Eurasian Journal
of Veterinary Sciences

www.eurasianjvetsci.org

# RESEARCH ARTICLE

## Evaluation of the hypocholesterolemic efficacy of lyophilized *Nerium oleander* distillate

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Received:13.04.2022, Accepted: 20.06.2022
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## *Nerium oleander*'in liyofilize distilatının hipokolesterolemik etkinliğinin değerlendirilmesi

**Eurasian J Vet Sci, 2022, 38, 3, 137-142**
DOI: 10.15312/EurasianJVetSci.2022.375

**Öz**

**Amaç:** Bu çalışmanın amacı *Nerium oleander* distilatının hiperkolesterolemik sıçanların serum biyokimyasal parametreleri üzerindeki etkisini değerlendirmektir.

**Gereç ve Yöntem:** 30 erkek Sprague-Dawley rattan oluşan üç eşit grup oluşturuldu. Kontrol grubu için herhangi bir uygulama yapılmadı. İkinci gruba yüksek kolesterol diyeti verilirken, üçüncü gruba günde bir kez oral gavaj yoluyla liyofilize *Nerium oleander* distilatına ek olarak yüksek kolesterol diyeti verildi. Üç ay sonra, sıçanlardan sedasyon altında kan alındı ve ötenazi yapıldı. Serum açlık kan şekeri, trigliserit, yüksek yoğunluklu lipoprotein, total kolesterol, düşük yoğunluklu lipoprotein, alanin aminotransferaz, aspartat aminotransferaz, albümin, total protein, alkalin fosfataz, laktat dehidrojenaz, kreatinin ve üre düzeyleri otoanalizörde belirlendi.

**Bulgular:** Yüksek kolesterol diyeti ile beslenen grupta, kontrol grubuna kıyasla, alkalin fosfataz, alanin aminotransferaz, aspartat aminotransferaz, kolesterol, glukoz, düşük yoğunluklu lipoprotein ve trigliserit seviyeleri arttı ($p < 0.05$). Ancak *Nerium oleander* uygulaması yükselmiş olan aspartat aminotransferaz, kolesterol, düşük yoğunluklu lipoprotein ve trigliserit düzeyini düşürdüğü ($p < 0.05$) belirlendi.

**Öneri:** Özetlemek gerekirse, *Nerium oleander* distilatının antihiperkolesterolemik ve karaciğer koruyucu özelliklere sahip olduğu ifade edilebilir.

**Anahtar kelimeler:** *Nerium oleander*, hiperkolesterolemi, rat

**Abstract**

**Aim:** The purpose of this study was to assess the effect of administering *Nerium oleander* distillate on hypercholesterolemic rats' serum biochemical parameters.

**Materials and Methods:** Three equal groups of 30 male Sprague-Dawley rats were formed. No application was made for the control group. The second group received a high cholesterol diet, while the third group received a high cholesterol diet in addition to lyophilized *Nerium oleander* distillate by oral gavage once daily. After three months, blood was drawn after sedation and they were euthanized. Serum fasting blood glucose, triglyceride, high-density lipoprotein, total cholesterol, low-density lipoprotein, alanine aminotransferase, aspartate aminotransferase, albumin, and total protein levels, as well as alkaline phosphatase, lactate dehydrogenase, creatinine, and urea levels, were determined using an autoanalyzer.

**Results:** Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, cholesterol, glucose, low-density lipoprotein, and triglyceride levels increased ($p < 0.05$) in the group fed a high cholesterol diet compared to the control group, but *Nerium oleander* treatment decreased the elevated aspartate aminotransferase, cholesterol, low-density lipoprotein, and triglyceride ($p < 0.05$).

**Conclusion:** To summarize, it can be stated that *Nerium oleander* distillate has antihypercholesterolemic and liver-protective properties.

**Keywords:** *Nerium oleander*, hypercholesterolemia, rat

## Introduction

Hyperlipidemia is defined as a lipid metabolism disorder characterized by low high-density lipoprotein (HDL) levels in the body and an increase in total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol levels (El-Tantawy and Temraz 2019). Studies have shown that a sedentary lifestyle causes obesity and metabolic diseases such as cancer, cardiovascular diseases, diabetes mellitus, hyperlipidemia, and dyslipidemia, increasing death risk. According to reports, a sedentary lifestyle leads to an increase in triglyceride levels in the blood, causes a decrease in HDL-cholesterol levels, and increases insulin resistance. It is stated that combating obesity caused by a sedentary life is an important factor to prevent the occurrence of cardiovascular diseases (Helvacı et al 2014, Park et al 2020) .

Metabolic syndrome (MetS) is defined as multiple cardiovascular risk factors that cluster together and result from genetic and environmental factors. Hyperglycemia, hypertension, dyslipidemia, visceral obesity, and hypercoagulability are among the components of MetS. Treatment is aimed at lowering LDL cholesterol. Drug treatment includes statins, fibric acid derivatives, bile acid sequestrants, drugs that inhibit cholesterol absorption, and nicotinic acid (Kayaalp 2002). MetS is defined as an important disease that causes many diseases, which can cause serious morbidity and mortality if appropriate precautions are not taken and treated, and especially increases the risk of cardiac events. It is stated that MetS is an important health problem in both developed and developing countries, and its incidence varies according to country and gender. In European countries, the incidence of MetS has been reported to be comparable between men and women. It has been determined that this rate is higher in women in Turkey. In addition, it is reported that the probable reason for it to be seen more frequently in women is that obesity is more common in women. According to studies conducted in Turkey, one out of every three adults has been found to have MetS (Üçler 2014, Abacı et al 2018). It has been reported that maintaining normal blood lipid levels decreases the risk of suffering a cardiovascular event (Jankowski et al 2011).

Recently, it has been recommended that individuals with hyperlipidemia receive further treatment through diet restriction and exercise. In addition, it has been stated that lipid-lowering drugs consisting of statins and fibrates have been used in the treatment of hyperlipidemia for a long time. However, it is stated that natural hypolipidemic drugs of herbal origin can be used due to the side and undesirable effects of statins (El-Tantawy and Temraz 2019). Herbal therapy is preferred by different societies as an alternative and complementary therapy (Roghani-Shahraki et al 2021). Studies have shown that some medicinal plants are effective in reducing blood cholesterol levels by inhibiting the activity of the hydroxymethylglutaryl CoA reductase enzyme, which is important in cholesterol synthesis in the human body (Mahdavi et al 2020).

*Nerium oleander* (NO), which belongs to the family of Apocynaceae, is a 2–5 m evergreen plant. Although the use of NO in some diseases is under investigation, its serious toxicity limits its use (Baytop 1999). In contrast, the water distillate of NO is non-toxic (Dik et al 2012) and has beneficial effects on fat and glucose metabolism (Bas et al 2012).

This study considered that NO water distillate is non-toxic (Dik et al 2012) and has positive effects on type 2 diabetes (Bas et al 2012, Yazihan et al 2013). It was hypothesized that administering NO distillate to rats with experimental hypercholesterolemia might positively affect glucose and lipid metabolism.

The primary objective of this study was to assess the effect of NO distillate on blood lipid metabolism markers such as glucose, cholesterol, triglycerides, HDL, and LDL. Additionally, the study sought to assess the effect of NO distillate on several serum biochemical indicators, including albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, urea, creatinine, and lactate dehydrogenase.

## Material and Methods

### *Animals*

The study utilized thirty male Sprague-Dawley rats (8–12 weeks of age, 300 g). Individual rats were maintained in metabolic cages in a room with automatically controlled atmospheric humidity (50±5%), temperature (22±2°C), and light-dark ratio (12:12). Water was available on a first-come, first-served basis.

### *Preparation of solution*

NO was gathered in May in Turkey's Mediterranean region. The Faculty of Science's Biology Department found and approved the NO plant. After washing, the NO leaves were chopped and distilled in hot water at a concentration of 100 g/1000 mL. The distillate obtained was concentrated using a lyophilizer (FDT-8618 Freeze Dryer, Operon, Korea) at the concentrations (10 mL) utilized in the experimental groups.

### *Experimental design*

Three equal groups of rats were formed. The control group was fed conventional rat chow (ME: 2850 kcal/kg; cellulose: up to 5%; calcium: 1%–2%; hp: 21%; phosphorus: 0.5

%-1%; ash: up to 10%; sodium chloride: 0.5%; dry matter: 89%). The high cholesterolemic (HC) group was fed a high-cholesterol diet (Table 1) (Kuo et al 2008). The HC + NO group was fed with a hypercholesterolemic diet, and the lyophilized material equivalent to ten milliliters of NO distillate was diluted with 0.5 milliliters of physiological saline and supplied once daily via gavage.

Three months after the start of the study, animals were euthanized after blood collection from their hearts under sodium pentobarbital (50 mg/kg) anesthesia. Serum glucose, cholesterol, triglyceride, LDL, HDL, total protein, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urea, albumin, and lactate dehydrogenase levels were determined using a commercial kit in an autoanalyzer.

### *Statistical analyses*

The data are expressed as mean ± std. error (SE). Data from 8 animals from each group were used. Parameters measured in the study were evaluated with ANOVA and a post hoc Duncan test (SPSS 22.0). Statistical significance was defined as a P-value of less than 0.05.

## Results

Table 2 summarizes the changes in glucose and lipid metabolism markers. Cholesterol, glucose, triglyceride, and LDL levels were higher in the HC group than in the control group ($p < 0.05$, Table 2). Increased cholesterol, triglyceride and LDL levels in control group were decreased ($p < 0.05$) in HC + NO distilled group, but did not affect glucose levels ($p > 0.05$). HDL levels did not differ across the groups ($p > 0.05$, Table 2).

Table 3 contains additional serum biochemical characteristics for the groups. Alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels increased significantly in the HC group compared to the control group ($p < 0.05$), and NO distillate administration to hypercholesterolemic animals decreased these parameters ($p < 0.05$, Table 3). Albumin, creatinine, urea, and lactate dehydrogenase levels remained unchanged ($p > 0.05$, Table 3).

Table 1. Hypercholesterolemic ration content

| Ration content | % |
|---|---|
| Cholesterol | 1.00 |
| Animal fat | 5.00 |
| Cornstarch | 35.10 |
| Casein | 20.10 |
| Soybean oil | 5.00 |
| Sucrose | 20.00 |
| AIN-76 minerals | 3.50 |
| AIN-76 vitamins | 1.00 |
| Choline | 0.40 |
| Methyl alpha cellulose | 9.00 |

Table 2. Effect of NO distillates on glucose and lipid metabolism parameters

| Parameters | Control group (n=8) | HC Group (n=8) | HC + NO distillated (n=8) |
|---|---|---|---|
| Gluc (mg/dL) | 94.5 ± 7.56$^{b}$ | 127±6.13$^{a}$ | 139±6.77$^{a}$ |
| Chol (mg/dL) | 44.6 ± 6.14$^{c}$ | 241±38.4$^{a}$ | 126±15.3$^{b}$ |
| TG (mg/dL) | 58.1 ± 4.27$^{b}$ | 101±12.1$^{a}$ | 55.8±5.06$^{b}$ |
| HDL (mg/dL) | 30.0 ± 1.70 | 26.0±2.64 | 25.3±1.48 |
| LDL (mg/dL) | 31.1 ± 2.77$^{c}$ | 289±45.1$^{a}$ | 188±22.9$^{b}$ |

HC: Hypercholesterolemic group, HC + NO distillated: Hypercholesterolemia + *Nerium oleander* distillate, Gluc: Glucose, Chol: Cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein. $^{a, b, c}$: Different letters in the same line are statistically important (Duncan, $p<0.05$).

Table 3. Effect of NO distillates on other serum parameters

| Parameters | Control group (n=8) | HC Group (n=8) | HC + NO distillated (n=8) |
|---|---|---|---|
| Alb (g/dL) | 3.63±0.06 | 3.71±0.19 | 3.41±0.12 |
| ALP (IU/L) | 178±8.48$^{c}$ | 813±65.5$^{a}$ | 348±26.1$^{b}$ |
| ALT (IU/L) | 51.7±2.38$^{b}$ | 343±77.1$^{a}$ | 79.8±8.89$^{b}$ |
| AST (IU/L) | 102±7.95$^{b}$ | 301±44.4$^{a}$ | 168±14.7$^{b}$ |
| TP (g/dL) | 5.81±0.31 | 5.92±0.40 | 6.30±0.41 |
| Creat (mg/dL) | 0.35±0.04 | 0.31±0.03 | 0.37±0.04 |
| Urea (mg/dL) | 51.7±3.57 | 46.5±1.88 | 50.2±2.82 |
| LDH (IU/L) | 1295±175 | 1204±310 | 1114±125 |

HC: Hypercholesterolemic group, HC + NO distillated: Hypercholesterolemic group + *Nerium oleander* distillate, Alb: Albumin, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TP: Total protein, Creat: Creatinine, LDH: Lactate dehydrogenase. $^{a, b, c}$: Different letters in the same line are statistically important (Duncan, $p<0.05$).

## Discussion

In this study, it was observed that the distillate obtained from NO caused a decrease in the increased lipid parameters in hypercholesterolemic rats. Lipid disorders are among the most important factors affecting cardiovascular mortality and morbidity today (Özbey and Orhan 2003). The increase in cardiovascular diseases in developing countries is increasing faster than in western countries. It is important to make changes in lipid metabolism in the management of cardiovascular diseases. An increase in cardiovascular diseases is inevitable due to increased blood cholesterol levels. Keeping the LDL-cholesterol level at a low level reduces this risk (Mahdavi et al 2020). It is stated that statins are widely used to lower blood cholesterol levels in the body. Studies have shown that statins act by inhibiting the activity of the enzyme hydroxymethyl CoA reductase (HMGCoAR), which has an important role in cholesterol synthesis in the body. However, it is stated that the use of statins, which have been used in the treatment field for more than twenty-five years, causes concern due to some side effects such as the effect on the muscles, the increase in the incidence of diabetes, and recently, the formation of cataracts (Sirtori 2014). It is recommended that patients treated with statins regularly monitor their blood glucose or HbA1c levels, as well as engage in physical activity (Agouridis et al 2015). It is stated that various medicinal plants are used to lower the level of HMGCoAR, which has a critical role in lowering blood cholesterol levels. Although statins and new LDL-lowering drugs continue to be used in treatment, it is reported that medicinal plants can be preferred for patients who cannot use statins (Mahdavi et al 2020). It can be stated that NO distillate is anticholesterolemic, but molecular-based studies are required to determine the drug action point.

This study discovered that giving a hypercholesterolemic diet to healthy rats increased their glucose, cholesterol, triglyceride, and LDL levels in comparison to the control group ($p<0.05$, Table 2). It was determined that NO distillate administration to hypercholesterolemic rats decreased elevated cholesterol, triglyceride, and LDL levels ($p < 0.05$), as well as other parameters ($p < 0.05$), but did not affect glucose levels ($p > 0.05$). Studies with plants have shown that soybean (Duranti et al 2004), Kangen-karyu extract (Yokozawa et al 2006), *Agaricus bisporus* (Jeong et al 2010), *Cynara scolymus* L. (Kiraz et al 2010), *Taiwanofungus camphoratus* (Suk et al 2008), *Allium sativum* (El-Sayyad et al 2010), *Cinnamomum* (Amin and Abd El-Twab 2009), and *Nigella sativa* (Zaoui et al 2002) plants have antihypercholesterolemic effects. In addition to these, statins are used to treat elevated lipids (Gotto 1995). Because all parts and extracts of the NO plant are poisonous, its medicinal use is very limited (Baytop 1999; Ozdemir et al 2011). Studies with NO water distillate have reported that it is not toxic after oral administration in rats (Dik et al 2012), has antiviral activity (Avci and Dik 2014), has no antibacterial effect (Dik et al 2013), has an antioxidant effect (Er et al 2015), is not embryotoxic (Karabulut et al 2014), and displays anticancer activity (Er et al 2019). In particular, NO distillate administration to type 2 diabetic rats reduces cholesterol, LDL, and triglyceride-HDL ratios. The study concluded that it could be a treatment approach in type 2 diabetes (Bas et al 2012, Demirel Kars et al 2014). It has been reported that NO distillate can cause positive results by affecting cholesterol metabolism-related gene-expression levels. A study on cell culture reported that NO distillate increased glucose uptake (Yazihan et al 2013). Collectively, the research results suggest that NO distillate may exert antihyperlipidemic effects by regulating genes related to cholesterol metabolism (Demirel Kars et al 2014), showing antioxidant activity (Er et al 2015) or affecting glucose metabolism (Yazihan et al 2013).

This research revealed that following NO distillate administration, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels decreased in the hypercholesterolemic group ($P<0.05$, Table 2). Serum alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, and albumin levels

are used to define liver injury in mammals (Er et al 2015, Turgut 2000). The increase in alanine aminotransferase is considered a very specific parameter in demonstrating hepatocellular damage (Panteghini and Bais 2008). In this study, the reduction in levels of elevated liver-injury markers in hypercholesterolemic animals upon NO distillate administration suggests hepatoprotective effects. This effect can be attributed to its lipid metabolism regulatory (Demirel Kars et al 2014) or antioxidant effects (Gözükara 1990, Er et al 2015).

## Conclusion

In conclusion, NO distillate may have antihypercholesterolemic and hepatoprotective effects by affecting genes involved in lipid metabolism or by exerting antioxidant effects. For the study results to be fully elaborated, these findings need to be confirmed by molecular techniques and histopathological examinations.

## Acknowledgement

This research was summarized from a doctoral thesis. Other authors are supervisors. YOK thesis number 406956.

## Conflict of Interest

The authors did not report any conflict of interest or financial support.

## Funding

This study was supported by the Scientific Research Projects Coordination Unit, Selcuk University (Project Number: 0820207).

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## Ethical Approval

Selçuk University Experimental Research and Application Center, Animal Experiments Ethics Committee 2010/028 Number Ethics Committee Decision

**CITE THIS ARTICLE:** *Kizilay H, Bas AL, Yazihan N. 2022. Evaluation of the hypocholesterolemic efficacy of lyophilized Nerium oleander distillate. Eurasian J Vet Sci, 38 3, 137-142.*