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AMELIORATIVE STUDIES OF *Cucumis melo* (MELON SEEDS) OIL IN TETRACYCLINE-INDUCED HEPATIC TOXICITY IN ANIMAL MODELS

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Abstract

This study evaluated the hepatoprotective effect of ***Cucumis melo*** (melon) seed oil against tetracycline-induced liver toxicity in mice. Thirty adult male mice (20–38 kg) were divided into four groups: control, tetracycline-only, tetracycline plus low-dose melon seed oil (0.3 mL/kg), and tetracycline plus high-dose melon seed oil (0.5 mL/kg). Hepatic toxicity was induced by oral tetracycline (0.5 mg/kg) for 48 days, with treatment groups receiving melon seed oil concurrently. Following treatment, body weights were recorded, liver function markers (ALT, AST, ALP) were measured, and liver tissues examined histologically. Tetracycline-only mice showed significant elevations in ALT, AST, and ALP, along with hepatocyte degeneration and necrosis. In contrast, mice receiving melon seed oil demonstrated reduced enzyme levels and preserved liver architecture. These results indicate that melon seed oil mitigates tetracycline-induced hepatic damage, suggesting its potential as a natural hepatoprotective agent.

Keywords: Melon seeds oil, Tetracycline, Hepatotoxicity, Antioxidants, Liver function, Oxidative stress, Hepatoprotection

1.0 Introduction

Drug-induced liver injury has become the most common cause of acute liver injury nowadays and also accounts for around one in ten cases of adverse drug reactions (Garcia-Cortes *et al*., 2020, Kullak-Ublick *et al*., 2017). The incidence of Drug-induced liver injury has been reported to be between 14 and 20 per 100 000 patients (Shen *et al.,* 2019, Spangenberg, 2016). Serious liver injury may lead to liver failure

which is life threatening (Squires *et al.,*2018). The hepatotoxicity by drug-induced liver injury is a pathophysiological process (Sarges *et al.*, 2016). The major cellular changes involve hepatocytes apoptosis, as well as death of cholangiocytes and endothelial cells and most of the drugs leading to this toxicity are antibiotics such as tetracycline (Guicciardi *et al*., 2023).

Tetracycline is a broad-spectrum antibiotic medication used in the treatment of variety of bacterial infections (Sheykhsaran *et al*., 2019). It belongs to the tetracycline class of antibiotics, which work by preventing bacteria from producing the proteins they need to survive (Peyriere *et al*., 2018). High doses of tetracycline can induce fatty liver disease and may result in severe hepatic dysfunction, acute liver failure and death (Massart *et al*., 2017). The instances of acute fatty liver attributed to tetracycline have been reported in nonpregnant women and in men and even in children (Okagbue *et al.*, 2019). The injury is characterized by minimal-to-moderate elevations in serum aminotransferase and alkaline phosphatase levels with mild jaundice, with presence of hyperammonemia and coagulopathy (Naqvi *et al*., 2021). Therefore, in other to mitigate this toxicity substance with antioxidants and anti-inflammatory properties such as melon seed oil are considered.

Melon seed oil is a vegetable oil extracted from the seeds of various species of melons, including cantaloupe (*Cucumis melo*) (Rabadán *et al.,* 2020). It is rich in essential fatty acids, vitamins, minerals, and bioactive compounds, making it a valuable ingredient in both culinary and cosmetic applications (Mondal *et al.*, 2021). Melon seed oil is a good source of essential fatty acids, including linoleic acid (omega-6) and oleic acid (omega-9), which are important for maintaining healthy liver, skin, heart, and overall well-being. It also contains vitamins such as vitamin E, which acts as an antioxidant, protecting cells from damage caused by free radicals (Mondal *et al.*, 2021). Due to its nutrient content, melon seed oil is believed to offer various health benefits. Traditional medicine systems in various cultures have used melon seed oil for its potential medicinal properties. It has been suggested to have anti-inflammatory, antioxidant, antimicrobial, and hepatoprotective effects (Rabadán *et al.,* 2020), although more research is needed to fully understand its therapeutic potential. Therefore, this research was aimed at evaluating the effect of melon seed oil on tetracycline-induced hepatic dysfunction in male mice.

2.0 Material and methods

2.1 Ethical approval

Ethical approval for the experiment was obtained from the Faculty of Basic Medical Ethical Committee for the use of experimental animals, with an ethical certificate No. FBMS/2023/05/1024 issued. The guidelines for using animals in research were duly followed.

2.2 Plant Materials

One paint rubber of melon seeds (*cucurmis melo*) weighing 3kg was procured from the neighborhood agro

market. The melon seed were properly washed, dried in an air-dried room temperature of approximately 27^0 C for three weeks, and blended powder.

2.3 Extract Preparation

The extract preparation was in accordance with (Ingle *et al*, 2017; Abdullahi & Haque, 2020) where the powdered residue extract was moistened with dilute ammonia solution and then packed loosely in the thimble of the soxhlet apparatus and the solvent, n-hexane (98-99%) was placed in the round bottom flask. 1000g of pulverized melon seed was poured into a thimble and the thimble was plugged with cotton wool. The thimble with content was placed into the extractor chamber; the n-hexane in the flasks was then heated from the bottom flask. N-hexane passes through the condenser where it condenses and flow down to the extractor chamber where it extracts the oil by coming in contact. As the level of solvent in the extraction chamber reaches the top of the siphon, n-hexane and seed oil entered back to the round bottom flask. The process was repeated for days until the seed oil was completely extracted without any residue left behind. The thimble was removed and n-hexane distilled from the flask into the extractor. The flask was then disconnected and seed oil placed in a water bath and evaporated at 40 ^{0}C for 4 hours, cooled in a desiccator.

2.4 **Experimental Animals**

Thirty (30) adult male mice weighing between 20-38kg were purchased from the animal house of the Department of Human Anatomy and Forensic Anthropology, University of Cross River State (UNICROSS), Okuku Campus and were used for this study. Four groups of animals were formed at random from the animals: Eight (8) control mice, seven (7) tetracycline only, (7) Tetracycline + Melon Seed oil low dose, and eight (8) Tetracycline + oil high dose mice, respectively. The animals were kept for seven days acclimatization. They were kept in plastic cages covered with wire merge under regulated lighting (12 hours of daylight and 12 hours of darkness), and before the administration began, they were fed with regular growers' vita feed and given water.

2.5 **Experimental Design**

The thirty (30) male Wistar mice were divided into four (4) groups; control, TC only, TC+oil low dosage, and TC + oil high dose respectively. Group A (the control) only received meals and water only. Group B (TC only) were given food, water, and 0.5mil of tetracycline capsule orally using a 5-mil syringe. Group C (TC+oil low dose) were given food, water, and a combine therapy of tetracycline 0.5mil/kgBw+0.3mil/kgBw of soxhlet fractionate of melon seed oil using a 5-mil syringe. Group D (TC+oil high dose) received food, water, and 0.5mil/kg body weight of tetracycline + 0.5mil/kgBw of soxhlet fractionate of melon seed oil administered orally by cannula once daily for 48 days.

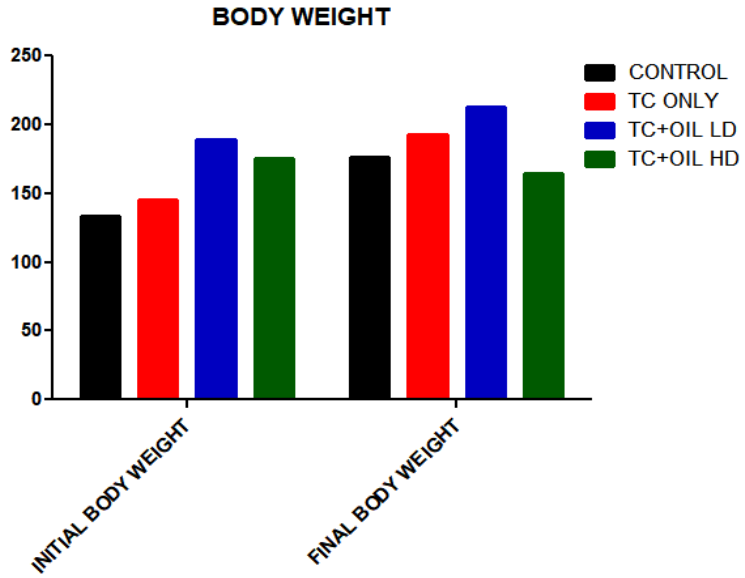
2.6 Termination of Experiment

Three mice from each group were randomly chosen at the end of the forty-eight (48) days dosing period, and they were sacrificed by cervical dislocation one day later. In order to determine the impact of the extract given to each of the study groups, the liver from each animal in each group were collected, stored in 10% formalin, and then assessed.

3.0 Results and analysis

3.1 Effect of Tetracycline (TC) and Melon seeds oil on the body weight

Morphological observation from the study as display below shows an observable significant ($P<0.05$) increase in the final mean body weight when compared with the initial body weight observable in control, TC only and TC + oil low dose with a significant ($P<0.05$) decrease in the final body weight of TC + Oil high dose when compared to it initial weight. The final body weight of the control animals (27.00 ± 4.47) was significantly ($P<0.05$) higher than its initial body weight (22.17 ± 2.78). However, the mean final body weight of TC only group (32.17 ± 4.31) and TC + Oil low dose (36.33 ± 3.14) was significantly ($P<0.05$) higher than their initial body weights (24.17 ± 2.71) and (31.50 ± 3.14) respectively, but TC + Oil high dose group showed a significant weight reduction in the final body weight (27.83 ± 1.94) compared to the initial body weight (29.17 ± 3.13). However, when comparing the mean differences among the groups, they was significant ($P<0.05$) differences groups.

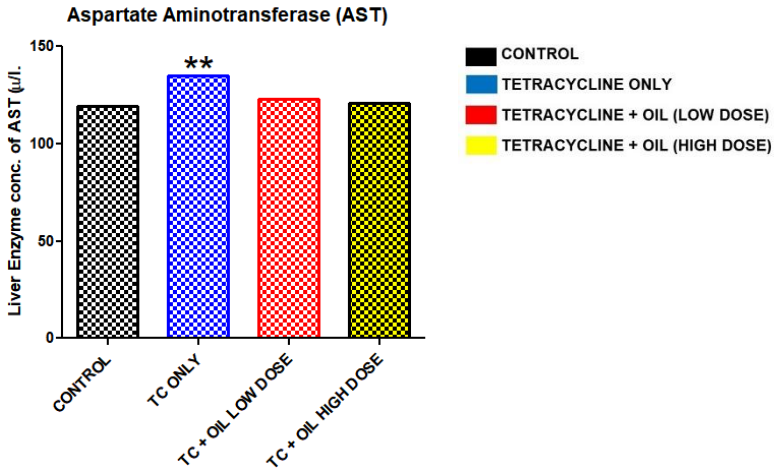


Graph 1: A graph showing the significant ($p<0.05$) difference between the initial and final body weights among the test groups.

3.2 Aspartate Aminotransferase (AST)

Animals in control group showed a normal level of Aspartate

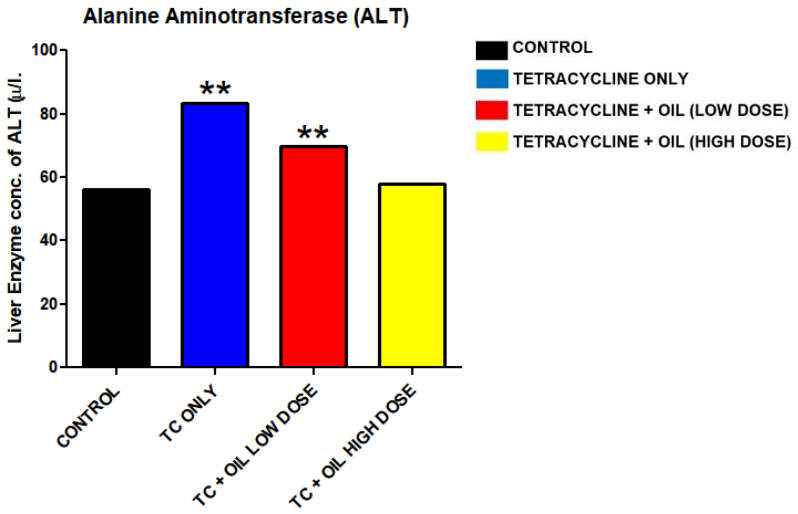
Aminotransferase (AST) (119.24 mmol/L), test groups (tetracycline only) show a significant (P< 0.05) increase in the AST level (134.76 mmol/L) when compared to the control group. Whereas they were a significant (P<0.05) decrease in the level of AST following the treatment with melon seeds oil (low & high dose) (122.86 mmol/L) and (120.84 mmol/L) respectively when compared to Tetracycline only but not significant when compared to the control group.



Graph 2: Chart showing the effect of Tetracycline and of melon seeds oil on the liver enzyme AST concentration in male mice.
Values are expressed in mean ± SEM, n=5, **=P<0.05 vs Control.

3.3 Alanine Aminotransferase (ALT)

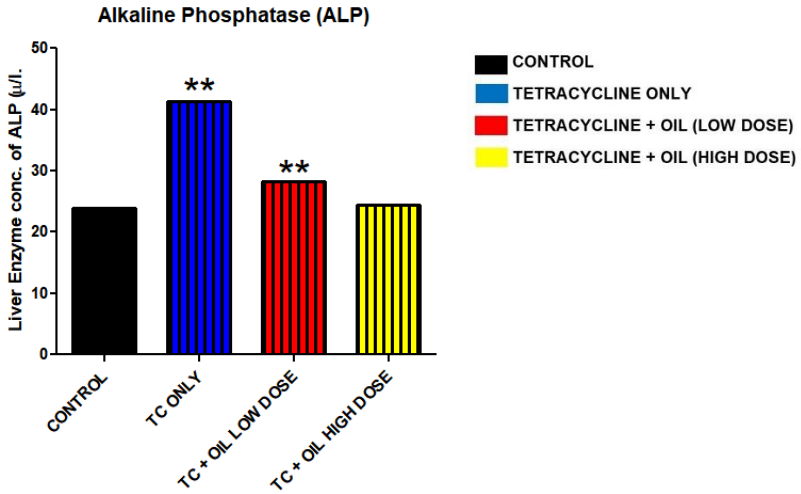
Animals in control group showed a normal level of Alanine Aminotransferase (ALT) (56.30mmol/L), tetracycline only group showed significant (P<0.05) increase (83.41 mmol/L) in the level of ALT when compare to other groups with a gradual reduction following melon seeds oil treatment, they was no significant (P<0.05) differences observed between the TC + oil high dose when compared to the control group.



Graph 3: Chart showing the effect of Tetracycline and of melon seeds oil on the liver enzyme ALT concentration in male mice.
Values are expressed in mean ± SEM, n=5, **=P<0.05 vs Control.

3.4 Alkaline Phosphatase (ALP)

Animals in control group showed a normal level of Alkaline Phosphatase (ALP) (23.82µ/l), tetracycline only and TC + low dose oil group showed significant (p>0.05) increase in ALP respectively when compared to the control group (41.34µ/l) and (28.26µ/l). However, there was no significant (P<0.05) differences between the control group and the High dose melon seeds oil treatment as shown in the graph below.



Graph 4: Chart showing the effect of tetracycline and of melon seeds oil on the liver enzyme ALP concentration in male mice.
Values are expressed in mean ± SEM, n=5, **=P<0.05 vs Control.

3.5 Histological Result

From the micrographs display below, Plate 1 shows the Photomicrograph of the liver in the control group with the tissues appearing normal with a central vein (V) surrounded by several hepatocytes. Plate 2 displays a Photomicrograph of the liver administered with 0.5mil of tetracycline capsule only with tissues showing general ballooning, hepatic degeneration and pyknosis. Plate 3 is a Photomicrograph of the liver administered with Tetracycline 0.5mil+0.3mil of soxhlet fractionate of melon seed oil showing a central vein (V) with several hepatocytes being regenerated (dark dotted cells). Plate 4 shows the Photomicrograph of a liver microstructure administered with tetracycline + high dose melon seeds oil showing a central vein (V) with several hepatocytes (dark dotted cells). Tissue shows focal pyknosis (arrow).

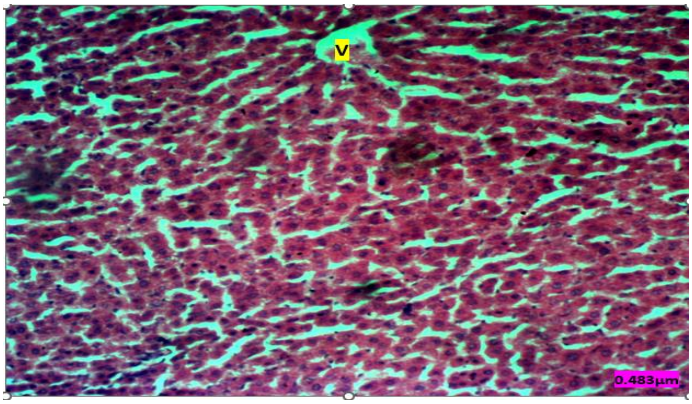


Plate 1: Photomicrograph of the liver microstructure in the control group with the tissues appearing normal showing a central vein (V) surrounded by several hepatocytes. (H & E, X300).

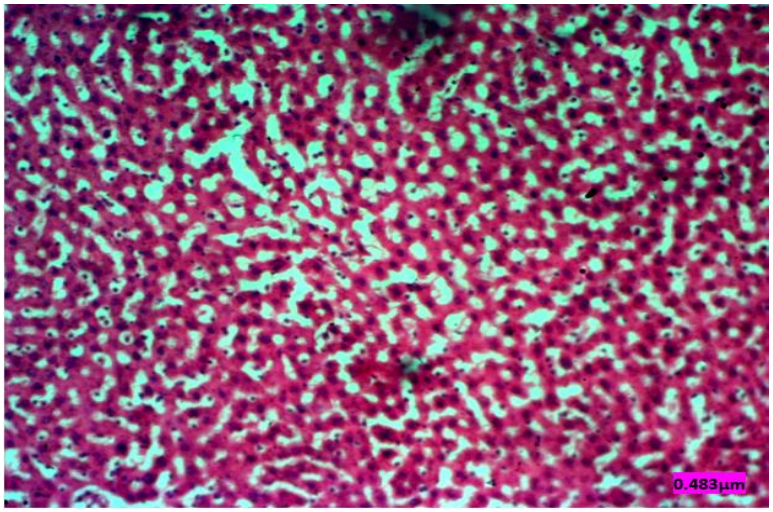


Plate 2: Photomicrograph of the liver administered with 0.5mil of tetracycline capsule showing general ballooning hepatic degeneration and pyknosis. (H & E. X300)

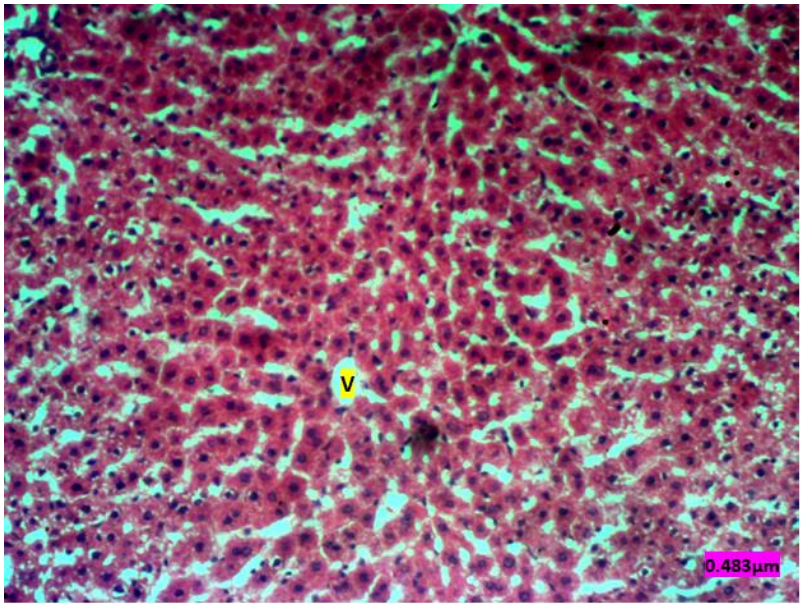


Plate 3: Photomicrograph of the liver microstructure administered with Tetracycline 0.5mil+0.3ml of soxhlet fractionate of melon seed oil showing a central vein (V) with several hepatocytes being regenerated (dark dotted cells). (H & E. X300)

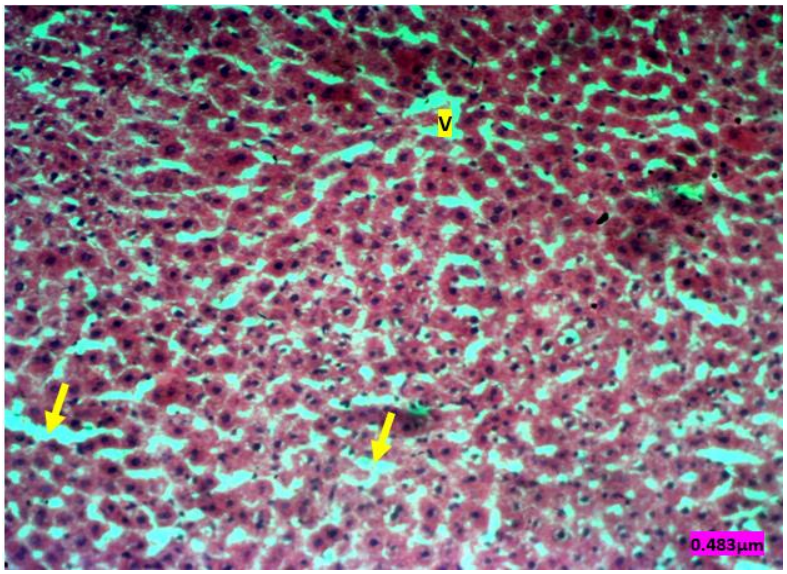


Plate 4: Photomicrograph of the liver microstructure of tetracycline + high dose melon seeds oil showing a central vein (V) with several hepatocytes (dark dotted cells). Tissue shows focal pyknosis (arrow). (H & E. X300)

4.0 Discussion

4.1 **Body Weight**

The body weight observations from this study shows an observable significant ($P<0.05$) increase in the final mean body weight when compared with the initial body weight observable in control, TC only and TC + oil low dose with a significant ($P<0.05$) decrease in the final body weight of TC + Oil high dose when compared to it initial weight. This study is evidence that tetracycline can significantly be beneficial in body weight gain which is in total agreement with the study of Keerthisinghe *et al.*, (2021) reporting that tetracycline and other antibiotics impact gut microbiota, which can indirectly affect metabolism and weight. In veterinary medicine as reported in the recent study of Redwan Haque *et al.*, (2023), tetracycline was used as a growth promoter in livestock, which suggests a potential for weight gain in animals. This effect is likely due to changes in gut bacteria following tetracycline intake that improve nutrient absorption and metabolism.

Also noticeable in this study was the administration of high dose melon seeds oil following tetracycline which causes a significant ($P<0.05$) decrease in the body weight of the animals with the final body weight of (27.83 ± 1.94) compared to the initial body weight (29.17 ± 3.13). These findings contradict with a lot of findings from previous studies Adebayo-Gege *et al.*,

(2022) stating that the consumption of any oil, including melon seed oil, in excessive amounts can lead to an increase in caloric intake, which may contribute to weight gain if not balanced with physical activity and overall caloric expenditure, also supported by the study of Oyebanji *et al.*, (2020) also reporting a significant ($P<0.05$) increase in the body weight of the animals following melon seeds oil consumption, as shown in graph 1.

4.2 Biochemical Parameters

In this study, our results showed an increase in the liver enzymes such as aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) enzyme activity in tetracycline intake. Under pathological conditions caused by toxins, AST, ALP and ALT activity is increased and this serves as a clear marker for liver damage, diseases or degeneration (Pingili *et al.*, 2020). Results obtained in this study clearly showed such increases and therefore agrees with the previous reports by Al-Baqami *et al.*, 2021; Prasanna *et al.*, (2020).

One mechanism by which Tetracycline (TC) induces liver damage is by impairing mitochondrial function, leading to a decrease in ATP production and an increase in the generation of reactive oxygen species (ROS). All of these cause changes in hepatocellular morphology resulting in protein unfolding and cell arrest (Xu *et al.*, 2022; Fromenty, 2020). Mitochondria are critical for energy production in liver cells, and their dysfunction can result in hepatocyte damage and cell death as reportted by Xu *et al.*, (2022).

The co-administration of tetracycline and melon seeds oil caused a significant ($P<0.05$) reduction in liver enzyme activity when compared to the tetracycline only induce group thus demonstrating an ameliorative function. Melon seeds oil has been reported to function via activation of the nitric oxide pathway and by scavenging reactive oxygen species in the body (Tan *et al.*, 2022, Salehi *et al.*, 2021) thus demonstrating it anti-inflammatory and antioxidant properties, as shown in graph 2 to 4.

4.3 Histological Results

The histological results from our study as display above all stain with hematoxylin and eosin (H&E), the control group shows normal tissues with a central vein (V) surrounded by several hepatocytes which is in agreement with the study of Mak & Png, (2020) reporting similar structures in a normal liver cell. The cytoarchitecture of the liver administered with 0.5mil of tetracycline capsule only showed general ballooning, hepatic degeneration and pyknosis. Our result indicated that tetracycline induced hepatic toxicity as previously reported by Wei *et al.*, (2022). Also supporting our results, is the findings of Emmanuel *et al.*, (2020) which observed accumulation of small fat droplets within hepatocytes, giving a foamy appearance to the cytoplasm.

Infiltration of inflammatory cells, primarily lymphocytes and macrophages, into the liver parenchyma following tetracycline exposure. Recently, Duan *et al.*, (2024) reported enlargement and increased activity of Kupffer cells (liver macrophages) due to increased phagocytic activity and inflammatory response following long term exposure to tetracycline treatment (Duan *et al*., 2024).

The microarchitecture of a liver treated with melon seeds oil at low dose of 0.3mil following tetracycline-induced toxicity shows several
hepatocytes regeneration (dark dotted cells) which is an indication that melon seeds oil possesses anti-inflammatory properties that helps in liver cells repair. The findings from this present result, is n consonance with the results of Li *et al*., (2020) stating melon seed oil possesses anti-inflammatory properties that is essntial in the repair and protection of liver cells. The oil is rich in bioactive compounds, including essential fatty acids, antioxidants, and vitamins, which contribute to its anti-inflammatory and hepatoprotective effects (Lepionka *et al.*, 2021). At high dose administration 0.5mil of melon seeds oil, the liver microstructure shows focal pyknosis as indicated with yellow arrows in plate 4.4 above which is in agreement with the result of Stawarska *et al.*, (2020) which state that excessive consumption of healthy oils like melon seed oil, can interfere with liver cell structure and function. And was later supported by study of Eke *et al.*, (2021) saying while oils contain essential fatty acids and other beneficial nutrients, their overconsumption can lead to several adverse effects on the liver (Eke *et al.*, 2021). These activities can suggest the hepatoprotective potential of melon seeds oil at a minimum consumption with a deteriorative effect following excess consumption, as shown in plate 4.

5.0 Conclusion

Tetracycline is an antibiotic that, at high doses or prolonged use, proved to induce hepatic toxicity. This toxicity is often characterized by elevated liver enzymes (e.g., ALT, AST), oxidative stress, inflammation, and liver tissue damage. It was also observable in this study that tetracycline causes significant weight again when compared to other experimental groups. Melon seed oil has the potential to mitigate tetracycline-induced hepatic toxicity through its antioxidant and anti-inflammatory properties. Further research, is needed to confirm its efficacy and safety on other organs of the body.

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APPENDICES

Table 1: Morphological observation of body weight

BODY WEIGHTS		
GROUPS	**INITIAL**	**FINAL**
Control	22.17 ± 2.78	27.00 ± 4.47
TC Only	24.17 ± 2.71	32.17 ± 4.31
TC+ Oil Low Dose	31.50 ± 3.14	36.33 ± 3.14
TC + Oil High Dose	29.17 ± 3.13	27.83 ± 1.94

Values are presented as Mean ± SEM

Table 2: Table showing the Biochemical parameters of the liver enzymes on the mitigatory role of melon seeds oil on tetracycline induced hepatotoxicity

Measured Parameters	**AST (U/L)**	**ALT (U/L)**	**ALP (U/L)**
Animals group			
Control	119.24	56.30	23.82
Tetracycline Only (TC)	134.76	83.41	41.34
Low dose	122.86	69.76	28.26
High dose	120.84	57.90	24.46