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ORIGINAL RESEARCH

Effects of *Catha edulis* Extract on Atorvastatin-Induced Myotoxicity in Rats: Biochemical and Histopathological Evidence

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Background: Rhabdomyolysis (RML) is a complex disorder caused by muscle cell injury and the subsequent release of intracellular components into circulation. Statins are widely used and generally well tolerated; however, some patients report muscle weakness, particularly in the lower extremities. The concomitant use of statins with other substances, including herbal products such as khat (*Catha edulis*), may increase the risk of adverse events. Khat chewing is known to cause multiple health problems and has been associated with musculoskeletal weakness.

Aim: This study aimed to evaluate the effects of khat extract on atorvastatin-induced rhabdomyolysis in rats.

Methods: Methanolic extraction of khat leaves was performed, and phytochemical analysis confirmed the presence of alkaloids, tannins, flavonoids, and other bioactive compounds. Twenty-four healthy rats were randomly divided into four groups: control, khat extract (500 mg/kg), atorvastatin (40 mg/kg), and khat extract plus atorvastatin. Treatments were administered orally for 28 days. On day 28, blood samples were collected for biochemical assays of myoglobin, creatine kinase (CK-MM), lactate dehydrogenase (LDH, LDH5), alkaline phosphatase (ALP), troponin fast skeletal (fsTnI), creatinine, albumin, and total protein. Histopathological analysis of skeletal muscle and kidney tissues was also conducted. Data were analyzed using the Kruskal–Wallis, expression by median(IQR), CI(95%) with significance set at $p < 0.05$.

Results: The khat–atorvastatin group showed significant weight reduction and marked increases in biochemical markers compared with controls. The khat-only and atorvastatin-only groups also demonstrated elevated biomarkers but at lower levels. Histopathology confirmed severe muscle necrosis and kidney tubular injury in the khat–atorvastatin group, while mild myopathy was evident in the khat-only and atorvastatin-only groups.

Conclusion: Khat extract contributes to biochemical and histopathological changes indicative of muscle injury. When combined with atorvastatin, these effects are exacerbated, leading to pronounced myopathy and kidney damage. These findings suggest that khat use may potentiate statin-induced rhabdomyolysis and increase the risk of musculoskeletal and renal complications.

Keywords: rhabdomyolysis, *Catha edulis*, atorvastatin, biochemical and histopathological analysis

Introduction

Rhabdomyolysis (RML) is a clinical syndrome characterized by skeletal muscle breakdown and necrosis, with the subsequent release of intracellular contents—such as myoglobin, creatine kinase (CK), lactate dehydrogenase (LDH), and other enzymes—into the circulation.[1] Primary muscle fiber necrosis may arise from genetic or structural abnormalities, whereas secondary necrosis more commonly results from trauma, medication side effects, toxins, or infections. Despite its clinical importance, the true prevalence of RML remains poorly defined.[2] Historical accounts suggest that the earliest description of RML can be traced back to the Old Testament.[3]

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Biochemically, serum creatine kinase CK—particularly the CK-MM isoform localized in skeletal muscle—is the most precise marker of muscle injury.[4] During early RML, increased myoglobin levels exceed plasma-binding capacity, filter through the glomeruli, and appear in urine. Thus, the detection of serum or urinary myoglobin within 24 hours is considered pathognomonic.[4] Additionally, elevated troponin levels have been reported in neuromuscular disorders, suggesting an extracardiac skeletal muscle source.[5] LDH, particularly the LDH-5 isoenzyme, is another important biomarker, reflecting skeletal muscle pathology and assisting in diagnosis, monitoring, and prognosis.[6–8] Acute kidney injury (AKI) represents the most severe complication of RML, substantially increasing morbidity and mortality.[9]

Among pharmacological causes, statins (HMG-CoA reductase inhibitors) represent the most widely recognized drug-induced trigger of rhabdomyolysis.[1] Statins are taken by nearly 200 million individuals globally for primary and secondary prevention of cardiovascular diseases, and their prescription rates increased more than threefold between 2000 and 2012.[10,11] While generally well tolerated, statin-associated muscle symptoms (SAMS) remain the most common adverse effect, ranging from myalgia to life-threatening RML.[12] Although the underlying mechanisms are not fully understood, proposed pathways include skeletal muscle necrosis through mitochondrial dysfunction and ubiquinone depletion, seen in Figure 1.[13]

The plant known as *Catha edulis* was discovered in Yemen in the eighteenth century by botanist Peter Forskal, who published the first scientific account on khat in the Western world and Yemen is home to the largest chewer population, since the plant serves as a social enhancer there. Studies indicate that 80–90% of adult males and 10–60% of adult females in East Africa regularly chew khat leaves.[14] Global migration and better transportation infrastructure have contributed to the development of this habit, and chewing khat is becoming more common in Europe.[15] Historical accounts state that the use of khat dates back to the 13th century in ancient Ethiopia (Abyssinia), and that in the first half of the 15th century, Khat leaves were brought to Yemen.[16] Around 400 million people in the Horn of Africa and the Arabian Peninsula are chewing Khat leaves and has been a social custom for centuries.[17] The use of Khat plant has expanded to other parts of the world, including Australia and the USA, The estimated number of global users is between 10 and 20 million.[18]

Catha edulis (khat) is a psychostimulant plant first documented in Yemen during the eighteenth century by botanist Peter Forskal, who provided the earliest Western scientific account. Yemen has the world's highest prevalence of khat chewing, where it plays a major sociocultural role. Epidemiological surveys report that 80–90% of adult men and 10–60% of adult women in East Africa chew khat regularly.[14] The practice, historically traced back to 13th-century

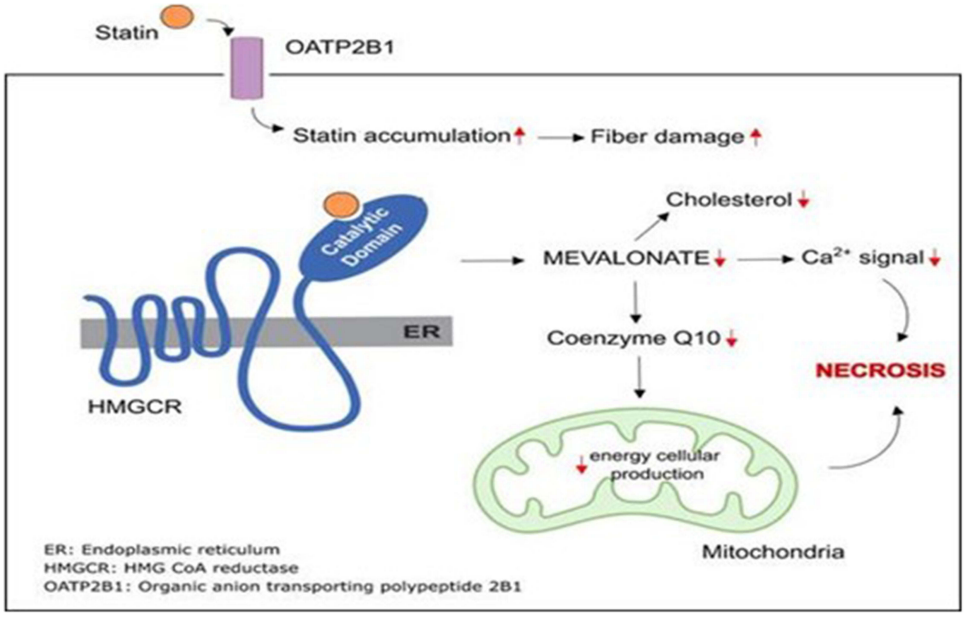

Figure 1 Potential mechanism underlying statin-induced Rhabdomyolsis.[13]

Ethiopia and introduced to Yemen in the 15th century,[16] has since expanded globally, facilitated by migration and improved transportation. Today, khat chewing is estimated to involve 10–20 million individuals worldwide, including populations in Europe, the USA, and Australia.[17,18]

Khat consumption produces both acute and chronic health effects. Acutely, it induces hyperthermia, tachycardia, tachypnea, heightened alertness, euphoria, increased energy, and appetite suppression. Chronically, khat chewing has been linked to depression, impotence, insomnia, anxiety, gastrointestinal problems, and oral.[19] Cardiovascular complications (including myocardial infarction, stroke, and reversible cerebral vasoconstriction) have also been associated with khat use (Pendl et al, 2021). Importantly, khat use raises the risk of concurrent drug exposure, increasing the likelihood of herb–drug interactions. Since khat contains single chemical entities that interact with drug-metabolizing enzymes, its potential for drug interactions may be even higher than that of conventional medications.[20]

Recent pharmacological studies demonstrated that khat extract significantly inhibits cytochrome P450 (CYP450) enzymes, including CYP2C9, CYP2D6, and CYP3A4, with inhibitory concentrations (IC50) of 42, 62, and 18 µg/mL, respectively, whereas cathinone, its major alkaloid, exerts only mild inhibition.[21] As atorvastatin and most statins are primarily metabolized by CYP3A4, concurrent CYP inhibition by khat could elevate statin plasma levels, thereby potentiating myotoxicity and increasing the risk of rhabdomyolysis.[22]

Despite these concerns, very few studies have investigated the pharmacological interactions between khat and therapeutic drugs, and the potential synergistic toxicity of *Catha edulis* with statins remains largely unexplored.

This study aims to evaluate whether co-administration of *Catha edulis* extract with atorvastatin exacerbates skeletal muscle toxicity leading to rhabdomyolysis, compared with atorvastatin treatment alone.

Methodology

Sample Collection and Extract Preparation

a. *Catha edulis* collection

Approximately 800 g of *Catha edulis* shoots, which are free of pesticides, were collected from the Wadi Aljanaat neighborhood in Ibb city, Yemen. Dr. Hassan M. Ibrahim, a taxonomist, was identified the plant materials and provided a voucher specimen (740), which was deposited in the Laboratory of Pharmacognosy at the Faculty of Pharmacy, Sana'a University, Yemen. Freshly grown leaves were washed with distilled water to remove dirt and debris. Freshly picked Khat leaves were separated from the stems in preparation for extraction.

a. Procedure for extraction of *Catha edulis*

The newly picked Khat leaves were removed from each branch. The new leaves were thoroughly washed in distilled water, dried gently, sliced on glass surfaces (using a mixer), and then crushed. This is the procedure for extracting methanol.[23] The crushed material was soaked in a sufficient amount of methanol in a conical flask and then placed on a rotary shaker for 20 hours.[24] The previous mixture was filtered in two steps: first, a mesh drum was used to remove larger particles, and then a second filtration with qualitative filter paper was performed.[24] The unfiltered plant material was also extracted with fresh methanol. The filtered liquid was mixed with the original filtered liquid. The filtrate obtained was collected and transferred into pre-weighed conical flasks. The methanol was completely removed at 65°C with the help of a rotary vacuum evaporator, resulting in a residue of semisolid material. Finally, the khat extract powder was mixed with distilled water, and a new khat extract mixture was immediately prepared and orally administered to the rats daily for 28 consecutive days during the study period.[24]

a. Phytochemical analysis of khat (*Catha edulis*)

The analysis of phytochemicals in *Catha edulis* was conducted to identify the active components responsible for their effects via previously described methods.[25]

1) Test of Alkaloids

Approximately 20 mg of the solution was dissolved in 2 mL of ethanol, and a small amount of 1% HCl was then added. The mixture was heated, exposed to steam, and cooled, and then one part was tested with Wagner's reagent and the other with Dragendroff's reagent.[23]

2) Test of Tannins

Braymer's test involved dissolving 20 mg of the extract in 1 mL of distilled water in a test tube and adding 1–3 drops of 1% $FeCl_3$. The other test was the gelatin test.[25]

3) Detection of Flavonoids

The initial test was performed with a ferric chloride solution combined with a small amount of 10% ferric chloride solution. The other test was the Conc. H_2SO_4 test.[25]

4) Detection of phenolic compounds

Aqueous solution + a few drops of 5% ferric chloride solution were extracted.

5) Test of Terpenoids (Salkowski's test)

Twenty milligrams of the extract was dissolved in 1 mL of chloroform, and 1 mL of concentrated H_2SO_4 was added.[25]

6) Test of Glycosides

The alcoholic extract was dissolved in 1 mL of water, and then a few drops of aqueous NaOH solution were added.[25]

Atorvastatin

It was acquired from the global pharmaceutical industry in Sana'a, Yemen.

Study Design

All the animals were chosen randomly and separated into four groups. All the substances were dissolved in 1 mL of distilled water and given orally via a metal gavage needle every day for 28 days. On the 28th day, all the animals were anesthetized with chloroform[26] and 5 mL of blood was drawn to analyze the levels of different enzymes.[27]

Serum biomarkers were measured using commercial ELISA kits: myoglobin (KLR0308, Krishgen Bio Systems, Mumbai, India), CK-MM (E1930Ra, BT -Laboratory, Jiaxing, China), LDH (OSR6128, beckman coulter, Ireland), LDH-5 (E3433Ra, BT -Laboratory, Jiaxing, China), alkaline phosphatase (ALP) (03333701190, Roche, Germany),troponine (fsTnI) (E0055Rb, BT-Laboratory, Jiaxing, China), kidney function tests (serum creatinine (11502, Biosystems, Barcelona, Spain), albumin (994120, QCA, Tarragona, Spain), total protein (Mo-165097 Monlab Test, Barcelona, Spain). According to the manufacturer's datasheets, the detection range, sensitivity, and intra-/inter-assay coefficients of variation (CV%) were <10%. All assays were validated prior to use, and quality controls were performed in duplicate. Skeletal muscles (quartriceps) and kidney tissue were collected for histopathologic evaluation. The tissue was fixed in 10% neutral buffered formalin and processed for routine hematoxylin and eosin staining (H&E). The muscle fibers were broken, rounded, and showed localized regions of inflammatory cell infiltration when stained with hematoxylin and eosin. All groups exhibited sarcoplasmic fragmentation and densely positioned central nuclei.[28] The tissue was evaluated without knowledge of the treatment group by the histopathologist.

Animal Housing

A total of twenty-four healthy, 4-week-old male albino rats with a weight of (145–170g). Animals were housed in the building and allowed to acclimatize for 14 days prior to the study under the following conditions (20 ± 4) °C, humidity (30 to 70) % and light/dark (12/12) hours. The animals were provided with unlimited access to a standard rodent diet and tap water ad libitum. The experiment with the rats was carried out according to the principles of laboratory animal care (GUIDELINES FOR PROPER CONDUCT OF ANIMAL EXPERIMENTS).[29]

Animals Grouping

The animals were randomly assigned to four groups, with 6 rats in each group,[30] as follows:

Group I (N= 6) = the normal control group, which received 1 mL of distilled water orally from the first day until the 28th day.

Group 2 (N= 6) = Atorvastatin – Treated Group

They received 40 mg/kg body weight atorvastatin[31,32] dissolved in 1 mL distilled water once daily orally starting from the first day until the 28th day.

Group 3 (N= 6) = Khat – Treated Group

They were given a single oral (500 mg/kg/day)[24,33] of khat extract dissolved in 1 mL of distal water from the first day until the end of the 28th day.

Group 4 (N= 6) = Khat–Atorvastatin Treated Group

They were given a mixture of khat (500 mg/kg) from the extract.[34] dissolved in 1 mL distilled water orally once/day with atorvastatin (40 mg/kg),[31] once from the first day until the 28th day.[34]

Blood Collection

Before blood samples were collected, the rats were anesthetized with chloroform.[26] Every blood sample was put into a gel tube with no anticoagulant and then left at room temperature for 20 minutes before being spun in a centrifuge at 6000 rpm for 5 minutes to collect the serum.[32]

Statistical Analysis

The results were expressed as median with interquartile range (IQR). Statistical analyses were performed using GraphPad Prism version 8. Nonparametric tests, including the Kruskal–Wallis test, were applied to evaluate differences among groups. Data were presented using box-and-whisker plots, with 95% confidence limits (CL). Post hoc pairwise comparisons were conducted with adjusted P values. A value of $P < 0.05$ was considered statistically significant.

Ethical Consideration

All animal experiments were carried out in accordance with the protocols established by the University Research Ethics Committee Department (URECD) and the World Health Organization. The Research Ethics Committee of the University of Science and Technology (UST) convened at the Faculty of Medicine. Every effort was made to minimize animal suffering, and all experiments received approval from the Ethical Committee at the University of Science and Technology (approval number ID: 1445/003/UREC/UST) on April 2, 2024.

Results

1. Phytochemical screening results

The different constituents of the *Catha edulis* plant are shown in Table 1.

2. Effects of khat extract and atorvastatin on the serum creatine kinase (Ckmm), myoglobin, troponin (fsTnl), lactate dehydrogenase (LDH) lactate dehydrogenase (LDH-5) and alkaline phosphatase (ALP) levels.

Creatine kinase-MM (CKmm, µU/L):No significant changes were observed in the khat-treated or atorvastatin groups compared with the control. However, the khat + atorvastatin group showed a significant elevation ($p \leq 0.003$), as shown in Figure 2.

Table 1 Results of Phytochemical Tests for Catha Edulis

Types	Results	*Catha edulis*
Alkaloids	Wagner's test -A brown/reddish precipitate	+
	Dragendorff's reagents- Reddish brown precipitate	
Tannins	Braymer's test- Blue–green color	+
	Gelatin test -White precipitate	
Flavonoid	Ferric chloride test -A green precipitate	+
	Conc. H_2SO_4 test- An orange color	
Terpenoids	Reddish brown color at upper layer indicates presence of steroids and golden yellow layer (at the bottom) shows the presence of terpenoid	+
Phenolic compounds	Dark green/bluish black color	+
Glycosides	Yellow color	+

In Figure 3, Myoglobin levels were elevated in all treated groups compared with the control. A statistically significant increase was detected only in the khat + atorvastatin group ($p \leq 0.003$) with control group.

A gradual rise in troponin was observed across the treated groups. Although the changes did not reach significance in the khat or atorvastatin groups, the khat + atorvastatin group exhibited a higher value approaching significance, as seen in Figure 4.

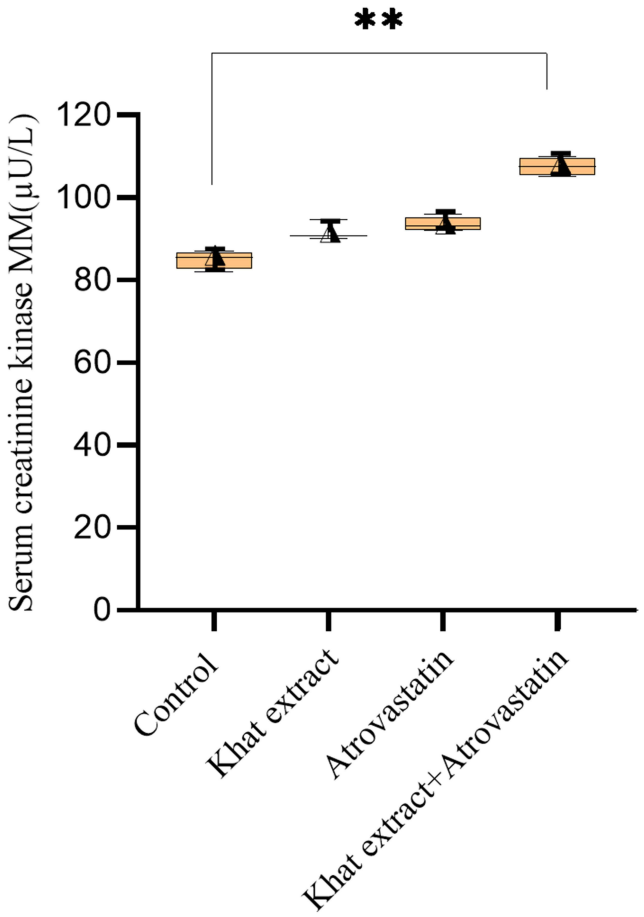

Figure 2 Serum Creatine kinase-MM (CKmm, µU/L) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). **p ≤ 0.003.

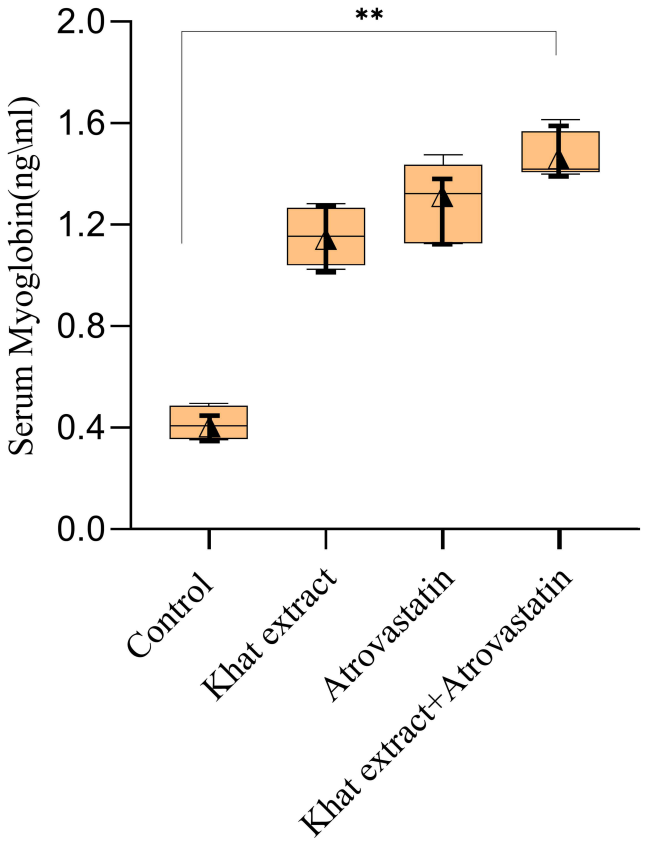

Figure 3 Serum Myoglobin (ng/mL) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). **p ≤ 0.002.

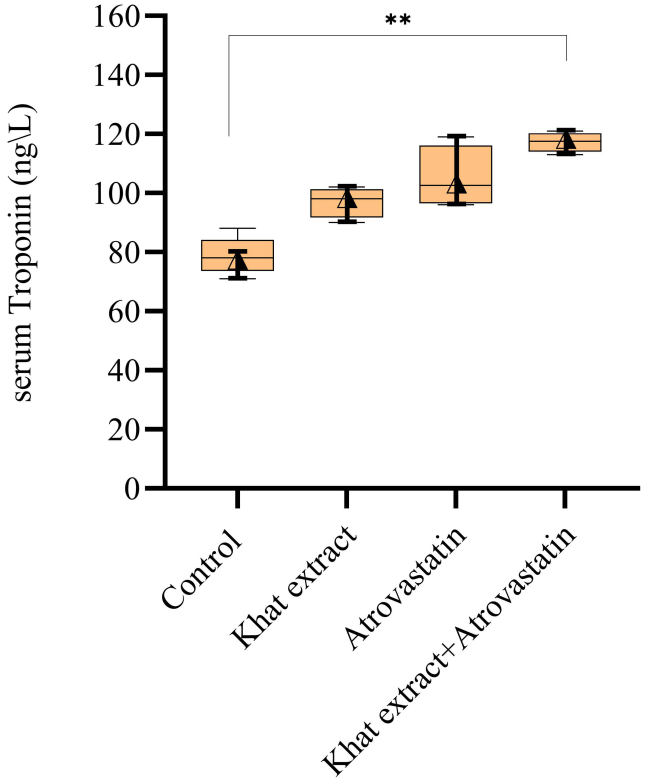

Figure 4 Serum Troponin (ng/L) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). **p ≤ 0.003.

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Figure 5 showed LDH activity was markedly elevated in the atorvastatin group compared with control ($p \leq 0.004$). Khat alone produced a moderate but nonsignificant rise. Importantly, the khat + atorvastatin group showed a dramatic and highly significant increase rather than control and Khat groups.

In LDH 5 measurements, both khat and atorvastatin groups induced slight increases compared with control group. The combined treatment group displayed a statistically significant elevation, shown in Figure 6.

ALP activity was elevated in all treated groups compared with control. The increase was significant in the atorvastatin group ($p \leq 0.035$) and more pronounced in the khat + atorvastatin group ($p \leq 0.0003$), shown in Figure 7.

3. Effects of Khat Extract and Atorvastatin on Kidney Function Tests (Renal Function Markers)

A significant elevation in serum creatinine was observed in the khat extract group compared with the control ($p \leq 0.006$). This effect was further pronounced in the khat+atorvastatin group when compared with control ($p \leq 0.001$). Additionally, serum creatinine levels in the khat extract group were significantly higher than those in the atorvastatin group ($p \leq 0.025$). Notably, the khat+atorvastatin group showed a further increase compared with atorvastatin alone ($p \leq 0.005$) shown in Figure 8.

Serum albumin levels were significantly reduced in the atorvastatin group compared with the control ($p \leq 0.005$). The khat + atorvastatin group showed the most pronounced reduction, with levels significantly lower than both the control ($p \leq 0.005$) and khat-treated ($p \leq 0.005$) groups. In addition, khat extract exhibited higher albumin levels compared with atorvastatin ($p \leq 0.006$) shown in Figure 9.

Serum total protein levels showed no significant change in the khat-treated group compared with the control. In contrast, atorvastatin administration produced a significant reduction compared with the control ($p \leq 0.015$). Moreover, khat extract treatment resulted in significantly higher protein levels compared with atorvastatin ($p \leq 0.0002$) shown in Figure 10.

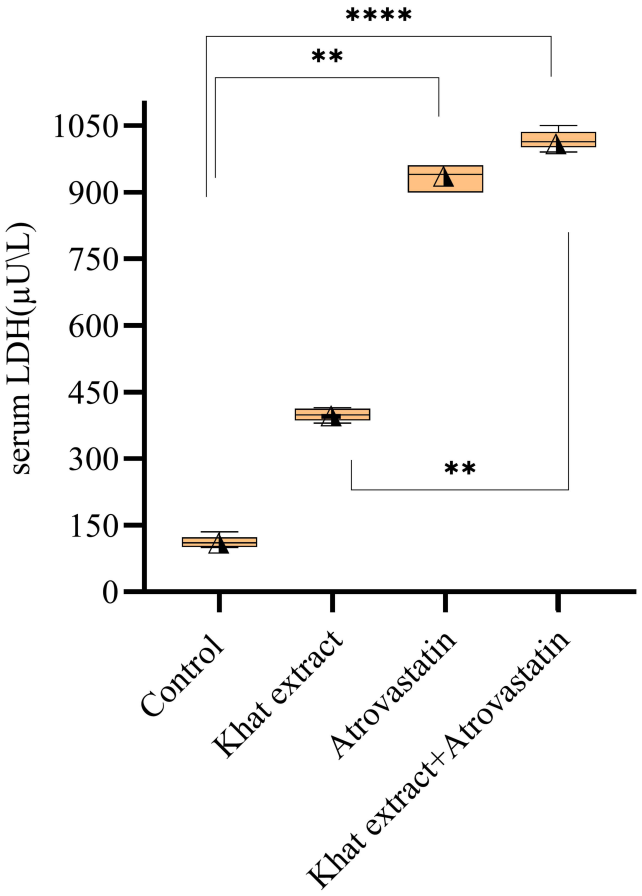

Figure 5 Serum Lactate dehydrogenase (LDH, µU/L) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). *p ≤ 0.037, **p ≤ 0.004, ****p ≤ 0.00001.

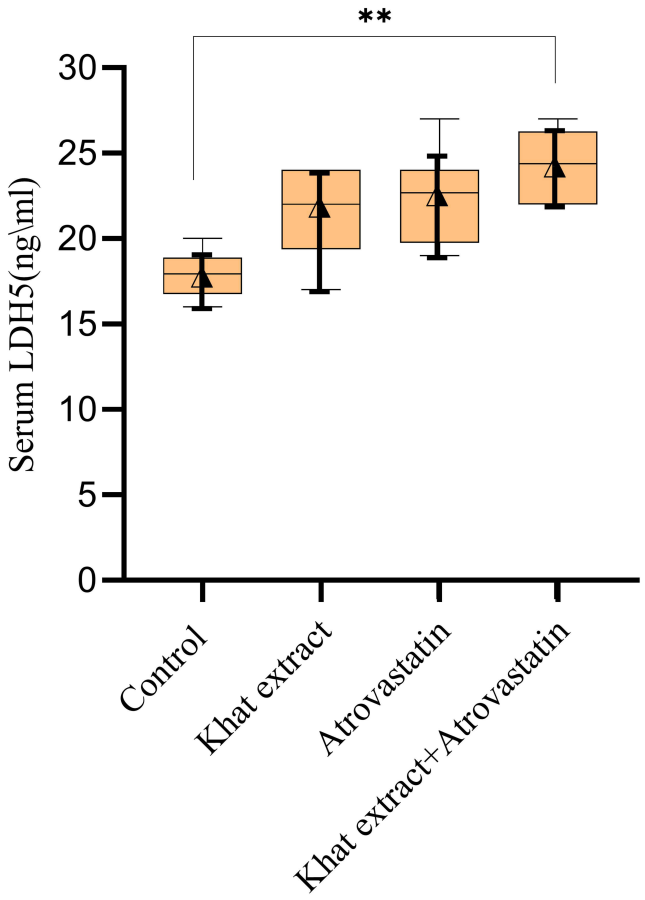

Figure 6 Serum Lactate dehydrogenase 5 (LDH5, ng/mL) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). **p ≤ 0.005.

4. Histopathology analysis

a. Skeletal muscle histopathology

Semi-quantitative scoring of histopathological lesions in skeletal muscle and kidneys of experimental groups was represented in Table 2. Histopathological lesions in the skeletal muscle were subjected to hematoxylin and eosin (H&E) staining (400x). In Figure 11a Examination of the skeletal muscle of the control group revealed normal architecture, which was characterized by long, cylindrical, multinucleated, and striated myofibers. The histology of the skeletal muscle of the rats given Khat extract indicated that no abnormalities were detected as represented in Figure 11b. Statin-induced and degenerative changes inskeletal muscle manifested as myocytes necrosis (yellow arrows), myocytes disruption (red arrow), intracellular muscle vacuoles (green arrow), and inflammatory infiltration (blue arrow), as represented in Figure 12.

The mixed Khat extract plus atorvastatin group was shown in Figure 13. In a: there are areas of myocyte necrosis admixed with mixed inflammation (arrowheads), alternating with normal appearing myocytes (stars). (H&E x100). In b and c: sections reveal areas of mixed inflammatory reaction (stars) formed of neutrophils (blue arrow) and macrophages (red arrow), in addition to disruption of myocytes (white arrow), and intracytoplasmic vacuoles (yellow arrow). (H&E, x400, x400). In d: sections showed extensive necrosis of myocytes with formation of intracytoplasmic vacuoles (arrowheads), and variable degree of surrounding inflammation (stars). (H&E x100). In 2e and 2f: muscle fibers are irregularly arranged with loss of normal architecture showing extensive necrosis (arrowheads), intracytoplasmic vacuolation variable in size (yellow arrow), muscle disruption (white arrows), extravasated blood (blue arrow), and dilated capillaries (star). Some of muscle fibers are more eosinophilic (red arrow), and some are pale (green arrows). (H&E x400, x400).

2. Kidney histopathology

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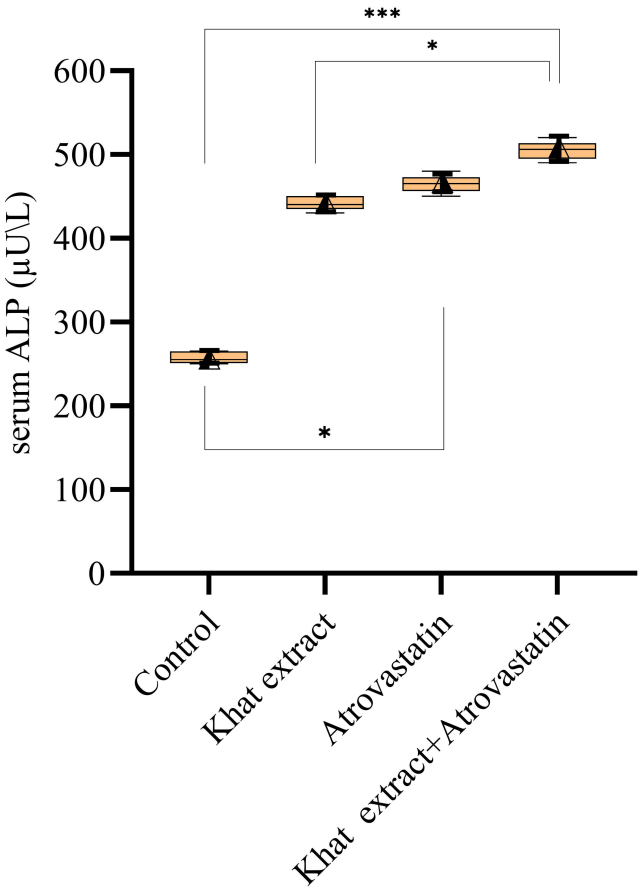

Figure 7 Serum Alkaline phosphatase (ALP, µU/L) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). *p ≤ 0.035, ***p ≤ 0.0003.

Photomicrographs of kidney tissue from different experimental groups of rats stained with PAS. Sections from the control group (Control-a and Control-b) showed a normal renal cortex with normal glomeruli and normal Bowman's capsule (green arrows), normal proximal convoluted tubules (red arrows), and normal distal convoluted tubules (yellow arrows), as shown in Figure 14. [400x, 400x].

In the Khat-treated group (Khat-a and Khat-b), the sections showed foci of hemorrhage (arrowheads). There was no evidence of glomerular or tubulointerstitial injury. [100x, 400x] as shown in Figure 15.

In the group which atorvastatin was given to the rats (Atro-a and Atro-b), the sections revealed focal tubular and interstitial injury, and some tubules were widened and distorted (blue arrows). Necrotic epithelial debris (arrowheads) and eosinophilic hyaline casts (red arrows) were observed inside the lumens of some tubules. Interstitial inflammation with loss of glomeruli and tubules (stars) was evident in some areas, as shown in Figure 16 [100x, 400x]

In the group of rats fed a mixture of Khat and atorvastatin (Mix-a and Mix-b), the sections revealed marked tubular and interstitial injury. Most of the tubules were widened and distorted (blue arrows). Necrotic epithelial debris (arrowheads) was observed inside the lumens of the tubules. There was extensive interstitial inflammation with loss of glomeruli and tubules (stars) as shown in Figure 17. [100x, 400x]

Discussion

In the present study, some drug-related myopathies, such as those caused by statins,were common, whereas others were very rare. The widespread use of statins has resulted in these drugs becoming the most common cause of myalgia in clinical practice, which is caused by pathological necrotizing myopathy, rhabdomyolysis, myotoxicity, and inflammatory myopathy. In addition, drugs such as amphetamine and its derivatives (such as Khat, which considers amphetamine

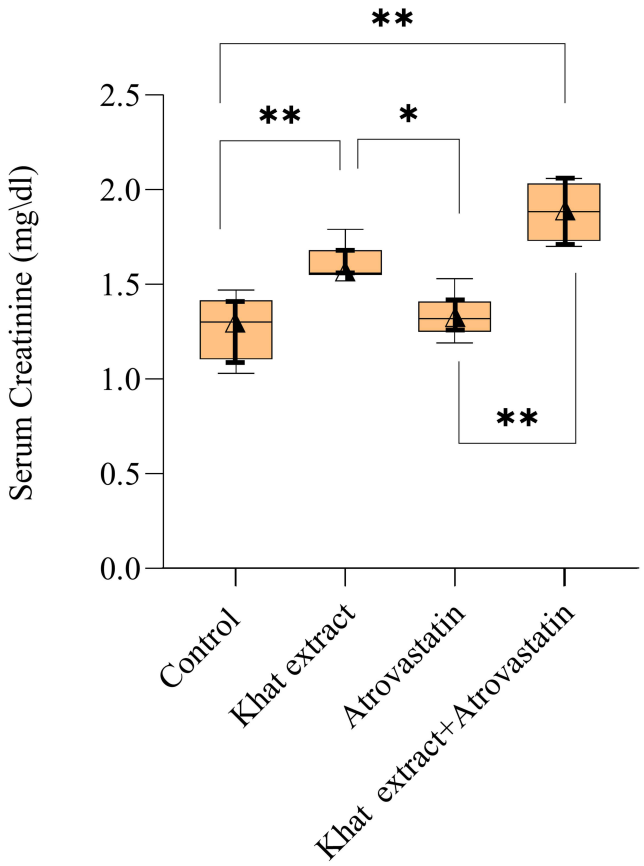

Figure 8 Serum Creatinine (Cr, mg\dl) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). Control vs Khat extract**p ≤ 0.006, Control vs Khat extract+Atrovastatin**p ≤ 0.001, Khat extract vs Atrovastatin *p ≤ 0.025, Atrovastatin vs Khat extract+Atrovastatin**p ≤ 0.005.

derivatives) caused myotoxicity through the inhibition of acetylcholinesterase; however, these drugs do not identify the exact mechanism and are recommended for the study of the exact mechanism.

Phytochemical screening of Khat extracts revealed the presence of alkaloids, tannins, flavonoids, terpenoids, phenolic compounds and glycosides. A phytochemical screening by Nigatu and Libsu revealed the presence of alkaloids, tannins, phenols, and flavonoids only,[35] and another study by Alele et al (2013) reported the presence of alkaloids and tannins steroids and terpenoids.[23] This is due to the different geographic areas of both the study area and the source of the Khat leaves and the season of harvesting. Khat extract and Atorvastatin caused alterations in the serum enzyme levels. The CKmm levels in the Khat-Atorvastatin treated group were the highest. However, CK-MM levels were notably higher in both the Khat-treated and atorvastatin groups compared with the other experimental groups. This observation is consistent with findings from previous research showing that administration of Khat extract at a dose equivalent to 1 g/kg (fresh leaves) led to a significant increase in serum CK levels in rats.[36,37] Also, Biomarker assessments revealed that the levels of total creatine kinase were significantly elevated at Khat extract dose 100 ($p < 0.05$), Khat extract dose 200, and Khat extract dose 400 ($p < 0.001$ in both cases).[38] A study conducted by Revikumar et al (2021) reported that administration of atorvastatin at doses of 10 mg and 20 mg for one year in hyperlipidemic patients was associated with an increase in serum creatine kinase levels.[39] In another study, multiple atorvastatin doses increased the level of serum CK.[40] Other studies indicated that Khat extract, or atorvastatin increased the level of the enzyme creatinine kinase, but they did not measure CK-MM or the effect of the combination of Khat extract and atorvastatin on the serum CK-MM. In our study, khat-atorvastatin treatment significantly increased CK-MM. This occurred because skeletal muscle damage appears to be directly correlated with the amount of CK-MM released into the serum; specifically, the greater the amount of CK-MM, the more extensive the damage to skeletal muscle.[41]

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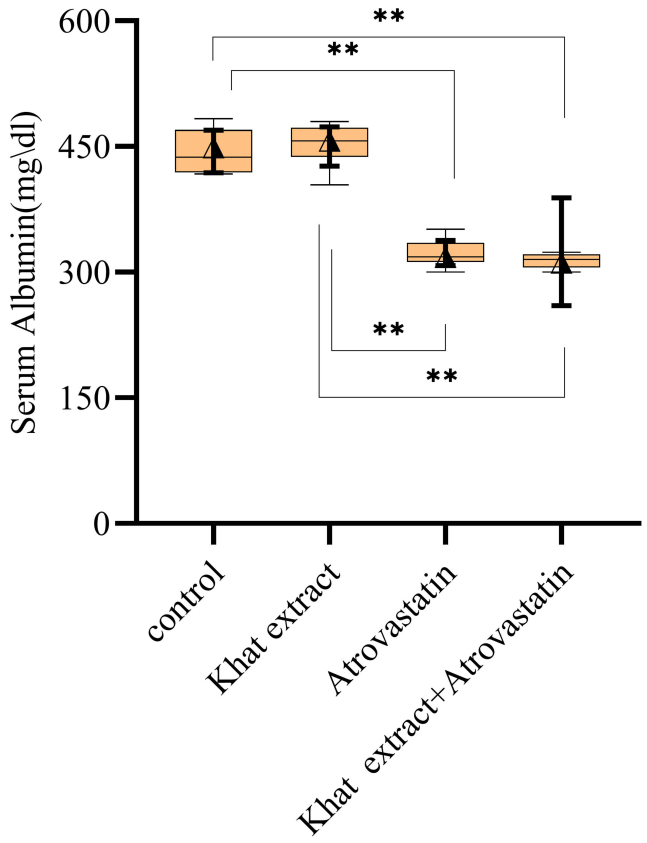

Figure 9 Serum Albumin (Alb, mg\dl) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). control vs Atrovastatin **p ≤ 0.005, Control vs Khat extract+Atrovastatin**p ≤ 0.005, Khat extract vs Atrovastatin **p ≤ 0.006 Khat extract vs Khat extract+Atrovastatin**p ≤ 0.005.

In general, myoglobin is an iron, and oxygen binding protein found in the cardiac and skeletal muscle tissues of vertebrates.[42] Compared with heart muscle, where it is found in trace amounts, skeletal muscle contains the majority of myoglobin.[43] Myoglobin is only found in the bloodstream following muscle injury in humans.[42] Myoglobin is an early sign of rhabdomyolysis, although its level usually returns to normal 24 hours after symptoms start. Importantly, rhabdomyoglobinuria is not always present or obvious, even if it is pathognomonic for rhabdomyolysis.[44]

The serum myoglobin in this study was increased in the atorvastatin- and khat-atorvastatin-treated groups. A study revealed a significant increase in myoglobin in Khat-treated rats.[34] In addition, myopathy is the most well-known side effect, and it is a prevalent problem worldwide. Elevated levels of creatinine kinase (CK), lactate dehydrogenase (LDH), and myoglobin provide biochemical indicators for the assessment of statin-induced myopathy.[45] Although rhabdomyolysis is the most severe statin-associated side effect, it causes the release of myoglobin in the bloodstream, which derived from muscle necrosis.[46] Approximately 2–3 per 100,000 patients will develop rhabdomyolysis with extremely high CK levels, and myoglobinemia with statin treatment.[47]

The serum Tn level in the atorvastatin-treated group was greater than that in the Khat-treated group, and Khat-Atorvastatin treatment caused the greatest increase in Tn. Similar results were reported by Mohan S et al,[34] in Dawley rats treated with two different dosages of Khat extract (250 and 500 mg/kg), with atorvastatin serving as a 28-day positive control. The results revealed that in the groups treated with statins and high dosages of Khat extract, Tn was increased. The modest dose of extract showed a modest increase but not a substantial increase. The results of this investigation revealed a highly significant increase in Tn with the administration of both Khat extract and Atorvastatin, indicating the possibility of serious consequences and the reported weakening of the muscles associated with chewing Khat.[34]

On the other hand, lactate dehydrogenase (LDH) is an enzyme implicated in the conversion of lactate to pyruvate in the cells of most body tissues and increases following tissue breakdown.[48] In this study, Khat extract increased the serum

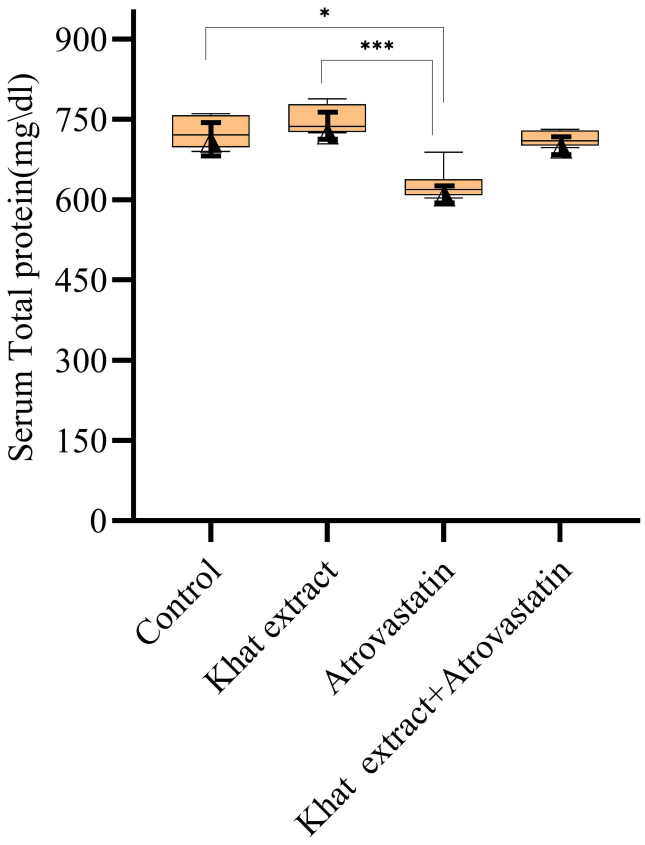

Figure 10 Serum Total protein (TP, mg\dl) in control, khat-treated, atorvastatin, and khat+atorvastatin groups (n = 6 rats/group). Data are presented as median with interquartile range (IQR); black triangles indicate the 95% confidence interval (CI). Control vs Atrovastatin *p ≤ 0.015, Khat extract vs Atrovastatin ***p ≤ 0.0002.

LDH level in the blood. Khat administration caused LDH and CK levels to significantly increase in the perfusate of isolated hearts compared with those of control rats.[36,37] In addition, a study in humans indicated that Khat chewing affects heart function by increasing the levels of cardiac enzymes (CK-MB, aspartate transaminase, LDH).[49]

Table 2 Semi-Quantitative Scoring of Histopathological Lesions in Skeletal Muscle and Kidneys of Experimental Groups

Lesions (Histopathology)	Control	Khat Extract	Atorvastatin	Atorvastatin + Khat Extract
Skeletal muscle				
Myocyte necrosis	–	–	++	+++
Myofiber fragmentation	–	–	+	+++
Myocyte disruption	–	–	++	+++
Intracytoplasmic vacuoles	–	–	+	++
Mixed inflammatory infiltrates	–	–	++	+++
Extravasated blood (hemorrhage)	–	–	–	++
Dilated capillaries	–	–	–	++
Eosinophilic (hyalinized)	–	–	++	++
Pale fibers	–	–	–	++

(*Continued*)

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Table 2 (Continued).

Lesions (Histopathology)	Control	Khat Extract	Atorvastatin	Atorvastatin + Khat Extract
Kidneys tissue				
Tubular epithelial necrosis	–	–	+	++
Tubular dilation/distortion	–	–	+	++
Hyaline casts	–	–	+	+
Interstitial inflammation	–	–	+	++
Hemorrhage	–	+	–	–

Notes: Symbols: – = **none**; + = **mild**; ++ = **moderate**; +++ = **severe.**

Additionally, LDH was increased by atorvastatin in our study. The serum levels of the muscle enzymes CK and LDH increase in patients with muscle pain or statin-associated muscle symptoms.[40] In contrast, the levels of serum LDH, and atorvastatin in cyclophosphamide-treated rats were significantly lower than those in the cyclophosphamide (CP)alone group.[50] For this reason, the administration of atorvastatin with other agents can lead to synergistic or antagonistic effects. For example, the khat extract used in our study with Atorvastatin elevated the serum LDH to its maximum value.

Lactate dehydrogenase-five (LDH-5) is an isoform known as an isozyme of lactate dehydrogenase (LDH).[51] The LDH-5 isozyme consists of four muscle subunits (4 M) and is expressed predominantly in the liver and skeletal muscle.[6] Our research represents an initial investigation into the effects of khat extract, atorvastatin, or the combination of khat extract and atorvastatin on the serum LDH-5level.Khat extract and atorvastatin significantly increased LDH-5 levels, and Khat-Atorvastatin treatment significantly increased LDH-5 levels compared with those in the control group. This elevated the degree of muscle injury (rhabdomyolism).

In addition, increased serum ALP could represent not only liver, but also heart, bone, and muscle damage.[52] In this study, the serum ALP concentration increased in the Khat extract plus atorvastatin group. An article by Muema E et al,[53] on the toxicity and safety of Khat (*Catha edulis*) reported an increase in the level of ALP in the Khat extract group

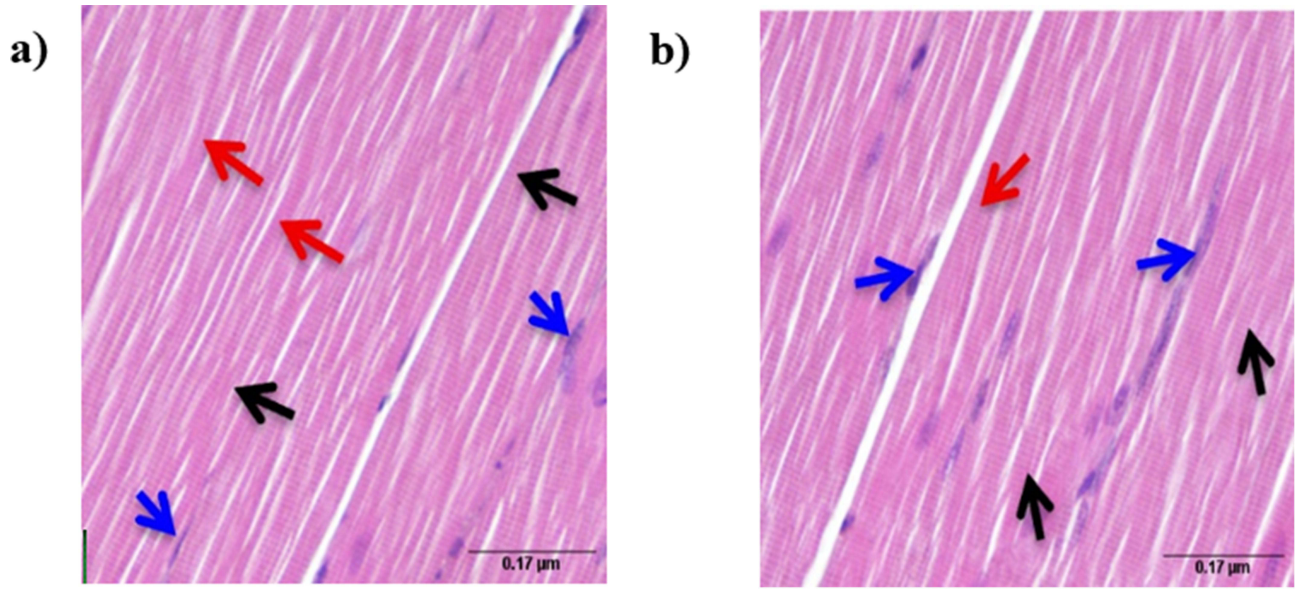

Figure 11 In (**a**) Normal histology of skeletal muscle of rat "control" group, hematoxylin and eosin stain. It showed normal structure and morphology: nucleus (blue arrow), myocytes (black arrow) and obvious cross-striation (red arrow). (H&E x400). In (**b**): Histology of skeletal muscle of rat given Khat extract group, hematoxylin and eosin stain: No abnormalities are detected: nucleus (blue arrow), myocytes (black arrow) and obvious cross-striation (red arrow). (H&E x400).). Scale bar=100µm.

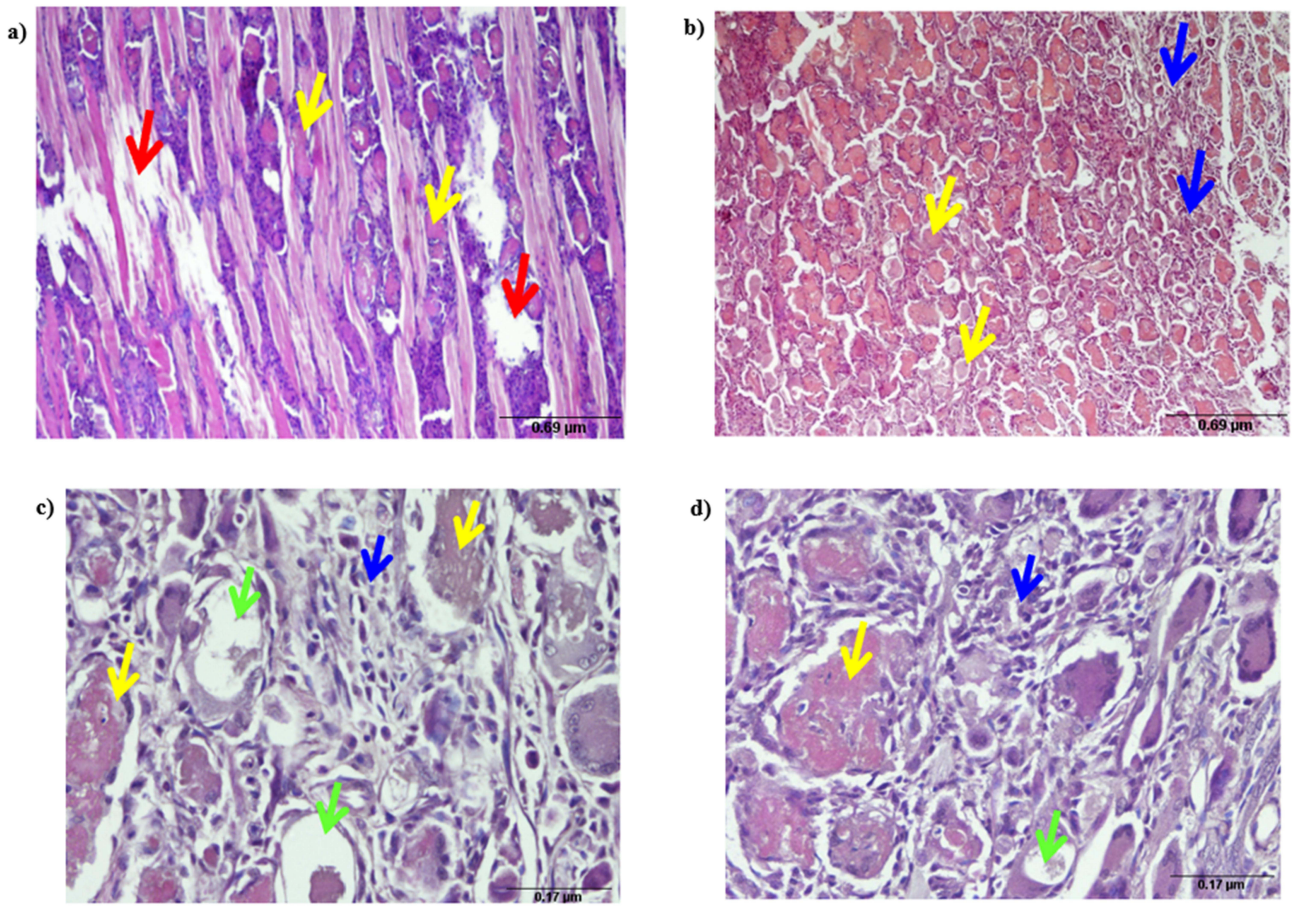

Figure 12 In (**a**–**d**) Atorvastatin group showed muscle necrosis (yellow arrows), muscle disruption (red arrow), intracellular muscle vacuoles (green arrow), and inflammatory infiltrate (blue arrow). (H&E. (**a** and **b**) ×100, (**c** and **d**) ×400). Scale bar=100µm.

compared with the control group. Moreover, compared with nonusers, Khat users presented increased serum concentrations of alkaline phosphatase (ALP).[54] Additionally, atorvastatin treatment significantly increased the serum levels of ALP.[55,56] In rats, these findings confirmed that the increase in ALP in the serum caused by the addition of Khat extract with atorvastatin resulted in muscle damage.

The serum creatinine level was greater in all the groups than in the control group, but the difference was not significant. An animal study revealed that Khat at different doses (100 and K00) did not result in detectable changes in serum marker levels, but Khat at a dose of 400 significantly increased creatinine.[57] In a clinical trial, khat chewers had higher serum creatinine levels than nonchewer.[54,58] A previous study reported a decrease in the albumin level in Khat chewers, which disagrees with the findings of this study,[54] and another study by Othman et al2024 reported an increase in the albumin and total protein levels in Khat chewers; these findings are similar to those of this study.[59]

Several studies reported the effect of statin use on the serum creatinine level and reported no significant difference in the serum creatinine level between the statin group and the control group or lower urinary protein excretion,[60] as shown in our study. Khat extract-atorvastatin had greater effects than atorvastatin alone and lower effects than did khat alone, which indicated that atorvastatin maintained renal function and that Khat increased renal functions.

Histopathological examination of skeletal muscle sections from the group that received 40 mg/kg atorvastatin revealed that the long segment of the muscle fibrils had a wavy look. Certain myofibers exhibited conspicuous euchromatic nuclei that surrounded by additional satellite cells and oriented in a linear fashion. Numerous fibers also presented with myonuclear alterations. These alterations included clumping, asymmetrical forms, and nuclear expansion.[28] In the present study, these changes became more obvious with atorvastatin plus khat extract.

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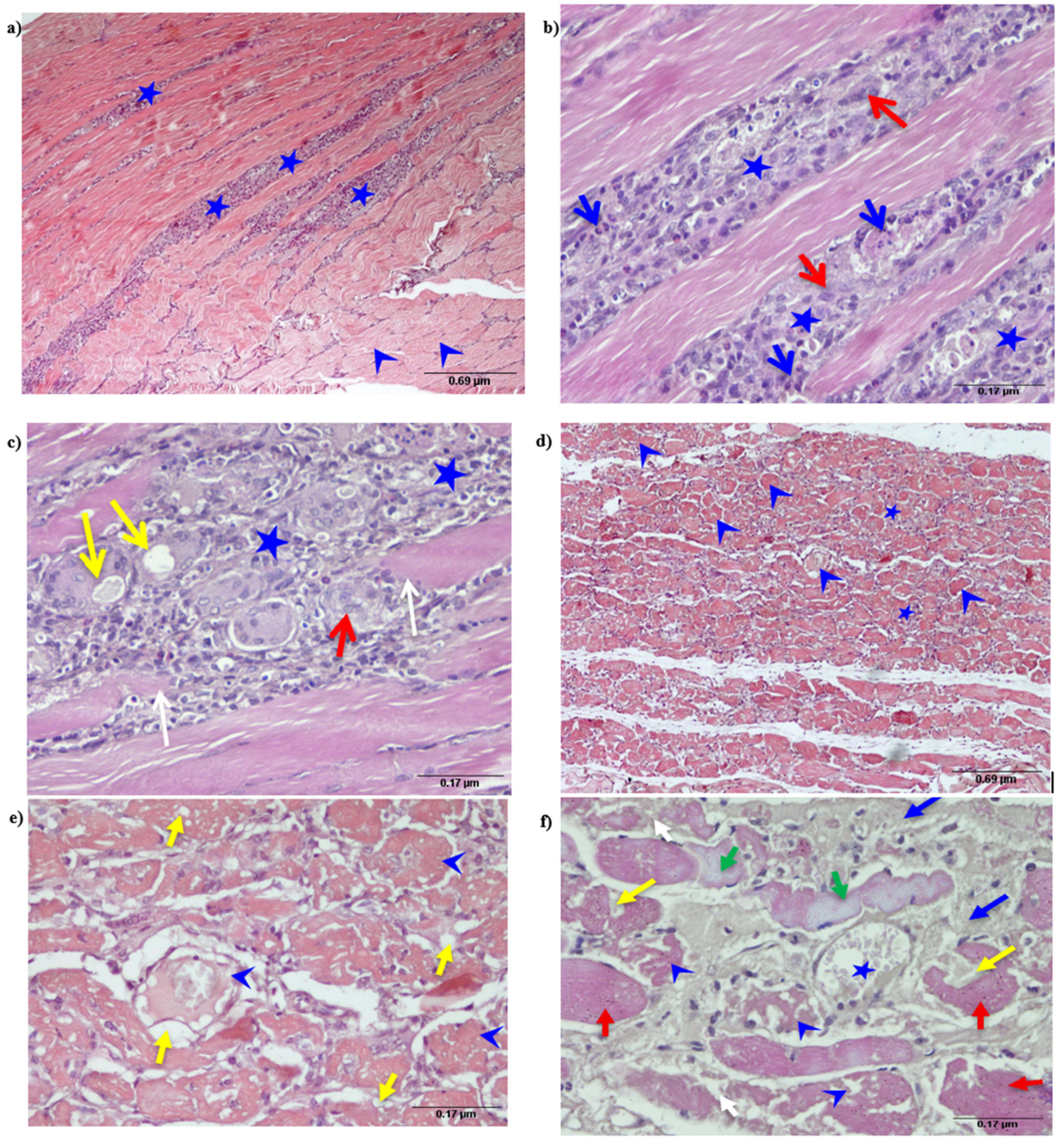

Figure 13 (**a–f**) Atorvastatin plus khat extract group. In (**a**) there are areas of myocyte necrosis admixed with mixed inflammation (arrowheads), alternating with normal appearing myocytes (stars). (H&E x100). In (**b** and **c**) sections reveal areas of mixed inflammatory reaction (stars) formed of neutrophils (blue arrow) and macrophages (red arrow), in addition to disruption of myocytes (white arrow), and intracytoplasmic vacuoles (yellow arrow). (H&E, x400, x400). In (**d**) sections showed extensive necrosis of myocytes with formation of intracytoplasmic vacuoles (arrowheads), and variable degree of surrounding inflammation (stars). (H&E x100). In 2e and 2f: muscle fibers are irregularly arranged with loss of normal architecture showing extensive necrosis (arrowheads), intracytoplasmic vacuolation variable in size (yellow arrow), muscle disruption (white arrows), extravasated blood (blue arrow), and dilated capillaries (star). Some of muscle fibers are more eosinophilic (red arrow), and some are pale (green arrows). (H&E x400, x400). Scale bar=100µm.

Khat-treated sections presented foci of hemorrhage but no evidence of glomerular or tubulointerstitial injury, and other studies reported kidney tissue injuries.[61–63] However, with atorvastatin, the sections revealed focal tubular and interstitial injury. Some tubules are widened, and distorted. Necrotic epithelial debris, and eosinophilic hyaline casts are observed inside the lumens of some tubules. Interstitial inflammation with loss of glomeruli and tubules is evident in some areas, as studies have indicated

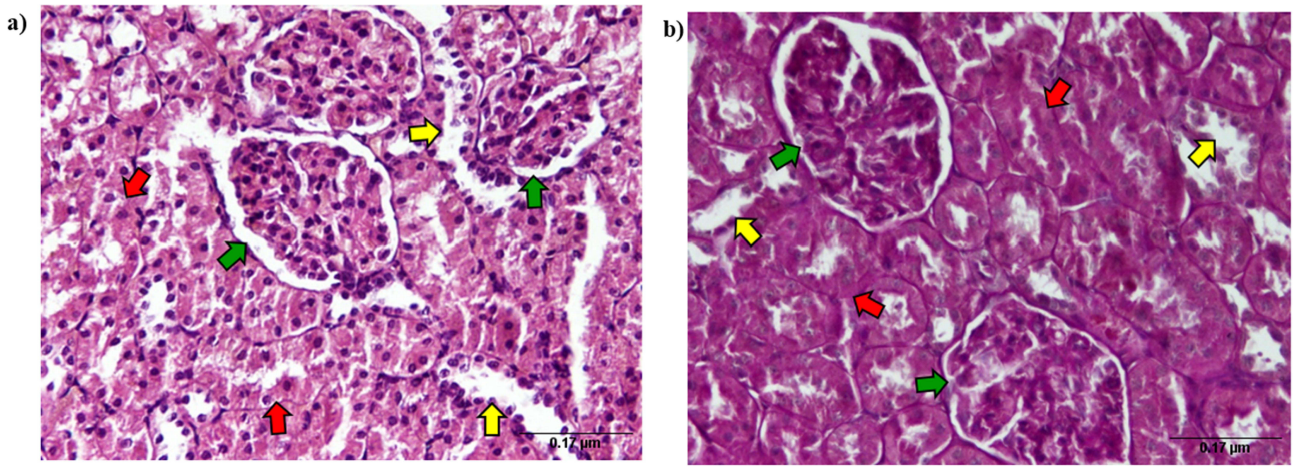

Figure 14 Photomicrographs of kidney tissue stained with PAS from different experimental groups of rats. Sections in the Control group (**a** and **b**) show normal renal cortex with normal glomeruli and normal Bowman's capsule (green arrows), normal proximal convoluted tubules (red arrows), and normal distal convoluted tubules (yellow arrows). [400x, 400x] Scale bar=100µm.

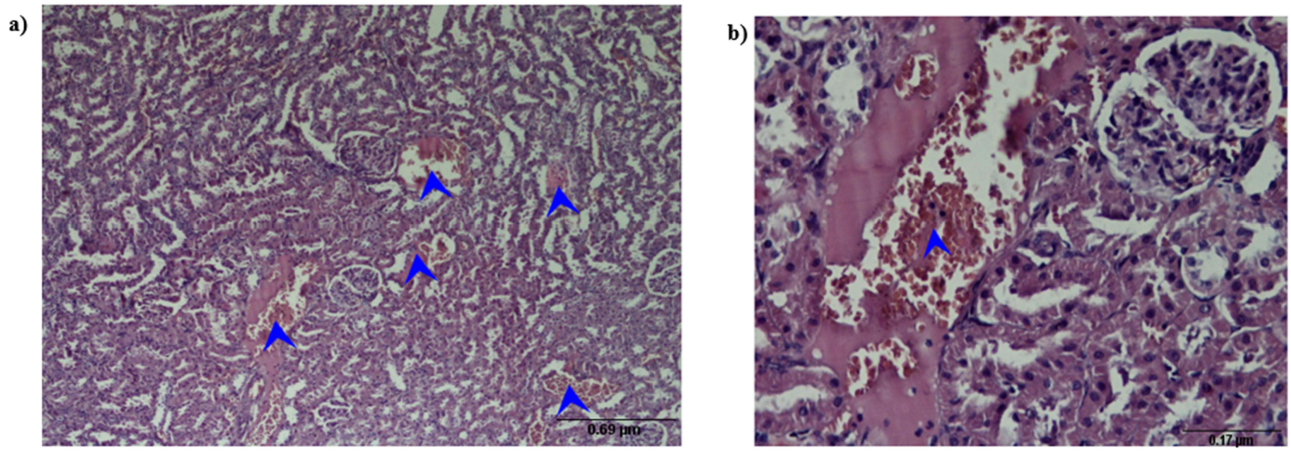

Figure 15 In Khat-extract group (**a** and **b**), sections show foci of hemorrhage (arrowheads). No evidence of glomerular or tubulointerstitial injury. [100x, 400x]. Scale bar=100µm.

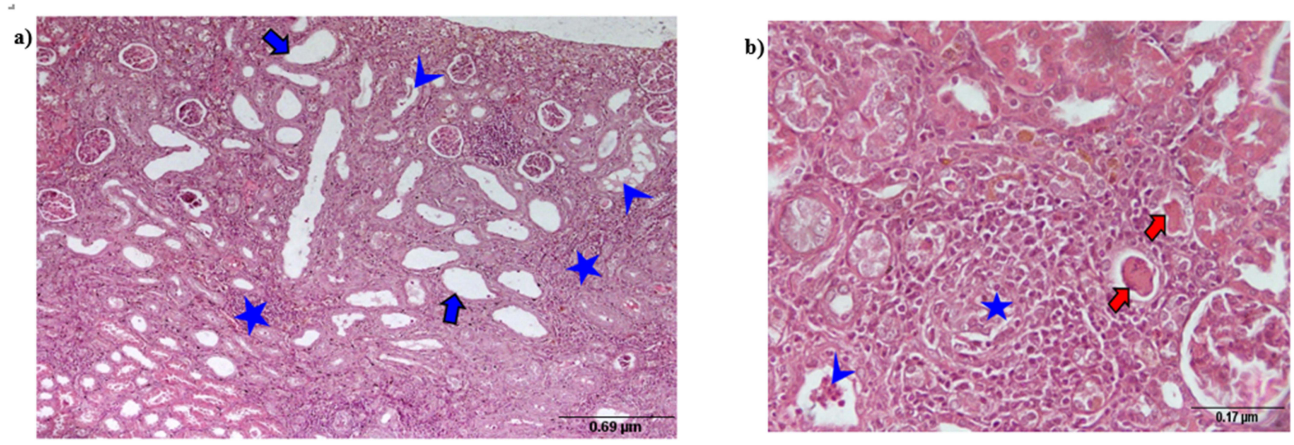

Figure 16 Group where Atorvastatin was given to rats (**a** and **b**), sections reveal focal tubular and interstitial injury. Some tubules are widened, and distorted (blue arrows). Necrotic epithelial debris (arrowheads), and eosinophilic hyaline casts (red arrows) are seen inside lumens of some tubules. Interstitial inflammation with loss of glomeruli and tubules (stars) is evident in some areas. [100x, 400x]. Scale bar=100µm.

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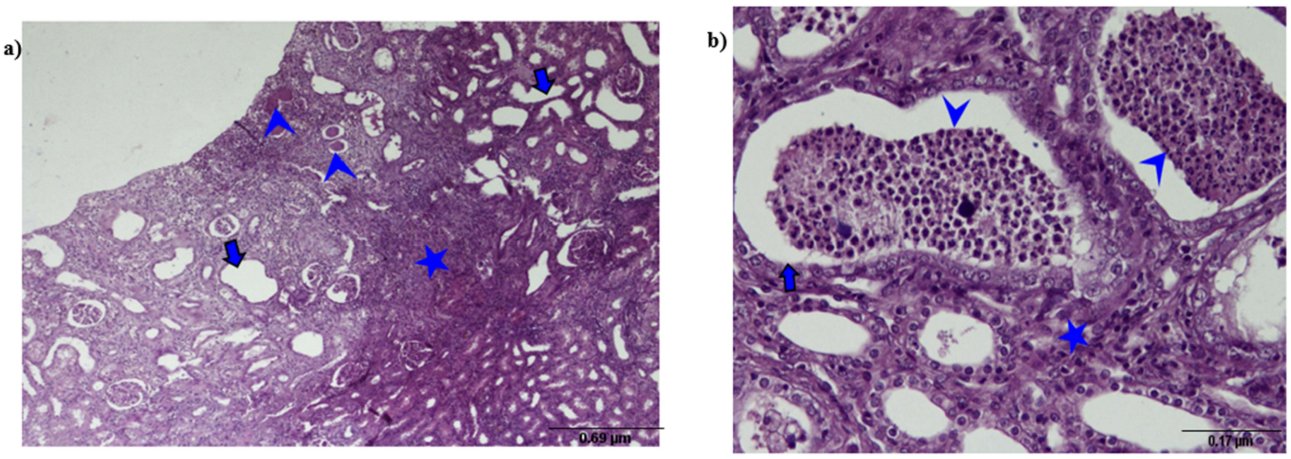

Figure 17 In group where rats fed with mixture of Khat and Atorvastatin (**a** and **b**), sections reveal marked tubular and interstitial injury. Most of tubules are widened, and distorted (blue arrows). Necrotic epithelial debris (arrowheads) are seen inside lumens of tubules. There is extensive interstitial inflammation with loss of glomeruli and tubules (stars). [100x, 400x]. Scale bar=100µm.

many changes in kidney sections.[64] In the group in which the rats were fed a mixture of khat and atorvastatin, there was marked tubular and interstitial injury in these sections. Some drug-related myopathies, such as those caused by statins, are common, whereas others are very rare. Statin-induced rhabdomyolysis, most often precipitated by drug-drug interactions, affects only a tiny proportion of statin users, because of the widespread prescription of statins, which is an important clinical problem.[65] In addition, statin-induced rhabdomyolysis occurs through interactions with other factors, which we suggest as Khat chewing. This study is the first to investigate the impact of combining Khat extract with atorvastatin on skeletal muscles. Consequently, our parameters exhibited considerable variability compared with those of other studies, which can be attributed to several factors, including the diverse species of Khat, varying geographic locations, extraction methods and solvents employed, differences in the duration and dosages of the Khat extract and atorvastatin, and specific areas of research.

Strength and Limitations of This Study

This study is among the few experimental investigations exploring the combined effects of *Catha edulis* extract and atorvastatin on skeletal muscle injury and rhabdomyolysis.

Integration of both biochemical markers by using specific muscle markers (CKmm,LDH5,fsTN,LDH5) and serum myoglobin and histopathological scoring provides a comprehensive assessment of muscle damage. The use of blinded histological scoring increases the reliability of the findings.

Biochemical and histological evaluations were performed only at terminal time points, without serial measurements of CK or urinary myoglobin to assess progression or recovery. The Catha edulis extract was not chemically standardized (eg, LC-MS profiling), which may introduce variability in active constituents. Chloroform anesthesia may have introduced biochemical confounding. Important diagnostic criteria for rhabdomyolysis (CK $\geq$ 5× ULN, serial CK, or urinary myoglobin) were not fully addressed. The atorvastatin dose may not directly translate to human therapeutic exposures, limiting clinical relevance.

Conclusions

The present findings demonstrate that while khat or atorvastatin alone produced only mild elevations in muscle injury and biochemical markers, their combined administration resulted in pronounced and statistically significant increases in CKmm, myoglobin, LDH, LDH5, and ALP. These results suggest a potential synergistic interaction between khat and atorvastatin that markedly exacerbates muscle and cellular toxicity, highlighting the risk of co-exposure.

Future Research

Further studies are warranted to evaluate the dose–response relationship of khat and atorvastatin, explore the underlying molecular mechanisms of muscle injury, and assess whether protective interventions (eg, antioxidants) could attenuate

the observed changes. In addition, long-term studies and translational research linking these findings to clinical populations may provide deeper insights into the potential health risks.

Disclosure

The authors report no conflicts of interest in this work.

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