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Effect of *Catha edulis* and Atorvastatin on Electrolyte Imbalance: An Experimental Study

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ABSTRACT

Background: Chewing the leaves of *Catha edulis*, commonly known as khat, is a habitual practice embraced by individuals across various societal strata in Yemen and East Africa. The interaction of medications used to treat chronic diseases with khat has not been adequately studied, particularly in relation to electrolyte imbalances. Therefore, this study aimed to investigate the effect of khat extract and atorvastatin, either alone or in combination, on electrolyte imbalance in a rat model.

Methods: Khat was extracted by the methanolic extraction protocol. A total of 24 healthy albino rats were randomly divided into four groups of six rats: control group, khat extract-treated group, atorvastatin-treated group, and khat *plus* atorvastatin-treated group. All drugs were administered orally using a metal gavage needle from day 1 to 28, and body weight was measured weekly. Blood samples were collected from the tail vein to measure serum levels of sodium, potassium, chloride, calcium, and ionized calcium. The mean values of body weight and serum electrolytes were compared using appropriate statistical tests.

Results: On day 28, the mean body weights of rats treated with khat *plus* atorvastatin (153.17±30.30), atorvastatin (155.67±19.53) and khat extract (194.17± 26.73) were significantly lower than the mean body weight of the control group (246.50±39.73). In addition, significantly higher mean serum sodium levels (mmol/L) were observed in rats treated with khat extract (157±2.22), atorvastatin (161±7.21) and khat *plus* atorvastatin (167±4.14) compared to the control group (139±1.71). However, there were no statistically significant differences in the mean serum potassium levels (mmol/L) in rats treated with khat extract (5.07±0.33), atorvastatin (5.21±.036) and khat *plus* atorvastatin (5.48±0.68) compared to the control group (4.66±0.39). Regarding serum chloride, significantly higher mean levels (mmol/L) were observed in rats treated with khat extract (111±5.49), atorvastatin (114±3.31) and khat *plus* atorvastatin (120±2.64) compared to the control group (99±1.77) on day 28. However, significantly lower mean serum calcium and ionized calcium levels (mmol/L) were observed in rats treated with atorvastatin (2.68±0.16 and 1.24±0.09, respectively) and khat *plus* atorvastatin (2.61±0.10 and 1.23±0.05, respectively) compared to the control group (2.82±0.09 and 1.37±0.08, respectively).

Conclusion: Khat and atorvastatin alone or in combination can reduce body weight and potentially induce hypernatremia, hyperchloremia and hypocalcemia, with no obvious effects on serum potassium levels in the rat model. Therefore, clinicians should be aware of these electrolyte imbalances induced by khat and statins in people who chew khat. Clinical studies are needed to better understand the mechanisms behind these effects and to determine the extent of risk in the human population.

Keywords: *Catha edulis* ▪ Atorvastatin ▪ Electrolyte imbalance ▪ Rat model

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1. Introduction

Catha edulis, commonly known as khat, is an evergreen shrub whose fresh leaves are chewed as a stimulant in many parts of the world, particularly in East Africa and Yemen. Chewing khat leaves induces a feeling of euphoria, primarily due to its two main components: cathinone and cathine.[1] It is often chewed alone or in combination with smoking and alcohol.[2] It is estimated that there are up to 20 million khat consumers worldwide.[3] Long-term consumption of khat affects almost every organ in the human body and can lead to oral histopathological changes.[4] Therefore, abuse of *C. edulis* has become an important public health problem.[5] Chronic exposure to *C. edulis* can cause dependency, psychosis, hepatotoxicity, hypertension, cardiovascular problems, and sexual dysfunction, among other adverse effects.[5] Despite its potential connection to electrolyte imbalance, limited research has been conducted on its effect on serum electrolytes in animal models.[6]

Statins are commonly used as lipid-lowering medications because they are potent competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase.[7] Atorvastatin is one of the most commonly recommended statins[8] and has been the best-selling lipid-regulating medication worldwide in the new millennium.[9] While statins are typically considered safe as a class of medications, they are associated with muscular issues.[10] These issues range from mild myalgia to potentially fatal rhabdomyolysis, with skeletal muscle complaints being the most common. Damage to skeletal muscle tissue can have serious consequences.[11] In addition, there are numerous underappreciated side effects of statins that should be considered, including hepatic and renal failure, myopathy, and the development of type 2 diabetes.[12] Although these side effects may not occur frequently, their impact is significant due to the large number of people worldwide who take statins on a daily basis.[12]

Electrolytes are minerals that can conduct electricity and form ions in solutions. They play a vital role in the functioning of the body.[13] Optimal electrolyte levels both inside and outside cells are essential for various metabolic activities and maintaining normal organ function.[14] Critically ill individuals often experience electrolyte imbalance. Numerous consequences, including respiratory failure, edema, muscular weakness, altered mental status and arrhythmias, have been documented in patients admitted to intensive care units due to electrolyte imbalance.[15] Studying the effect of khat and atorvastatin on electrolyte levels in rats is necessary to investigate how this combined effect may affect electrolyte levels in humans. Therefore, this study aims to investigate the effect of the khat extract and atorvastatin, either alone or in combination, on electrolyte imbalance in a rat model.

2. Methods

2.1. Khat collection and extraction

Two and a half kilograms of fresh, pesticide-free shoots of *C. edulis* were collected from Wadi Al-Jannat area in Ibb Governorate, Yemen. The plant materials were identified by a taxonomist, which were assigned a voucher specimen (739) and stored in the Pharmacognosy Laboratory of the Faculty of Pharmacy at Sana'a University, Yemen. The freshly collected shoots were rinsed in distilled water to remove any debris and dust particles. The fresh khat leaves were then separated from the shoots and prepared for the extraction step.

The extraction process was performed using the methanolic extraction protocol.[15] The fresh khat leaves were removed from the stems, thor-

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oughly cleaned in distilled water, carefully chopped on glass plates, and then crushed. The crushed material was placed on a rotating shaker for 20 hours after being immersed in a conical flask filled with 99.5% methanol. The mixture was filtered twice: first through a gauze roll to remove larger particles, and then through qualitative filter paper. Any remaining unfiltered plant material was subjected to an additional extraction with fresh methanol. The filtrate was admixed with the initial filtrate. The resulting filtrate was then collected and placed in conical flasks that had been previously weighed. The methanol was entirely evaporated at 65°C using a rotary vacuum evaporator.[15] Finally, the khat extract solution was prepared by dissolving the extract powder in distilled water just before daily oral administration to the rats throughout the experiment for 28 days.[15]

2.2. Study design and rats housing

An experimental study was conducted on 4-week-old male albino rats weighing 170 to 190 grams. These rats were obtained from the Animal Experimentation Unit of the Faculty of Medicine and Health Sciences at Sana'a University. The rats were housed in the animal facility and allowed to acclimatize for two weeks at a controlled temperature of 20 ± 4°C, relative humidity of 30% to 70%, and a 12-hour light and 12-hour dark cycle.[6] They had free access to a rodent diet and tap water *ad libitum*. The rats were maintained according to the Guidelines for Proper Conduct of Animal Experiments.[6] The rats' body weight was measured weekly.

2.3. Drug preparation and administration

Atorvastatin powder was purchased from Global Pharmaceutical Industries in Sana'a, Yemen. Khat extract and atorvastatin were dissolved in 1 ml of distilled water and administered orally using a metal gavage needle from days 1 to 28.

2.4. Animal grouping and drug dosing

The rats were randomly divided into four groups, each consisting of six rats:[17] Group I (control group), which received 1 ml of distilled water orally from day 1 to day 28; Group II (atorvastatin-treated group) received a single daily oral dose of 40 mg/kg of atorvastatin dissolved in 1 ml distilled water from day 1 to day 28;[11, 13] Group III (khat-treated group) received a single daily oral dose of 500 mg/kg of khat extract dissolved in 1 ml distilled water from day 1 to day 28; Group IV (khat *plus* atorvastatin-treated group) received a single daily oral dose of khat *plus* atorvastatin dissolved in 1 ml distilled water from day 1 to day 28.[17] The dose of the extract administered to each rat was calculated based on the total body weight of each rat. The appropriate volume of vehicle (2.5 ml/kg body weight) was used to determine the amount of volume used to dissolve the calculated dose of khat extract and atorvastatin.[6]

2.5. Blood collection and electrolyte measurement

On day 28, all rats were anesthetized, and 5 ml of blood were collected from the tail vein into a plain tube without anticoagulant and left at room temperature for 20 minutes. The serum was then separated by centrifugation at 6000 rpm for 5 minutes.[19] All samples were sent in a cool container to the National Center of Public Health Laboratories in Sana'a. They were stored at -20°C until sodium, potassium, chloride, total calcium and ionized calcium were measured using commercial kits.

2.6. Data analysis

Data were analyzed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Electrolyte levels were presented as mean ± standard deviation (SD). The Kruskal-Wallis H test was used to

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compare the mean ranks of electrolyte levels among groups, with post hoc pairwise Mann-Whitney tests performed to identify specific groups that had significant differences. The significance level was set at a *P* value of <0.05.

3. Results

3.1. Effect of khat extract, atorvastatin and their combination on body weight

Table 1 shows that the mean body weight of rats in grams was significantly different among all groups on all measurement days. It was significantly lower in khat *plus* atorvastatin-treated group than khat-treated group (148.17±16.12 *vs.* 172.33±13.75). On days 8 and 21, the mean body weights were significantly lower in khat *plus* atorvastatin-treated group (155.67±25.67 and 161.00±31.94, respectively) and atorvastatin-treated group (157.83± 16.82 and 163.50±13.35, respectively) compared to the mean body weight of the control group (188.33±30.72). However, on day 28, all three treatment groups showed lower mean body weights than the control group. In addition, the mean body weights of rats treated with khat *plus* atorvastatin (153.17±30.30), atorvastatin (155.67±19.53) and khat extract (194.17 ±26.73) were significantly lower than the mean body weight of the control group (246.50± 39.73).

Table 1: Effect of khat extract, atorvastatin and their combination on body weights of rats

Measurement day	Mean body weight ± SD (grams)				*P* value
	Control (*n*=6)	Khat extract (*n*=6)	Atorvastatin (*n*=6)	Khat *plus* atorvastatin (*n*=6)	
Day 1	154.83±27.63	172.33±13.75	150.33±18.28	148.17±16.12 [a]	0.030
Day 8	188.33±30.72	182.33±19.23	157.83±16.82 [b]	155.67±25.67 [b]	0.037
Day 21	210.67±34.61	187.33±16.05	163.50±13.35 [b]	161.00±31.94 [b]	0.020
Day 28	246.50±39.73	194.17± 26.73 [a]	155.67±19.53 [a, b]	153.17±30.30 [a, b]	0.004

SD, standard deviation; [a] significantly different from khat extract group; [b] significantly different from the control group.

3.2. Effect of khat extract and atorvastatin and their combination on serum sodium levels

Table 2 shows significantly higher mean serum sodium levels (mmol/L) in rats treated with khat extract (157±2.22), atorvastatin (161±7.21) and khat *plus* atorvastatin (167±4.14) compared to the control group (139±1.71). However, there were no statistically significant differences in mean serum sodium levels among the three treated groups.

Table 2: Effect of khat extract, atorvastatin and their combination on serum sodium levels in rats

Group	Sodium
	Mean ± SD (mmol\L)
Control	138.78±1.71
Khat extract	156.83±2.22 [a]
Atorvastatin	161 ±7.21 [a]
Khat plus atorvastatin	167±4.14 [a]

SD, standard deviation; [a] significantly different from the control group.

3.3. Effect of khat extract, atorvastatin and their combination on serum potassium levels

Table 3 shows that there were no statistically significant differences in the mean serum potassium levels (mmol/L) in rats treated with khat extract (5.07±0.33), atorvastatin (5.21±0.36) and khat *plus* atorvastatin (5.48±0.68) compared to the control group (4.66±0.39). In addition, there were no statistically significant differences in mean serum sodium levels among the three treated groups.

Table 3: Effect of khat extract, atorvastatin and their combination on serum potassium level in rats

Group	Potassium
	Mean ± SD (mmol\L)
Control	4.66±0.39
Khat extract	5.07±0.33
Atorvastatin	5.21±.036
Khat *plus* atorvastatin	5.48±0.68

SD, standard deviation.

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3.4. Effect of khat extract, atorvastatin and their combination on serum chloride levels

Table 4 shows significantly higher mean serum chloride levels (mmol/L) in rats treated with khat extract (111.21±5.49), atorvastatin (113.57±3.31) and khat *plus* atorvastatin (120±2.64) compared to the control group (98.63±1.77). Moreover, significantly lower serum chloride levels were observed in rats treated with khat extract and atorvastatin compared to those treated with Khat *plus* atorvastatin.

Table 4: Effect of khat extract, atorvastatin and their combination on serum chloride levels in rats

Group	Chloride
	Mean ± SD (mmol\L)
Control	98.63±1.77
Khat extract	111.21±5.49 [a, b]
Atorvastatin	113.57±3.31 [a, b]
Khat *plus* atorvastatin	120.20±2.64 [a]

SD, standard deviation; [a] significantly different from the control group; [b] significantly different the khat *plus* atorvastatin group.

3.5. Effect of khat extract, atorvastatin and their combination on serum calcium and ionized calcium levels

Table 5 shows significantly lower mean serum calcium and ionized calcium levels (mmol/L) in rats treated with atorvastatin (2.68±0.16 and 1.24±0.09, respectively) and khat *plus* atorvastatin (2.61±0.10 and 1.23±0.05, respectively) compared to the control group (2.82±0.09 and 1.37±0.08, respectively). Furthermore, there were significantly lower mean serum ionized calcium levels in rats treated with atorvastatin and khat *plus* atorvastatin compared to those treated with khat extract alone.

Table 5: Effect of khat extract, atorvastatin and their combination on serum calcium and ionized calcium levels in rats

Group	Calcium	Ionized calcium
	Mean ± SD (mmol\L)	
Control	2.82±0.09	1.37±0.08
Khat extract	2.73±0.21	1.49±0.22
Atorvastatin	2.68±0.16 [a]	1.24±0.09 [a ,b]
Khat *plus* atorvastatin	2.61±0.10 [a]	1.23±0.05 [a, b]

SD, standard deviation; [a] significantly different from the control group; [b] significantly different from khat extract-treated group.

4. Discussion

The present study found a significant reduction in body weight of rats in all groups treated with khat alone, atorvastatin alone and their combined use. This finding is consistent with a previous study that demonstrated the efficacy of microencapsulated khat extract in increasing weight loss in rats.[20] Khat reduces appetite and weight by reducing hunger and promoting satiety. Cathinones in khat may reduce appetite by influencing the hypothalamus.[21] Following intensive chewing of khat (400 g), elevated levels of the anorectic hormone leptin were detected in plasma after four hours.[21] Similarly, atorvastatin reduces leptin mRNA expression and leptin secretion and serum levels of leptin,[22] which explains the rapid weight loss observed when atorvastatin was administered together with khat extract in the present study from the second to the fourth week.

The effect of khat extract and atorvastatin on electrolyte imbalance varied based on the type of electrolyte in the present study. Khat extract caused hypernatremia, which is consistent with hypernatremia reported with khat in humans.[23] In contrast, Limenie et al.[6] reported hyponatremia in rats administered with various doses of khat extract for 12 weeks. The difference between these findings could be attributed to the extraction protocol, which used diethyl ether and chloroform at a 3:1 v/v ratio in the previous study, besides using different small doses of khat extract and durations of administration.[6] However, a single dose combined with atorvastatin was used for four weeks in the present study.

In the present study, it was observed that atorvastatin also induced hypernatremia. It is noteworthy that there have been no published studies on the effect of atorvastatin on serum sodium levels. However, atorvastatin was found to reduce urinary sodium excretion compared to placebo, leading to

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hypernatremia.[24] In addition, no published studies have measured the effect of khat extract in combination with atorvastatin on serum sodium levels, making this study the first to assess the combined effect of khat *plus* atorvastatin on these levels. Remarkably, this combination induced the most pronounced hypernatremia in rats compared to either component alone. This electrolyte imbalance has also been observed in several disorders, including rhabdomyolysis, due to dysfunction of energy-dependent ion pumps such as Na^+/K^+-ATPase and Ca^{2+}-ATPase in the sarcolemma and other intracellular membranes, leading to hypocalcemia and hypernatremia.[25]

In the present study, khat extract induced significant hyperchloremia. This finding aligns with a human study showing that khat extract can induce hypernatremia and hyperchloremia.[23] It has been suggested that mechanisms that lower sodium levels also lower chloride levels and vice versa.[26] In contrast, Limenie et al.[27] showed that khat extract had no significant effect on serum chloride. However, in the latter study, different doses of khat extract (100, 200, and 300 mg/kg body weight) dissolved in Tween 80 and distilled water were used.

Few studies have addressed the effect of atorvastatin on serum chloride levels. For instance, Onwuchekwa et al.[28] showed that serum chloride levels were significantly higher in rats treated with atorvastatin (80 mg and 120 mg) within 21 days compared to controls. Although the doses were different, this finding agrees with our finding.

In the present study, serum potassium levels were not significantly affected by khat extract, atorvastatin, or their combination. Likewise, serum potassium levels were not significantly increased in rats receiving khat extract (300 mg/kg) compared to rats receiving Tween 80 and ascorbic acid (200 mg/kg).[6] Chewing khat was also not significantly associated with changes in serum potassium levels in Kenyan consumers.[29] Furthermore, these findings agree with the finding by Limenie et al,[27] who found that serum potassium levels in rats receiving khat extract sub-chronically at a dose of 300 mg/kg were significantly higher compared to rats receiving Tween 80.[27] In contrast, atorvastatin doses of 80 mg/kg and 120 mg/kg were found to be significantly associated with hyperkalemia.[19] Among the intracellular components that leak from damaged skeletal muscles, potassium is the most important one. Because potassium shifts from cells with high levels to the serum where a low level is normal, lethal hyperkalemia can rapidly develop.[30] Furthermore, this study is the first to report on the effect of khat extract and atorvastatin, alone or in combination, on serum potassium levels.

In the present study, significant hypocalcemia was induced in rats receiving atorvastatin and khat *plus* atorvastatin. However, khat extract did not induce significant hypocalcemia. This finding is consistent with other studies,[6, 27] which found that different doses of khat extract did not induce significant hypocalcemia. Atorvastatin was found to significantly suppress intracellular calcium levels.[31] Furthermore, in lithium users with relatively normal calcium levels, atorvastatin was found to be associated with hypocalcemia.[32] In contrast, a previous study found that atorvastatin had no effect on serum calcium levels in rats.[33] Although previous studies have assessed the effects of khat extract or atorvastatin on serum calcium levels, the present study is the first to assess the effect of their combination on these levels.

Ionized calcium plays a pivotal role in muscle fibers during the excitation-contraction process.[26] In the present study, atorvastatin and khat *plus* atorvastatin were found to be significantly associated with reduced levels of ionized calcium. However, khat extract caused hypercalcemia. These effects cannot be compared because this study is the

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first to assess the effects of khat extract and atorvastatin, alone and in combination, on the levels of ionized calcium.

The present study has several limitations that should be considered, including the small sample size and the use of fixed doses throughout the study. Renal function tests and cardiac parameters were not included in this study. However, this study still provides insights into the effects of khat extract, atorvastatin and their combination on electrolyte imbalance as a preliminary step for clinical trials.

5. Conclusion

Khat and atorvastatin alone or in combination can reduce body weight and potentially induce hypernatremia, hyperchloremia and hypocalcemia, with no obvious effects on serum potassium levels in the rat model. Therefore, clinicians should be aware of these electrolyte imbalances induced by khat and statins in people who chew khat. Clinical studies are needed to better understand the mechanisms behind these effects and to determine the extent of risk in the human population.

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Ethical approval

The experimental protocol was approved by the Research Ethics Committee of the University of Science and Technology, Sana'a, Yemen (Ethical Clearance No.: 1445/003/UREC/UST). In addition, all efforts were made to minimize animal suffering.

Conflict of Interest

The authors declare no conflict of interest associated with this article.

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