



THE PROTECTIVE EFFECT OF EXTRA VIRGIN OLIVE OIL ON ARSENIC INDUCED CARDIOMYOPATHY IN ALBINO RATS

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ABSTRACT

Background: Arsenic contamination of drinking water is a major public health concern in Pakistan and globally. Chronic exposure induces oxidative stress, inflammation, and structural cardiac damage leading to cardiomyopathy. Extra virgin olive oil (EVOO), rich in polyphenols and antioxidants, has shown protective effects in various organs, but its role in arsenic-induced cardiac injury is not well established.

Objective: To evaluate the protective effect of EVOO against arsenic-induced gross and histological alterations in the heart of albino rats.

Methods: Forty-five adult male albino rats were divided into three groups (n = 15 each): Group I (control, distilled water), Group II (arsenic, 40 mg/kg sodium arsenate), and Group III (arsenic + EVOO, 0.2 ml/day). After four weeks, hearts were excised, weighed, and examined histologically for congestion, inflammatory infiltration, edema and myocyte hypertrophy. Data were analyzed using ANOVA, post hoc Tukey, and Chi-square tests, with $p \leq 0.05$ considered significant.

Results: Arsenic significantly increased heart weight (1.77 ± 0.04 g) and myocyte diameter (36.9 ± 1.0 μ m) compared with controls (1.32 ± 0.03 g; 22.0 ± 0.9 μ m; $p < 0.001$). EVOO prevented these changes, with values (1.38 ± 0.02 g; 24.4 ± 1.1 μ m) comparable to controls ($p > 0.05$). Edema and inflammatory infiltration were absent in controls, but present in 80% and 93% of arsenic-exposed rats, respectively. EVOO reduced these to 60% each ($p < 0.0001$). Congestion was observed in 27% of arsenic-only and 33% of arsenic + EVOO rats, with no significant difference ($p = 0.054$).

Conclusion: EVOO confers significant cardioprotection against arsenic-induced cardiomyopathy by normalizing heart weight and myocyte size and reducing histological damage.

Keywords: Arsenic toxicity, Cardiomyopathy, Extra virgin olive oil, Oxidative stress.

INTRODUCTION

The heart, a vital muscular organ, is central to the circulatory system, ensuring the distribution of oxygenated blood throughout the body. ¹Structurally, it consists of four chambers—two atria and two

ventricles—encased within layers such as the epicardium, myocardium, and endocardium.² The atrial walls are thin due to their role in receiving blood, with limited muscle fibers and structures like the fossa ovalis in the right atrium. Ventricular walls are thicker, especially the left ventricle, to pump blood under high pressure. Both ventricles feature trabeculae carneae (muscular ridges) and papillary muscles, which prevent valve prolapse during contraction.³ These structural differences support the heart's dual roles in receiving blood and maintaining systemic circulation. Its histological organization includes cardiac muscle fibers, connective tissue, blood vessels, and conduction fibers, which coordinate electrical impulses.⁴ This intricate anatomy allows it to function effectively, though it is highly susceptible to environmental toxins.

Arsenic, a naturally occurring toxic element, is widely recognized for its contamination of drinking water and soil, particularly in regions such as Pakistan, Bangladesh, and parts of the Americas.⁵ In Pakistan, groundwater arsenic levels have been reported to exceed the WHO permissible limit of 10 µg/L, with concentrations as high as 200 µg/L in certain areas.⁶ Globally, arsenic exposure stems from industrial processes, pesticides, and mining activities.⁷ Arsenic-induced oxidative damage primarily involves the generation of reactive oxygen species (ROS), which disrupt mitochondrial function, impair antioxidant defenses, and lead to cellular apoptosis, particularly in cardiac tissue.⁸ Arsenic exposure triggers acute inflammation with neutrophil infiltration, edema, and vascular damage due to ROS and pro-inflammatory cytokines, potentially leading to early fibrosis.⁹ Chronic exposure causes persistent inflammation, extracellular matrix buildup, and architectural disruption.¹⁰ Arsenic affects most of the organs involved in absorption, accumulation, and excretion.¹¹ Long-term exposure to inorganic arsenic can cause dysfunction of the endocrine system, the nervous system, and the reproductive system, and may also lead to weight loss. Exposure to arsenic also causes liver fibrosis, metabolic disorders such as diabetes^{12,13}, chronic lung disease, gangrene of toes¹⁴, cancer of internal sites and skin¹⁵. It has been found to have toxic effects on the gonadal tissues of laboratory animals as well. Arsenic also induces cardiac hypertrophy via ROS and signaling pathways (PI3K/Akt, MAPK), leading to muscle thickening, stiffness, and eventual heart failure.¹⁶ Arsenic also causes various histopathological changes in the heart, including congestion with haemorrhage, myocardial disruption, edema, and also congested hemorrhagic coronary arteries.¹⁷

Extra virgin olive oil (EVOO), a staple of the Mediterranean diet, is celebrated for its health benefits, particularly its antioxidant properties. Studies have shown that EVOO mitigates oxidative damage in various organs, including the liver, kidneys, and brain, due to its polyphenol-rich composition.^{18,19} However, evidence on its effects specifically on the heart is scarce. This gap in the literature highlights the need for further investigation, which this study aims to address by evaluating EVOO's potential in preventing arsenic-induced cardiomyopathy.

Rationale of the study

Arsenic in drinking water is a current issue in Pakistan. According to the WHO, about 150 million people around the world rely on groundwater contaminated with arsenic. About 10 µg per liter of arsenic is permissible in drinking water according to WHO guidelines, but the government of Pakistan says that 50 µg per liter is acceptable. This new study shows that 50-60 million people living in the Indus valley are drinking water that very likely exceeds their government's safe level. In 5 villages of Pakistan, the levels of arsenic in groundwater have exceeded 100 µg per litre; moreover, it also causes cardiovascular diseases.^{20,21} Moreover, now in Rawalpindi and Islamabad, drinking water is also contaminated with arsenic.²²

Objectives

To determine the protective effect of extra virgin olive oil on arsenic-induced histological changes in the heart of albino rats.

Hypothesis

a. Null hypothesis

Extra virgin olive oil has no protective effect on arsenic-induced histological changes in the heart of albino rats.

b. Alternate Hypothesis

Extra virgin olive oil has a protective effect on arsenic-induced histological changes in the heart of albino rats.

MATERIAL AND METHODS

This study was conducted after approval from the Ethical Review Committee.

Sampling and Grouping

- **Sample Size:** 45 adult male albino rats (2–4 months old, ~250–300 g).
- **Study Design:** Simple random sampling using balloting.
- **Exclusion Criteria:** Female rats and those with known pathology.
- **Groups:**
 - **Group I (Control):** 15 rats received distilled water for 4 weeks.
 - **Group II (Arsenic):** 15 rats received sodium arsenite (40 mg/kg)²³ for 4 weeks.
 - **Group III (Arsenic + Olive Oil):** 15 rats received sodium arsenite (40 mg/kg) with olive oil (0.2 ml/day) for 4 weeks.

Duration: 4 weeks

Materials

- **Sodium Arsenite Preparation:** Powder dissolved in drinking water (40 mg/kg body weight).
- **Olive Oil Preparation:** 0.2 ml/day mixed with drinking water.
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Housing and Environment

Rats will be housed in three groups under standard conditions (20–26 °C, 12-hour light/dark cycles) with pellet diets and water ad libitum.

Dissection and Sample Collection: After 4 weeks, rats were anesthetized with chloroform. Each rat was placed in a supine position, secured to a dissection board with limbs immobilized. A midline incision was made from the neck to the abdomen to expose the thoracic cavity. The sternum was carefully cut and retracted to reveal the heart. The heart was identified within the pericardial sac. The pericardium was removed, and major vessels (aorta and vena cava) were carefully ligated and severed. The heart was gently removed and immediately placed in a container of 10% formalin. The heart's external structure and any abnormalities were noted before histological analysis.

Study variables

The heart will be taken out, and the following gross and histological parameters will be observed. On gross appearance, the thickness of the wall of ventricles was increased in group II rats, and there was a significant decrease in thickness in the heart of rats of group III due to the protective effect of extra virgin olive oil. The gross appearance of the heart's wall thickness is shown in Figure 1.

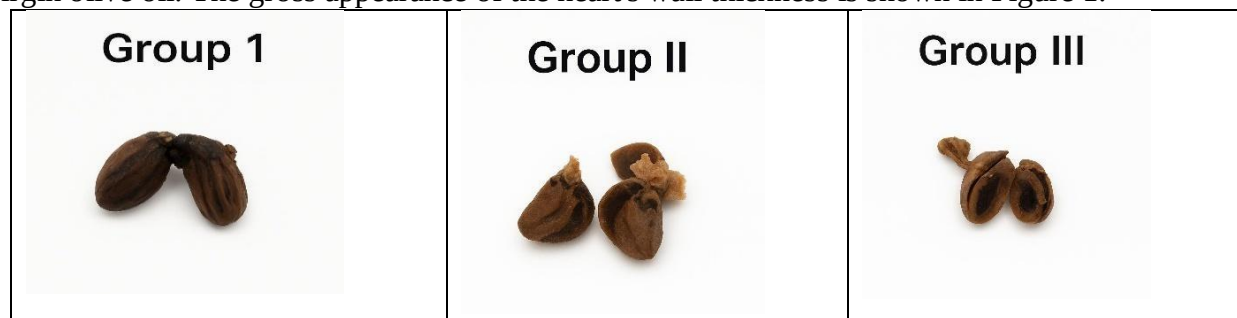


Figure 1 shows gross appearance of thickness of walls of hearts among three groups.

Gross parameter

Weight of heart

Light microscopic parameters**Qualitative**

1. Congestion
2. Inflammatory infiltrate
3. Edema

Quantitative

Diameter of cardiac myocytes

Data Analysis Procedure:

All data was analyzed by SPSS version 26 ,expressed as mean $\pm$ SD. Chi-square test was used for qualitative parameters, and ANOVA and post Hoc Tukey test was used for quantitative parameters. α -value ≤ 0.05 was considered significant.

RESULTS

Gross and microscopic parameters of the heart were analyzed to evaluate the effect of arsenic and the protective role of extra virgin olive oil (EVOO).

The mean heart weight in the control group (Group I) was **1.32 $\pm$ 0.03 g**, in the arsenic group (Group II) **1.77 $\pm$ 0.04 g**, and in the arsenic + EVOO group (Group III) **1.38 $\pm$ 0.02 g**. One-way ANOVA revealed a highly significant difference among groups . Post hoc Tukey's test showed that Group II had significantly higher heart weight compared with Group I (mean difference = 0.45 g, $p < 0.001$) and Group III (mean difference = 0.39 g, $p < 0.001$), whereas Group I and Group III did not differ significantly (mean difference = 0.06 g, $p > 0.05$).

Similarly, the mean myocyte diameter in Group I was **22.0 $\pm$ 0.9 μ m**, in Group II **36.9 $\pm$ 1.0 μ m**, and in Group III **24.4 $\pm$ 1.1 μ m**. ANOVA confirmed significant group differences . Tukey's test demonstrated that myocyte diameter was significantly increased in Group II compared with Group I (mean difference = 14.9 μ m, $p < 0.001$) and Group III (mean difference = 12.5 μ m, $p < 0.001$), while no significant difference was observed between Group I and Group III (mean difference = 2.4 μ m, $p > 0.05$). These results indicate that EVOO effectively prevented the arsenic-induced increase in both heart weight and myocyte. hypertrophy. The results of both these quantitative parameters are shown in Table 1 and Table 2.

Table 1.Group Wise Distribution of weight of heart and Myocyte diameter among control and experimental groups of Albino Rats.

Groups	Weight of Hearts(gm)			Myocytes diameters (um)		
	Group I (control)	Group II(experimental Arsenic)	Group III(arsenic and olive oil)	Group I(control)	Group II(experimental Arsenic)	Group III(arsenic and olive oil)
Mean	1.32	1.77	1.38	22	36.9	24.4
SEM	0.03	0.04	0.02	0.9	1	1.1
P value	≤ 0.0001					

Table 2. Multiple Comparison of mean weight of heart and mean Myocyte diameter among control and experimental groups of Albino Rats.

Groups	Weight of Hearts(gm)		Myocytes diameters (um)	
	Mean difference	P value	Mean difference	P value
I vs II	0.45 gm	≤ 0.001	14.9um	≤ 0.001
I vs III	0.06 gm	0.57	2.4 um (not significant)	0.31(not significant)
II vs III	0.39 gm	≤ 0.001	12.5 um	≤ 0.001

Histological evaluation revealed marked differences in the distribution of edema, inflammatory infiltrates, and congestion across groups. Edema was absent in Group I (0%), but present in **80%** of Group II and **60%** of Group III animals. The association between treatment group and edema was significant. Inflammatory infiltrates were observed in **93%** of Group II and **60%** of Group III animals, while no infiltration was detected in Group I. This association was also highly significant ($p < 0.0001$). Congestion was observed in **27%** of Group II and **33%** of Group III, but absent in Group I, and the differences among groups did not reach statistical significance ($p = 0.054$). These qualitative parameters are shown in bar diagram (figure 2). All parameters are also shown in histological figure 3.

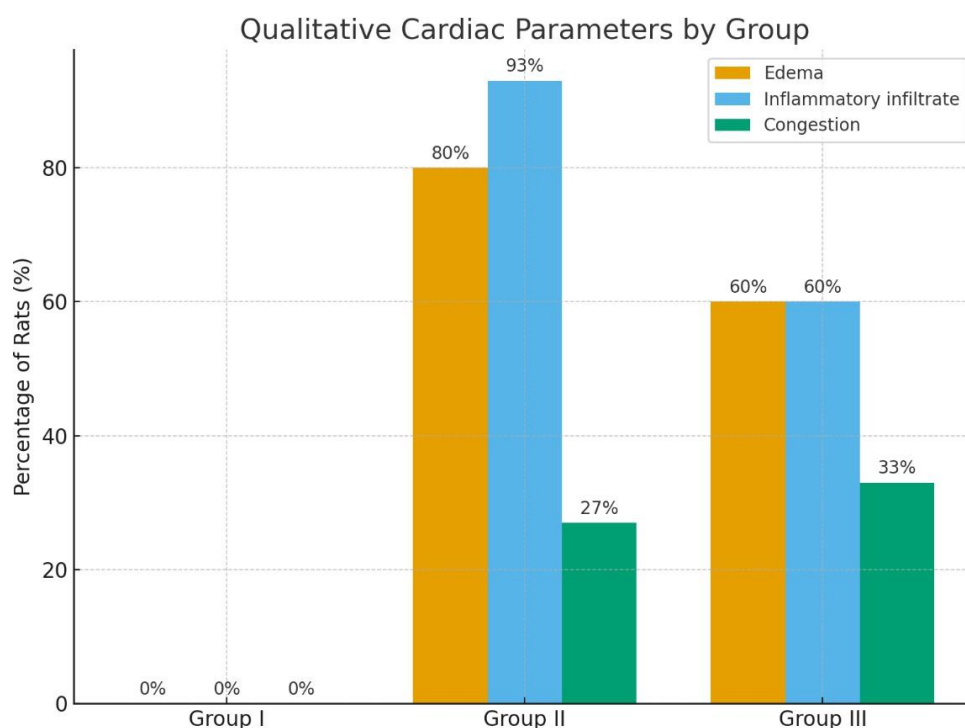


Figure 2. Diagram showing percentages of edema, inflammatory infiltrate and congestion among groups of Albino rats

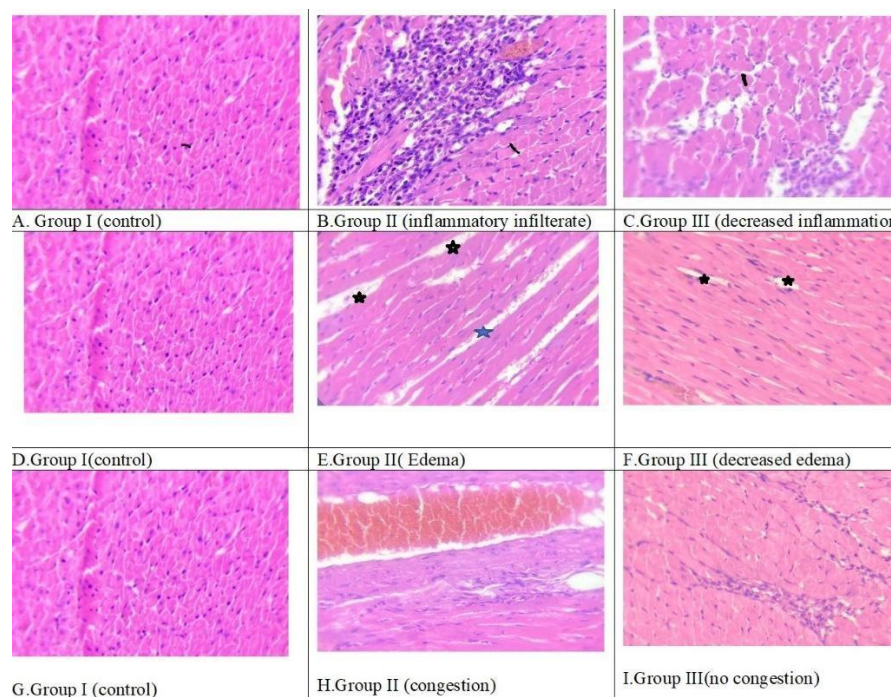


Figure 3. Group wise distribution of myocyte diameter, inflammatory infiltrate, Edema and Congestion

Figure 3 A, Showing normal myocyte width in group I, B shows increased inflammatory infiltrate and increased myocyte diameter shows decreased inflammatory infiltrate and decreased myocyte diameter shows increased edema and interstitial space. F shows decreased edema (indicated by stars). H shows congestion in blood vessels and I shows no congestion in group III (H and E, X 40)

Overall, these findings confirm that arsenic exposure induces significant structural and histological changes in the heart, while EVOO supplementation provides a strong protective effect, normalizing heart weight and myocyte dimensions and reducing histological damage

DISCUSSION

In Pakistan, water and soil pollution have become a pressing environmental concern. The widespread occurrence of arsenic in groundwater poses significant health risks, particularly when it is used for drinking, irrigation, or aquaculture (fisheries). Similarly, soil contamination with heavy metals, especially arsenic, disrupts cellular functions and damages organs, leading to various health issues such as skin disorders (keratosis and melanosis), reproductive toxicity, cardiovascular diseases, cancers, and neurological complications²⁴. Extra Virgin olive oil, commonly referred to as “liquid gold,” is a highly valued natural product with numerous health-promoting properties. Its anti-cancer, anti-angiogenic, and anti-inflammatory effects contribute to lowering the risk of cardiovascular disease²⁵.

In the present study, olive oil was evaluated as an antioxidant for its ability to mitigate arsenic-induced cardiomyopathy. A characteristic feature of this condition is cardiac hypertrophy, which leads to an increase in heart weight and impaired cardiac function. This study demonstrated cardiac hypertrophy in the arsenic-exposed group (Group II), which is in agreement with earlier research reported by Raihan et al. in their study²⁶. Group III demonstrated improved outcomes due to the protective role of olive oil. Yaha et al. (2022) highlighted the beneficial effects of olive oil on heart function and overall human health²⁵. Likewise, Yan Lu reported that the oleic acid and polyphenols present in extra virgin olive oil exert cardioprotective effects by suppressing inflammatory responses and reducing oxidative stress²⁷.

In this study, marked congestion was observed in the arsenic-exposed group (Group II) compared with the control group (Group I), which may be attributed to the inflammatory response and subsequent vascular damage induced by arsenic exposure. This finding is in line with the observations

of Dipanwita (2024), who demonstrated that arsenic-induced cardiotoxicity arises from enhanced free radical generation coupled with a decline in the antioxidant defense capacity of cells¹⁷. Similarly, Osama et al. (2024) reported arsenic-induced hepatotoxicity in rats, which was effectively alleviated through the administration of ginger or Omega-3, further emphasizing the role of oxidative stress in arsenic toxicity²⁸. In the present study, extra virgin olive oil supplementation attenuated congestion in Group III, supporting its protective role against arsenic-induced cardiac injury. Comparable outcomes have been reported by Fatma (2024), who highlighted the ameliorative potential of olive oil against cyclophosphamide-induced nephrotoxicity in Swiss albino rats²⁹. Furthermore, Qays et al. (2021) also demonstrated that olive oil exerts protective effects on sex hormones through the suppression of oxidative stress, underscoring its broad-spectrum antioxidant and cytoprotective properties³⁰.

In this research, Group II exhibited marked inflammatory infiltration, likely associated with the release of pro-inflammatory cytokines and reactive oxygen species (ROS), when compared with Group I. These findings are consistent with those of Zheyu Zhang (2022), who described arsenic-induced pro-inflammatory responses as a key contributor to various cardiovascular complications³¹. In contrast, Group III demonstrated reduced inflammatory infiltration, highlighting the cardioprotective effect of olive oil. Similar observations were made by Hira et al. (2021), who reported its protective role against arsenic-induced nephrotoxicity in albino rats¹⁹. In line with this, Ghadha (2021) demonstrated that curcumin mitigates doxorubicin-induced cardiotoxicity and hepatotoxicity by suppressing oxidative stress, further supporting the therapeutic potential of natural antioxidants in combating chemically induced organ toxicity³².

Under oxidative stress, free radicals preferentially attack polyunsaturated fatty acids in cellular membranes, initiating lipid peroxidation. This process compromises membrane integrity and alters permeability, ultimately leading to vacuole formation and the development of edema³³. In this study, such disruption was evident in Group II following arsenic exposure compared with the control group (Group I). Conversely, Group III exhibited reduced edema, indicating the protective effects of extra-virgin olive oil. These findings are in agreement with Gayatri (2023), who reported that hesperidin mitigates arsenic trioxide-induced cardiac toxicity in rats³⁴. Likewise, Luma (2023) documented edema in imatinib-induced cardiotoxicity³⁵, while Azza (2023) demonstrated the protective role of vitamin E against cyclophosphamide-induced cardiotoxicity in male rats³⁶.

In this study, Group II demonstrated an increased diameter of cardiac myocytes, indicating the detrimental effects of arsenic exposure and its role in the development of cardiomyopathy. Similar findings were reported by Buyan (2023), who observed myocyte enlargement associated with cardiac toxicity³⁷. In contrast, Group III, treated with extra virgin olive oil, showed a reduced myocyte diameter compared to Group II. This observation aligns with the results of Siamak et al. (2024), who demonstrated that olive oil protects against cardiac hypertrophy in D-galactose-induced aging rats³⁸. Likewise, Yingciu (2021) highlighted the cardioprotective effects of melatonin against myocardial infarction injury in rats, mediated through its antioxidant pathway³⁹.

This study demonstrates the cardioprotective effects of extra virgin olive oil against arsenic exposure, as evidenced by reductions in cardiac hypertrophy, inflammatory infiltration, edema, and congestion. Although alterations at the ultrastructural level, molecular pathways, and gene expression dynamics were not explored due to resource constraints, the findings underscore the therapeutic potential of olive oil, draw attention to the health risks associated with arsenic exposure, and emphasize the role of dietary interventions in promoting public health education.

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