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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

DENEYSEL MİYOGLOBİNÜRİK AKUT BÖBREK YETMEZLİĞİ MODELİNDE OLEİK ASİDİN KORUYUCU VE TERAPÖTİK ETKİLERİ

PROTECTIVE AND THERAPEUTIC EFFECTS OF OLEIC ACID IN EXPERIMENTAL MYOGLOBİNURIC ACUTE RENAL FAILURE MODEL

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ÖZET

AMAÇ: Bu çalışmanın amacı, antioksidan ve antiinflamatuar özellikleriyle bilinen oleik asidin, akut böbrek yetmezliği (ABY) üzerindeki potansiyel koruyucu ve tedavi edici etkilerini deneysel bir modelde incelemektir.

GEREÇ VE YÖNTEM: Bu çalışmada 24 adet Wistar Albino dişi sıçan randomize 8'erli 3 gruba ayrıldı. Grup 1 kontrol grubu olarak kullanıldı. Grup 2'ye böbrek hasarını indüklemek için %50 hipertonik gliserol (8 ml/kg, i.m.) verildi. Grup 3'e gliserol ve oleik asit (10 mg/kg, intragastrik) verildi. Böbrek hasarı, serum üre ve kreatinin değerleri ölçülerek değerlendirildi. Oksidatif stres ile antioksidan savunma sistemleri arasındaki dengeyi değerlendirmek amacıyla biyokimyasal belirteçler olan malondialdehit (MDA), total oksidan kapasite (TOS), total antioksidan kapasite (TAS), oksidatif stres indeks (OSI), total thiol, katalaz (CAT), paraoksonaz (PON) değerleri ölçüldü.

BULGULAR: Gliserol uygulaması, serum kreatinin ve üre seviyelerinde anlamlı bir artışa neden oldu ve bu da akut böbrek fonksiyon bozukluğunu gösterdi. Oleik asit tedavisi renal fonksiyonları gösteren bu parametrelerde kısmi iyileşme sağladı. Biyokimyasal parametrelere baktığımızda, gliserol uygulanan sıçanlarda oksidatif stresi yansıtan MDA, TOS ve OSI seviyeleri anlamlı derecede artış gözlemlenirken, TAS, total tiyol, CAT ve PON seviyeleri anlamlı seviyede azaldığı gözlemlendi. Oleik takviyesi, bu değişiklikleri önemli ölçüde tersine çevirerek antioksidan ve nefroprotektif etkiler göstermiştir.

SONUÇ: Elde edilen sonuçlar, oleik asidin böbrek üzerindeki potansiyel nefroprotektif etkilerine dair yeni bakış açıları sunmakta olup, bu etkinin altında yatan mekanizmaların aydınlatılması ve klinik uygulanabilirliğinin değerlendirilmesi amacıyla ileri düzey araştırmalara duyulan gereksinimi açıkça ortaya koymaktadır.

ANAHTAR KELİMELER: Gliserol, Miyoglobinürik akut böbrek yetmezliği, Oleik asit, Serbest radikaller, Oksidatif stres.

ABSTRACT

OBJECTIVE: This study aims to investigate the potential protective and therapeutic effects of oleic acid recognized for its antioxidant and anti-inflammatory properties on acute renal failure (ARF) in an experimental model.

MATERIAL AND METHODS: In this study, 24 Wistar Albino female rats were randomly divided into 3 groups of 8 each. Group 1 was used as the control group. Group 2 was given 50% hypertonic glycerol (8 ml/kg, i.m.) to induce renal injury. Group 3, glycerol plus oleic acid (10 mg/kg, intragastrically) respectively. Renal injury was assessed by measuring serum urea and creatinine. Biochemical markers malondialdehyde (MDA), total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), total thiol, catalase (CAT), paraoxanase (PON) values were measured to evaluate the balance between oxidative stress and antioxidant defense systems.

RESULTS: Glycerol administration caused a significant increase in serum creatinine and urea levels, indicating acute renal dysfunction. Oleic acid treatment provided partial improvement in these parameters indicating renal function. When we look at biochemical parameters, MDA, TOS and OSI levels reflecting oxidative stress were significantly increased in glycerol-administered rats, while TAS, total thiol, CAT and PON levels were significantly decreased. Oleic supplementation significantly reversed these changes, showing antioxidant and nephroprotective effects.

CONCLUSIONS: The results obtained provide new insights into the potential nephroprotective effects of oleic acid on the kidney and clearly demonstrate the need for further studies to elucidate the mechanisms underlying this effect and to evaluate its clinical applicability.

KEYWORDS: Glycerol, Myoglobinuric acut renal failure, Oleic acid, Free radicals, Oxidative stress.

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INTRODUCTION

Acute renal failure (ARF), described as acute loss of kidney function, is a disease that affects multiple organs and systems. The symptoms include a decline or loss of renal function over a period of hours to days, an inability to excrete nitrogenous waste due to kidney damage, and the failure to maintain body fluid and electrolyte balance. (1-4). Despite all the advances in health care, dialysis cases and deaths have unfortunately not been prevented in the last 50 years. Dialysis is required in 20% to 60% of ARF patients, and less than 25% of these require long-term dialysis. While the mortality rate due to ARF is approximately 7%, this rate can exceed 80% in hospitalized patients (5,6).

Rhabdomyolysis, which is defined as the destruction of striated muscle cells, can cause many systemic problems. The most important of these is acute renal failure (7). Myoglobinuric acute renal failure (MARF) develops after traumatic and non-traumatic muscle damage (8). Crush syndrome is a systemic condition that occurs as a result of rhabdomyolysis caused by trauma, paves the way for many medical/surgical complications, and is the second leading cause of death in earthquakes after the direct effects of trauma (9). Rhabdomyolysis has many non-traumatic causes, as well as traumatic causes such as mine collapses, traffic accidents, earthquakes, wars and natural disasters. Among traumatic causes, earthquakes have a significant place in our country (10). In this context, understanding the pathophysiology, early diagnosis, and timely management of rhabdomyolysis-induced acute kidney injury becomes particularly crucial, especially in disaster-prone regions such as our country. The high prevalence of earthquakes underscores the need for preparedness protocols that include the rapid identification and treatment of MARF cases to reduce morbidity and mortality.

Intramuscular injection of hypertonic glycerol into rats is a widely used model to create experimental MARF (10). This model is considered identical to the MARF that develops in humans (11). Intramuscular glycerol injection causes myolysis, hemolysis, and hypovolemia. It is evident that the iron present within myoglobin and hemoglobin, which is released into the circulation as a result of myolysis and hemolysis, plays an instrumental role in the pathogenesis of myo- and lipo-arginine-related fatty liver disease (MARF). The presence of such iron leads to the generation of free radicals and subsequent lipid peroxidation (12-14).

Many substances have been and are being tested for preventive and therapeutic purposes on experimental myoglobinuric kidney damage. In this context, various bioactive compounds with antioxidant and anti-inflammatory properties have been investigated for their potential renoprotective effects. Oleic acid (OA), a type of monounsaturated fatty acid that is found in abundance in dietary sources such as olive oil, has recently attracted significant attention due to its cytoprotective properties in a variety of models of tissue damage. Additionally, it is present in high amounts (about 72%) in olive oil, a crucial dietary fat source, mostly in the traditional Mediterranean diet, and a key ingredient in a number of therapeutic plant extracts (15).

Regular consumption of olive oil has been demonstrated to engender a number of health benefits in humans, including the prevention of certain cancers, the risk of coronary heart disease, as well as immune and inflammatory changes that may result from the presence of OA. Numerous in vivo and in vitro research studies have demonstrated the antioxidant and anticancer properties of OA, thus validating the claim. Evidence has been posited that OA may have a role to play in reducing blood pressure by enhancing endothelial function, potentially through the moderation of reactive oxygen species (ROS). In addition, there is evidence to suggest that OA exerts a chemoprotective role in the context of breast cancer, with the potential to reduce the risk of developing rheumatoid arthritis (16-19). This study's main goal is to assess the therapeutic and preventive benefits of oleic acid, which is known for its anti-inflammatory and antioxidant properties, in an animal model of acute kidney injury.

MATERIALS AND METHODS

Animals

The present study utilised a total of 24 female Wistar Albino rats, with an average weight ranging from 250 to 400 grams, obtained from the Experimental Animal Production Center of Aydin Adnan Menderes University Faculty of Medicine. Rats housed in the Experimental Animals Laboratory were provided with standard rat feed and tap water.

Drugs

All other chemicals and reagents used were of analytical quality, and glycerol was acquired from Merck KGaA (Darmstad, Germany) and oleic acid from Roche Chemicals and Pharmaceutics (Basel, Switzerland).

Study Design

The experiment was conducted on a total of 24 Wistar Albino female rats. The rats were randomly assigned to three groups, with each group consisting of eight animals. The rats were maintained under semi-climatized laboratory conditions, with an ambient temperature of 22±1˚C, a 12/12-hour light/dark cycle, relative humidity (40-50%) and controlled ventilation. All animals were free to feed, eat and drink water until 8-12 hours before the application. All animals were deprived of water for the last 24 hours, and glycerol was administered as a total volume of 8 ml/kg under light ether anesthesia (20).

Group 1 comprised the control group (n=8). Intramuscular saline solution was applied bilaterally to the lower extremities of the rats in the control group. After 1, 24 and 48 hours, distilled water was given orally. Group 2 glycerol (n=8) intramuscular 50% hypertonic glycerol was applied as 8 ml/kg to the lower extremities bilaterally. After 1, 24 and 48 hours, distilled water was given orally. Group 3 oleic acid+ARF (n=8) intramuscular 50% hypertonic glycerol was applied to the bilateral lower extremities as 8 ml/kg. After 1, 24 and 48 hours, 10 mg/kg of oleic acid was administered orally intragastrically (21). After oleic acid was prepared to contain 10 milligrams per kilogram, the amount prepared by weighing each rat was mixed with water and 1 ml of the resulting aqueous suspension was administered orally to the rats using intragastric gavage.

Renal Function Assays

The measurement of serum urea and creatinine levels was conducted using an autoanalyser (Bio-Tek ELx800 Microplate Reader, USA) in Aydin Adnan Menderes University Physiology Laboratory.

Biochemical Assays

Measurement of Malondialdehyde (MDA)

Kidney tissue samples were homogenised with ice-cold 150 mmol/L KCl for the determination of MDA levels. The homogenates were then subjected to a centrifugation process at 2600 g for a duration of 10 minutes at a temperature of 4°C. Assays were performed to assess the MDA concentrations in renal tissue samples, which is a recognised metric of lipid peroxidation. This analysis involved the measurement of thiobarbituric acid-reactive species (TBARS) (22). 200 µL of the supernatant was mixed with 0.6 mL of distilled water, 0.2 mL of 8.1% sodium dodecyl sulphate, 1.5 mL of 20% acetic acid (pH 3.5), and 1.5 mL of 0.8% thiobarbituric acid. The mixture was subjected to a heating process at a temperature of 95°C for a duration of 60 minutes, utilising oleic acid in the context of myoglobinuric renal failure. Following cooling with distilled water and tap water, and with a 1:1:1 volumetric ratio of n-butanol-pyridine mixture (15:1, v/v), the samples were vigorously shaken and subsequently subjected to centrifugation at 2600 g for 10 min at 25°C. The measurement of the organic layer was conducted at a wavelength of 532 nm. The quantification of MDA was conducted using an extinction coefficient of 1.56 × 105 L/mol per cm, with kidney levels expressed in nmol MDA/mg tissue.

Measurement of Total Oxidant Status (TOS)

The measurement of serum TOS levels was conducted by means of spectrophotometric analysis, employing the Genesys 10 UV Scanning UV/VIS Spectrophotometer (Shimadzu) at a wavelength of 530 nm, utilising designated kits (Rel Assay Diagnostics kit; Mega Tıp, Gaziantep, Turkey) developed by Erel (23).

Measurement of Total Antioxidant Status (TAS)

The measurement of serum TAS levels was conducted using a spectrophotometric approach, employing the Genesys 10 UV Scanning UV/VIS Spectrophotometer (Shimadzu, Kyoto, Japan). The measurement was conducted at a wavelength of 660 nm, utilising designated kits for this purpose (Rel Assay Diagnostics kit, Mega Tıp, Gaziantep, Turkey) developed by Erel (24).

Measurement of Oxidative Stress Index (OSI)

Oxidative Stress Index (OSI), a measure of oxidative stress, was calculated as the proportion of TOS levels to TAS levels. (25). Specifically, OSI (arbitrary unit) = TOS (μmol H2O2 Eq/L) / TAS (mmol Trolox Eq/L).

Measurement of Total Thiol

One technique used to determine the part oxidative stress plays in the etiology of erectile dysfunction is the thiol oxidative stress test, which has gained popularity recently. Since 1979, the measurement of this dual-sided balance has been conducted on a single side. However, the novel method devised by Erel and Neşelioğlu facilitates the separate measurement and cumulative evaluation of both sides, enabling a comprehensive and nuanced assessment (26).

Measurement of Catalase (CAT)

The activity of CAT was determined by measuring the decrease in the absorption of light at a wavelength of 240 nm due to the decomposition of hydrogen peroxide, according to the method of Aebi (1984). The activity of the enzyme was measured in units of 1 μM H_2O_2 per minute, representing the rate at which the enzyme catalysed the decomposition of hydrogen peroxide (27).

Measurement of Paraoxanase (PON)

The measurement of PON activities was conducted utilising commercially kits (RelassayR, Gaziantep, Turkey). The activity of PON was expressed in units per litre of serum. The measurement of arylesterase activity was conducted by utilising phenylacetate as a substrate. The activity of arylesterase was expressed as one unit, which was defined as 1 μmol of phenol generated per minute under the aforementioned conditions. This was expressed as KU/L serum (28).

Ethical Committee

Prior to the commencement of the study, approval was granted by the Aydin Adnan Menderes University Faculty of Medicine Experimental Animal Ethics Committee (decision numbered 64583101/2025/056) in complience with the ethical standards set out in the committee's guidelines.

Statistical Analysis

The IBM® SPSS® 26 software (SPSS Inc., Chicago, IL, USA) for Windows 22.0 was used to perform the statistical analysis. The Kolmogorov-Smirnov test was one of the analytical techniques used to determine whether the variables were normal. The mean and standard deviation were used to display descriptive analysis. The frequency and percentage values of the categorical variables related to sociodemographic and clinical data were determined using descriptive statistics. The independent two-sample t-test was employed for the purpose of comparing groups, on the assumption that the values in question were normally distributed. In instances where enzyme levels were non-normally distributed, the non-parametric Mann-Whitney U test and the Wilcoxon rank-sum test were employed to ascertain the significance of the observed differences between variables. Standard deviation (SD) ± mean values are used to display the data. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

Renal Function Results

When glycerol was administered, creatinine levels significantly increased in comparison to the control group, as indicated in figure 1 and table 1. Compared to the ARF group, oleic acid treatment reduced renal failure to a certain extent **(Figure 1, Table 1)**.

Glycerol administration significantly raised urea nitrogen levels in comparison to the control group, as indicated in figure 2 and table 1. Comparing the oleic acid group to the ARF group, the former showed partial improvement in renal failure **(Figure 2, Table 1)**.

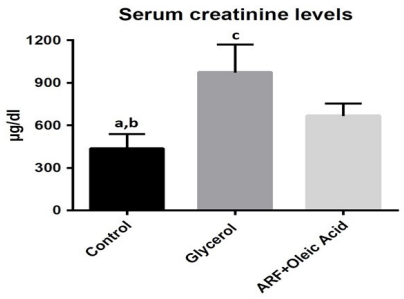

Figure 1: Serum creatinin levels.
a: Control vs Glycerol; p<0.0001
b: Control vs ARF+Oleic Acid; p=0.0108
c: Glycerol vs ARF+Oleic Acid; p=0.0030

Table1: Comparison against Control group

Groups	Control	Glycerol	ARF+Oleic Acid
Serum creatinine levels (µg/dl)	436±102.3	974.3±196.4[a]	666.8±87.76[b]
Urea nitrogen levels (mg/dl)	16.33±3.670	30.17±3.601[c]	25.17±3.430[d]

For serum creatinin levels;

a: Control vs Glycerol; p<0.0001, Control vs ARF+Oleic Acid;

b: p=0.0108. For serum urea nitrogen levels; Control vs Glycerol;

c: p<0.0001, Control vs ARF+Oleic Acid; d: p=0.0013.

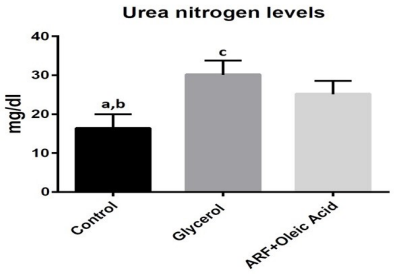

Figure 2: Serum urea nitrogen levels.
a: Control vs Glycerol; p<0.0001
b: Control vs ARF+Oleic Acid; p=0.0013
c: Glycerol vs ARF+Oleic Acid; p=0.0283

Biochemical Results

Biochemistry results are as shown in **Table 2**. Rats administered with glycerol showed significantly higher levels of MDA compared to the control group. When oleic acid was given to rats treated with glycerol, MDA levels were significantly lower than those of the glycerol group Table 2.

The TOS level of glycerol-treated rats was significantly higher compared to the control group. When oleic acid was given to rats treated with glycerol, the TOS levels were significantly lower compared to those of the glycerol group. Glycerol-treated rats showed significantly lower TAS levels compared to the control group. When oleic acid was given to glycerol-treated rats, TAS levels were significantly higher than in the glycerol group. Rats given glycerol had a considerably higher OSI level than the control group. When oleic acid was given to rats treated with glycerol, their OSI levels were considerably lower than those of the glycerol group. Total thiol level significantly decreased in rats rats treated with glycerol as compared to the control group. The administration of oleic acid to glycerol treated rats significantly increased the levels of total thiol as compared to glycerol group. Rats given glycerol had a considerably lower CAT level than the control group. Rats given oleic acid instead of glycerol showed a substantial rise in CAT levels (Table 2) compared to the glycerol group. Rats given glycerol had a considerably lower PON level than the control group. When oleic acid was given to rats treated with glycerol, their PON levels were noticeably higher than those of the glycerol group (Table 2).

Table 2: Evaluation of biochemical markers in rats subjected to experimental myoglobinuric acute renal failure and treated with oleic acid

Groups	MDA (nM/mg) ort± SD	TOS (µmol H_2O_2 Eq/L)	TAS (mmol Trolox Eq/L)	OSI (Arbitrary Unit	Total thiol (µmol/L)	CAT (U/mg protein)	PON (U/L)
Control group	0.327±0.110	9.01±1.96	1.39±0.11	0.648	378±71	38.65±3.88	15.47±2.20
Glycerol group	0.464±0.235*	11.66±2.63*	1.15±0.10*	1.01*	265±55*	27.43±2.89*	13.88±1.83*
ABY + Oleic Acid	0.396±0.177*#	10.29±2.42*#	1.29±0.12*#	0.79*#	321±64*#	34.45±3.45*#	14.68±2.05*#

*: p ≤ 0.05 In comparison with the control group #: p ≤ 0.05 In comparison with the ARF + Oleic Acid group.

DISCUSSION

Acute renal failure cases that develop due to muscle damage caused by trauma are frequently seen after major disasters. Many systemic problems can be encountered after rhabdomyolysis, which is defined as the destruction of striated muscle cells. The most important of these is acute renal failure. Earthquakes are the most common natural disasters. Earthquakes are frequently seen both in the world and in our country, and it is stated that new disasters are expected in the near future. The most common cause of death during earthquakes is, as expected, the direct effect of trauma.

The second leading cause of death is crush syndrome and its complications. Crush syndrome, which results from prolonged compression of muscle tissue, leads to massive release of intracellular contents such as myoglobin, potassium, phosphate, and creatine kinase into the systemic circulation. This re-

lease triggers a cascade of metabolic derangements, among which myoglobin-induced nephrotoxicity plays a pivotal role in the development of acute renal failure (29, 30).

The most popular and recognized method for causing ARF in rats as a result of experimental rhabdomyolysis is the intramuscular injection of hypertonic glycerol. This model is used as an experimental model of myoglobinuric ARF in humans. This model closely mimics the pathophysiological mechanisms observed in clinical rhabdomyolysis, including myoglobin-induced tubular injury, oxidative stress, and subsequent acute tubular necrosis, making it a reliable and widely accepted approach in nephrotoxicity studies. Myoglobinuric acute renal failure is a uremic condition that arises due to traumatic or non-traumatic causes to skeletal muscle (28-35). Many studies have investigated the protective effects of many natural antioxidant substances in the experimental myogloninuric ARF model (36). Hypertonic glycerol injection is the most widely utilised model for experimental myoglobinuric ARF (37). It induces muscle cell lysis leading to the release of myoglobin into the circulation, which subsequently accumulates in renal tubules and triggers oxidative damage, inflammation, and acute tubular necrosis. There is no specific treatment for acute renal failure other than the supportive treatments currently applied. Some interventions that have been shown to have beneficial effects in experimental studies, such as regulating hemodynamic status and reducing cell damage, have not been shown to be clinically useful. In our study, a methodology was established to investigate the possible protective effect of oleic acid administered before glycerol on glycerol-induced toxic nephropathy in a glycerol-induced ARF model in rats. To our knowledge, this is one of the first studies to evaluate the prophylactic effects of oleic acid in a glycerol-induced acute renal failure model, thus providing new insights into the literature regarding the potential therapeutic role of oleic acid in toxic nephropathy. A study has shown that vitamin C administration significantly reduces the development of oxidative stress and structural-functional nephron damage; the protective effect obtained with 150 mg/kg vitamin C administration significantly increases with 300 mg/kg administration (38). In our study, oleic acid administration similarly led to a significant decrease in the development of functional nephron damage.

It has been established that free radicals are significant in the pathogenesis of a number of kidney diseases, including myoglobinuric ARF. They also play a critical role in the formation of kidney damage, as in other organs and tissues. Free oxygen radicals produce different vasoactive effects depending on their different subtypes (39). Oleic acid (cis-9-octadecenoic acid) is a monounsaturated fatty acid found primarily in olive oil and has attracted intense scientific interest in recent years due to its antioxidant properties. Findings in the literature indicate that oleic acid plays an important role in reducing oxidative stress by suppressing free radical production and modulating cellular antioxidant defense systems. In particular, its lipid peroxidation inhibitory effect provides a critical advantage in maintaining cell membrane integrity (40). In another study, in the garlic myoglobinuric ARF model, a decrease in malondialdehyde levels, an increase in tissue nitric oxide levels and superoxide dismutase enzyme activity, and a decrease in necrosis and castration rates were observed in the garlic-administered group compared to the unadministered group (41). Glycerol-induced ARF was observed to have a considerably higher malondialdehyde content in the renal cortex than control levels, although proanthocyanidin therapy dramatically decreased this content (42). In our study, oleic acid administration similarly led to a significant decrease in the development of functional nephron damage. Another study investigated the effects of grape seed proanthocyanidins on myoglobinuric ARF. Rats were injected with 50% glycerol (8 mL/kg, IM) and then intraperitoneally with proanthocyanidins (20 mg/kg) or saline for the next three days. After 96 hours, the rats were sacrificed and rats receiving proanthocyanidins in addition to glycerol had significantly lower ($p<0.01$) blood urea and serum creatinine levels as compared to those receiving only glycerol (43). Similarly, in our study, oleic acid administration similarly led to a significant decrease blood urea and serum creatinine levels as compared to those receiving only glycerol.

It has been demonstrated that oleic acid enhances the expression of endogenous antioxidant enzymes, including SOD, CAT and GPx, through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Through these mechanisms, oleic acid contributes to the prevention of many inflammatory and degenerative processes by limiting cellular damage caused by oxidative stress (44). In a different investigation, catechin administration considerably enhanced the components generated in the myoglobinuric ARF model. Catechin demonstrated a renoprotective benefit in this rhabdomyolysis-mimicking model because of its antioxidative action, which decreased the toxicity of myoglobin in renal tissues (45). The effects of Narginine, a flavonoid, on myoglonuric ARF were investigated.

The pretreatment of animals with Narginine 60 minutes prior to glycerol injection resulted in a significant attenuation of renal dysfunction, as well as a reduction in morphological changes and TBARS. Furthermore, it led to the restoration of depleted renal antioxidant enzymes (46). In our study, TOS, TAS, OSI, total thiol, CAT and PON values were examined. Similar to the findings of previous studies, the ARF model was significantly improved by oleic acid treatment, which is known to have antioxidant effects.

Numerous studies also indicate that oleic acid is effective in preventing ischemic heart disease. Oleic acid has been shown to inhibit platelet aggregation and serotonin secretion induced by platelet aggregation factor (PAF). As a result of studies conducted to understand the molecular mechanism of this effect, it was discovered that oleic acid inhibits platelet aggregation induced by PAF by reducing phosphatidylinositide (PIP) and PIP2 levels (47,48).

The study conducted by Wu and colleagues sought to investigate the impact of oleic acid on HepG2 cells, with a view to inducing steatosis. Utilising a controlled incubation approach, the study revealed that oleic acid significantly increased the expression of Peroxisome Proliferator Activated Receptor gamma (PPARγ) in a calcium-dependent manner. It was also understood that oleic acid regulated insulin sensitivity due to its impact on phosphatase and tensin homolog (PTEN), a factor which was known to increase insulin resistance in hepatic steatosis. A number of studies have indicated that unsaturated fatty acids have an effect on the production of ROS in neutrophils. Nevertheless, it has been documented that the development of neutrophil activation can be enhanced or inhibited by fatty acids, depending on the specific experimental conditions employed. It has been observed in the course of certain studies that C18 fatty acids have the capacity to inhibit the production of ROS (49,50,51). These findings suggest that oleic acid has the potential to be evaluated as a therapeutic agent in metabolic diseases through its regulatory effects on insulin sensitivity, oxidative stress, and inflammatory responses. Further preclinical and clinical studies are warranted to elucidate its precise mechanisms of action and to determine its efficacy and safety in human subjects. In addition to its in vivo effects, oleic acid also provides effective protection and treatment properties at the cellular level. In the study conducted by Carrillo Pérez et al. (52), it was shown that oleic acid plays a role in the activation of different intracellular pathways that play a role in the inhibition of carcinoma cell development.

The study, however, is not without limitations. Despite the promising findings of our study regarding the protective and therapeutic effects of oleic acid in an experimental model of MARF, several limitations should be acknowledged. First, the study was conducted using a rat model, which, although widely accepted for investigating rhabdomyolysis-induced ARF, may not fully replicate the complexity of human pathophysiology. Therefore, the translational applicability of the findings to clinical practice remains limited. Second, while we assessed key biochemical and histopathological parameters, molecular mechanisms underlying oleic acid's renoprotective effects such as modulation of oxidative stress, inflammatory signaling pathways, or apoptosis-related cascades-were not deeply investigated. Further mechanistic studies are needed to clarify these pathways. Additionally, we did not include long-term follow-up to assess the durability of oleic acid's protective effects or its influence on renal regeneration. It is known that oleic acid can in-

hibit endogenous respiration of mitochondria. Oleic acid has effective radical scavenging activity and reduces the effects of kidney damage.

In conclusion, the experimental findings obtained in our study indicate that oleic acid has both protective and therapeutic potential in the myoglobinuric acute renal failure model and provide a valuable basis for future comprehensive and mechanistic studies.

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