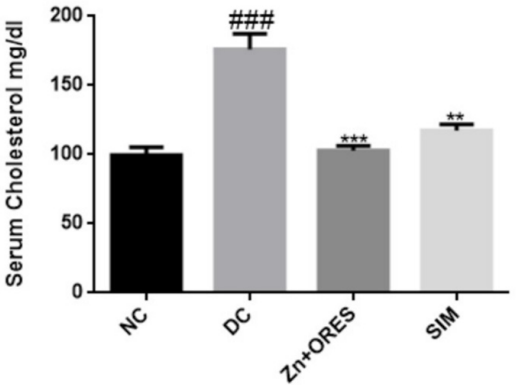
Total cholesterol was estimated by using Semi automated clinical chemistry analyzer, Merck microlab 300. Respective data was entered and analyzed in SPSS version 21. Mean ± SEM were calculated for the quantitative variables. One way ANOVA was applied to observe group mean differences between control group 1 and experimental groups 2, 3 and 4. The Post Hoc Tuckey test was used to compare the mean differences across groups.

RESULTS

Serum Total Cholesterol

Significant rise ($p<0.001$) in serum TC was seen in disease control group with a Mean ± SEM of 176.10 ± 11.36 as compared to negative control where Mean ± SEM was 99.50 ± 5.79. OXY + Zn with Mean ± SEM 102.90 ± 3.39 and SIM 117 ± 4.68 showed significant reduction ($p<0.001$) in TC levels respectively.

No.	NC	DC	OXY + Zn	SIM
Serum TC	99.50 ± 5.79	176.10 ± 11.36	102.90 ± 3.39	117 ± 4.68



Graphical presentation of results of serum TC in all four groups.

Denotes comparison between NC and DC, our results showed ### $p<0.001$ comparison of NC and DC. *denotes comparison of OXY and SIM with DC, our results showed *** $p<0.001$ when compared with DC. +++ denotes comparison between OXY + Zn and SIM, our results showed +++ $p<0.001$.

DISCUSSION

Hyperlipidemia is a modifiable risk factor for atherosclerosis and related cardiovascular diseases which includes CHD, cerebral stroke, MI and renal failure. It has becoming a major health problem worldwide.[15] To reduce ASCVD, a three-step approach has been advocated, which includes changing one's lifestyle, lowering blood cholesterol levels with effective medication therapy, and managing obesity. However, pharmacological therapy (mainly statins) has been the only approach that has shown an overwhelming response across decades.[16] Despite encouraging results, statins have been linked to a number of negative effects, according to many recent research.[17] Therefore, ACC/AHA published guidelines for the management of hyperlipidemia, which included recommendations for more research into the development of improved therapy choices for better hyperlipidemia management.[16]

In order to keep the afore mentioned propositions

in consideration, we focused this study primarily on a new compound, a stilbenoid oxyresveratrol and the trace element zinc and the outcome has been observed on a hyperlipidemic rat model. The overall increase in TC and TGs level augments LDL and VLDL synthesis and a consequent decrease in HDL levels which indicates hyperlipidemia.[18] Similarly various studies revealed that Zn can up regulate SREBP1 and PPARs expression. PPARα is responsible for regulating fatty acid oxidation, while PPARγ regulates processes like adipocyte differentiation and lipid storage and is also associated with insulin sensitivity.[19] According to some previous studies, Zn supplementation has also been linked to a better lipid profile, with lower total and LDL cholesterol.

Moreover, as cardio-metabolic risk is a result of combination of risk factors, out of which dyslipidemia is the consequent and modifiable risk factor. In scientific literature, it has been associated with the excursion of TC, TGs, LDL and HDL concentrations.[16]

In lipid profile TC is a measure of all the cholesterol included in the form of either cholesteryl esters as well as free cholesterol in serum. During dyslipidemia high levels of TC are observed which collectively show the cholesterol load on liver.[20]

Our study revealed that OXY and Zn, when given at a dose of 10 mg/kg/day significantly lowered the serum TC levels in group III. Jo SP et al[11] observed that serum TC levels were significantly reduced in hyperlipidemia rats treated with OXY at a dose of 10 mg/kg/day which was in accordance with study conducted by Oleichnowicz et al[21] who revealed that treatment with zinc decreased the high plasma TC levels in HFD induced hyperlipidemia mice.

CONCLUSION

In the present study it is concluded that, Oxyresveratrol and Zinc effectively and synergistically reduces total cholesterol levels in high fat diet induced hyperlipidemia as compared to simvastatin.

REFERENCES

1. Verma N. **Introduction to hyperlipidemia and its treatment: A Review**. Int J Curr Pharm Res 2016; 9(1):6.

2. Prasanna Kumar K, Rama Narsimha Reddy A, Narsimha Reddy Y, Anbu J. **Lipid lowering activity of lercanidipine in hyperlipidemic rats.** Iran J Pharmacol Ther 2010; 9(2):73–5.

3. Hwang D, Jo SP, Lee J, Kim JK, Kim KH, Lim YH. **Antihyperlipidaemic effects of oxyresveratrol-containing Ramulus mori ethanol extract in rats fed a high-cholesterol diet.** J Funct Foods [Internet] 2015; 19:353–62. Available from: http://dx.doi.org/10.1016/j.jff.2015.09.039.

4. Yoon NY, Kim HR, Chung HY, Choi JS. **Anti-hyperlipidemic effect of an edible brown algae, Ecklonia stolonifera, and its constituents on poloxamer 407-induced hyperlipidemic and cholesterol-fed rats.** Arch Pharm Res 2008; 31(12):1564–71.

5. Gan W, Liu Y, Luo KH, Liang SS, Wang H, Li M, et al. **The prevalence change of hyperlipidemia and hyperglycemia and the effectiveness of yearly physical examinations: An eight-year study in Southwest China.** Lipids Health Dis 2018; 17(1).

6. Zaid M, Hasnain S. **Plasma lipid abnormalities in Pakistani population: Trends, associated factors, and clinical implications.** Brazilian J Med Biol Res 2018; 51(9).

7. Zheng L, Zhai G, Zhang J, Wang L, Ma Z, Jia M, et al. **Antihyperlipidemic and hepatoprotective activities of mycelia zinc polysaccharide from Pholiota nameko SW-02.** Int J Biol Macromol [Internet] 2014; 70(July 2014):523–9. Available from: http://dx.doi.org/10.1016/j.ijbiomac.2014.07.037.

8. Al-Rasheed NM, Attia HA, Mohamed RA, Al-Rasheed NM, Al-Amin M. **Preventive effects of selenium yeast, chromium picolinate, zinc sulfate and their combination on oxidative stress, inflammation, impaired angiogenesis and atherogenesis in myocardial infarction in rats.** J Pharm Pharm Sci 2013; 16(5):848–67.

9. Jeon YH, Choi SW. **Isolation, Identification, and Quantification of Tyrosinase and α-Glucosidase Inhibitors from UVC-Irradiated Mulberry (Morus alba L.) Leaves.** Prev Nutr Food Sci 2019; 24(1):84–94.

10. Choi JH, Song NJ, Lee AR, Lee DH, Seo MJ, Kim S, et al. **Oxyresveratrol increases energy expenditure through Foxo3a-mediated Ucp1 induction in high-fat-diet-induced obese mice.** Int J Mol Sci 2019; 20(1).

11. Jo SP, Kim JK, Lim YH. **Antihyperlipidemic effects of stilbenoids isolated from Morus alba in rats fed a high-cholesterol diet.** Food Chem Toxicol [Internet] 2014; 65:213–8. Available from: http://dx.doi.org/10.1016/j.fct.2013.12.040.

12. Campolongo G, Riccioni CV, Raparelli V, Spoletini I, Marazzi G, Vitale C, et al. **The combination of nutraceutical and simvastatin enhances the effect of simvastatin alone in normalising lipid profile without side effects in patients with ischemic heart disease.** IJC Metab Endocr [Internet]. 2016; 11:3–6. Available from: http://dx.doi.org/10.1016/j.ijcme.2016.03.001.

13. Jo SP, Kim JK, Lim YH. **Antihyperlipidemic effects of stilbenoids isolated from Morus Alba in rats fed a high-cholesterol diet.** Food Chem Toxicol [Internet]. 2014; 65:213–8. Available from: http://dx.doi.org/10.1016/j.fct.2013.12.040.

14. Sadri H, Larki NN, Kolahian S. **Hypoglycemic and hypolipidemic effects of leucine, zinc, and chromium, alone and in combination, in rats with type 2 diabetes.** Biol Trace Elem Res. 2017; 180(2):246–54.

15. I K, N M, Y-J Y, J-Y L. **Induce hyperlipidemia in rats using high fat diet investigating blood lipid and histopathology.** J Hematol Blood Disord. 2018; 4(1):5–10.

16. Ms BBA, Jacobson TA. **New cholesterol guidelines for the management of atherosclerotic cardiovascular disease risk a comparison of the 2013 American college of cardiology / American heart association cholesterol guidelines with the 2014 national lipid association recommendation.** Cardiol Clin [Internet]. 2015; 33(2):181–96. Available from: http://dx.doi.org/10.1016/j.ccl.2015.02.001.

17. Chrysant SG. **New onset diabetes mellitus induced by statins: current evidence.** Postgrad Med [Internet]. 2017; 129(4):430–5. Available from: http://dx.doi.org/10.1080/00325481.2017.1292107.

18. Iqbal J, Al Qarni A, Hawwari A, Alghanem AF, Ahmed G. **Metabolic syndrome, dyslipidemia and regulation of lipoprotein metabolism.** Curr Diabetes Rev. 2017; 14(5):427–33.

19. Pandurangan M, Jin BY, Kim DH. **ZnO nanoparticles upregulates adipocyte differentiation in 3T3-L1 Cells.** Biol Trace Elem Res. 2016; 170(1):201–7.

20. Eid S, Sas KM, Abcouwer SF, Feldman EL, Gardner TW, Pennathur S, et al. **New insights into the mechanisms of diabetic complications: Role of lipids and lipid metabolism.** Diabetologia. 2019; 62(9):1539–49.

21. Olechnowicz J, Tinkov A, Skalny A, Suliburska J. **Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism.** J Physiol Sci. 2018; 68(1):19–31.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Aqsa Tazarrat	Data collection and corresponding author.	
2	Farhana Ayub	Principal investigator.	
3	Bushra Rehman	Sample collection, writing correction, data interpretation.	
4	Wajahat Ullah Khan	Writing support, Data interpretation.	
5	Salma Salim	Statistical analysis and data Interpretation.	
6	Sidra Ashfaq	Study design, Sample collection.	