Acute oral administration of Khat (*Catha edulis*) aqueous extract elevates blood pressure and prolongs QT and QTC intervals in Wistar albino rats

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ABSTRACT

الأهداف: دراسة التأثيرات الحادة لتناول نبته القات على مستوى ضغط الدم وتخطيط القلب لدى الفئران.

الطريقة: أُجريت هذه الدراسة خلال الفترة من يناير إلى فبراير 2009م في معامل جامعة الملك خالد بقسم علم وظائف الأعضاء في كلية الطب، أبها، المملكة العربية السعودية. تمت التجارب على مجموعتين من فئران ويستير البيضاء، وفي كل مجموعة 10 فئران تزن 200–190 غرام. لقد تم إعطاء المجموعة الأولى (مجموعة الشاهد) عن طريق الفم محلول يحوي الماء والملح، بينما تم إعطاء المجموعة الثانية (مجموعة الدراسة) مستخلص نبته القات. وتم تسجيل ضغط الدم وتخطيط القلب خلال 60 دقيقة. ولقد قمنا بتجميع وتحليل البيانات كل 10 دقائق، وبعد ذلك قمنا بعمل مقارنة بين المجموعتين.

النتائج: أدى تناول نبتة القات إلى زيادة في ارتفاع ضغط الدم بنوعيه الانقباضي والانبساطي وذلك عند الفئران التي تناولت مستخلص نبته القات (ضغط الدم الانقباضي– 34.1%، والانبساطي– 46.2%). كما أن معدل نبضات القلب قد زاد أيضاً لدى نفس المجموعة وكانت أكبر زيادة عند الدقيقة الأربعين (12.8%). أما بخصوص نتائج تخطيط القلب فقد كان هناك نقص ذو أهمية إحصائية في الفترات بي أر بحيث كان ذلك أكثر وضوحاً عند الدقيقة الأربعين من بدء التجربة (15.2%–)، بينما كان هناك زيادة في فتره كيو تي وكيو تي سي المصححة بدء ذلك بعد عشرين دقيقة من بدء التجربة وكانت أكبر زيادة عند الدقيقة الستين (كيو تي– 11.6%، كيو تي سي– 9.1%).

خاتمة: أشارت نتائج الدراسة بأن هذه التغيرات في تخطيط القلب عند الفئران التي تناولت نبته القات يستوجب علينا أن نأخذ في الحسبان التأثير الضار لتناول هذه النبتة على وظائف القلب.

Objectives: To investigate the effect of Khat (*Catha edulis*) acute administration on blood pressure (BP) and electrocardiogram (ECG) in vivo.

Methods: This study was performed between January and February 2009 at the Physiology Laboratory, Medical College of King Khalid University, Abha, Kingdom of Saudi Arabia. Two groups of Wistar rats (n=10), weighing 190-200 g were divided into control group and Khat treated group. Throughout the study, arterial BP and ECG were recorded for 60 consecutive minutes. The data were collected and analyzed by Power Lab Data Acquisition System every 10 minutes, and were compared within and between the groups.

Results: Oral administration of Khat resulted in significant time dependent increases in both systolic and diastolic BP with a maximum increase at minute 60 after extract administration (systolic BP - 34.1%; and diastolic BP - 46.2%). Heart rate was significantly increased at all minutes of the study with a maximum increase occurring at minute 40 (12.8%). There was a significant decrease in PR interval through the experiment, and the maximum decrease was observed at minute 40 (-15.2%). However, QT and QTc started to widen 20 minutes after extract administration with a maximum prolongation in both intervals to occur at minute 40 (QT - 11.6%; QTc - 9.1%).

Conclusion: These newly reported changes in the ECG of rats after Khat administration should be a warning regarding the cardiac hazards of Khat chewing.

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Cardiovascular disorder (CVD) is a broad term, which includes any condition causing pathological changes in blood vessels, cardiac muscle or valves, and cardiac rhythm. The electrocardiogram (ECG) offers a quick, non-invasive clinical and research screen for the early detection of CVD. Several ECG indices have been proposed to identify patients at risk of sudden death, including the QT interval length and/or dispersion.[1,2] Early ECG changes in raw and corrected QT intervals are indicators of evolving CVD and increased cardiovascular risk.[2] Prolonged QT and QTc intervals are considered reliable predictors of heart disease and fatal ventricular arrhythmias.[3,4] The habit of Khat (*Catha edulis*) chewing is considered a major medical and socio-economic problem in the many countries in the world.[5] People chew fresh young Khat leaves for its stimulant and pleasurable effects.[6] The stimulating and euphoric effects of Khat can provide a strong incentive for the user to obtain his daily supply, and to spend hours indulging in Khat chewing periods, especially as tolerance develops with regular use.[6] Intuitively, Khat has for long been considered harmful to health and especially its bad effect on the cardiovascular system. Current literature contains an increasing number of reports on this issue, and the list of possible adverse health effects of Khat chewing is rapidly expanding. Cerebral hemorrhages, myocardial insufficiency including infarcts, and pulmonary edema have been described after Khat intake.[7] Moreover, Ridder et al[8] have reported a case of Khat-induced thrombosis in 2 vascular territories. A well-performed study has confirmed earlier observations of worse in-hospital outcome among acute coronary syndrome patients who chew Khat, as shown in a previous study,[9] the importance of improving education concerning the cardiovascular risks of Khat chewing. However, the association between Khat-chewing and myocardial infarction (MI) has been reported by several workers, and in a case-control study, it has been reported that Khat-chewing increased the risk of MI, with an odds ratio of 3.[10] Al-Motarreb et al,[11] reported that Khat-chewing resulted in a significant shift in the presentation time of MI, most MI cases in Khat-chewers occurred in the afternoon. However, a well designed case-control study showed that after adjustment for the effect of potential confounders, that Khat chewing was associated with an increased risk of MI in a dose-dependent manner; heavy chewers had a 39-fold increased risk of MI.[12] More recently, we have reported that acute exposure to Khat extract exerted negative inotropic and chronotropic effects in vitro on isolated rabbit's hearts.[13] We showed that the extract had a vasoconstrictor effect on coronary vessels, independent of $\alpha 1$ adrenergic receptor stimulation. Histological examination of hearts perfused with 250 mg/ml of Khat hydroethanol extract was consistent with MI, whereas the levels of cardiac enzymes were high in the perfusates. Little is known regarding the effect of Khat on ECG changes in animals or human. This study was designed to determine the effect of Khat on ECG and blood pressure (BP) alteration in unconscious Wistar rats.

Disclosure. The authors have no conflict of interests, and the work was not supported, or funded by any drug company.

Methods. *Preparation of Khat shrub extract and dose selection.* This study was performed at the Physiology Laboratory, Medical College of King Khalid University, Abha, Kingdom of Saudi Arabia (KSA) from January to February 2009. The study was approved by the Ethical Committee of Scientific Research at the College of Medicine at King Khalid University, KSA, and all procedures were carried out in accordance to the National Institute of Health Guide for the Care and Use of Laboratory Animals. Fresh Khat whole plant were obtained from the General Department of Narcotics Control of Aseer region of southwestern KSA. The plant material was washed, dried, and extracted with 500 ml of water ethanol-mixture (70/30% V/V) at room temperature, and then filtered. Ethanol was removed from the filtrate by vacuum evaporization at 40°C. The resulting ethanol-free extract, which constituted approximately 5% of the original dry material was dissolved in freshly prepared normal saline to the desired final concentration.[13] Each rat in the treated group received the extract to a final concentration of 3 g/kg.

Dose selection. The dose used in our study was calculated according to the equation of Reagan-Shaw et al,[14] based on translation from human equivalent dose (HED), which is 0.5 g/kg that Khat-chewer consume in chewing sessions.[15,16] The dose was calculated to be approximately 3 g/kg rat's weight. The formula of dose translation used was as the following:

HED (mg/kg) = Animal dose in mg/kg x Animal Km / (human Km).

where: rats Km = 6, and adult human Km = 37[14,17]

Animals, surgical procedure, and experimental design. Twenty Wistar male-albino rats aged between 14 and 16 weeks, and weighing between 190-200 g,

which were obtained from the Animal House of the Medical College at King Khalid University, Abha, KSA were used for the study, fed standard rat pellets, and allowed free access to water. They were housed in plastic cages (5 rats/cage) at a controlled ambient temperature of 22 ± 2°C, and 50 ± 10% relative humidity, with 12 hour light/12 hour dark cycles. The rats were divided into 2 groups (n=10 each), and were classified as control and Khat treated groups. Before the beginning of the experimental procedure, the rats of both groups was anesthetized with Urethan (1.0 g/kg, intraperitoneally, Sigma Corp, Roedermark, Germany). The right carotid artery was located, and prepared for cannulation to measure the systemic arterial BP. The time required for the surgical procedure and preparing the carotid artery for cannulation was approximately 5 minutes. Directly after the surgical procedure, rats in the first group were treated with normal saline orally using stainless steel cavage needle, while rats of the second group were treated with Khat (equivalent to 3 g/kg per body weight) in the same route, and rapidly transferred to a well temperature-controlled table. All treatments were given to a final volume of 0.6 ml. Three touch electrodes (MLA1214, AD Instruments, New South Wales, Australia) that are connected to animal bioamplifier (FE136 Animal Bio Amp, AD instruments, New South Wales, Australia) were attached to the skin of the animals in a standard 3 positions for ECG recording. After that, the carotid artery was cannulated and attached to a fluid filled pressure transducer (MLT0670, AD Instruments, New South Wales, Australia) that is connected to a bridge amplifier (FE117 BP Amp, AD Instruments, New South Wales, Australia). The arterial line was prefilled with heparinized saline (50 U/ml). The signals recorded by BP and animal bioamplifier were collected by Power Lab Data Acquisition System (PL3516/P PowerLab 16/35, AD instruments, New South Wales, Australia), recorded and analyzed by Labchart Pro 7.2 software (AD Instruments, New South Wales, Australia). Later, the recorded ECG was used to calculate heart rate (HR), R-R, QRS, PR, QT and QTc intervals utilizing the same software. Throughout the experiment, the body temperature was maintained at 38°C. The time from the beginning of the recording was considered as 0.0 minute (between 2-3 minutes after any treatment). Corrected QT (QTc) was calculated with the help of Bazett's formula installed in the software.

Statistical analysis. Mean HR, RR, QT, and QTc were compared within, and between the groups at 0.0, 10, 20, 30, 40, 50, and 60 minutes by one-way ANOVA using the Statistical package for Social Sciences version 16 (SPSS Inc, Chicago, IL, USA) followed by Tukey's test. Data were expressed as mean ± standard deviation, and graphs were created utilizing GraphPad Prism (version 5). Statistical significance is defined at $p \leq 0.05$.

Results. All the data recorded in this study were compared within the groups at different time intervals

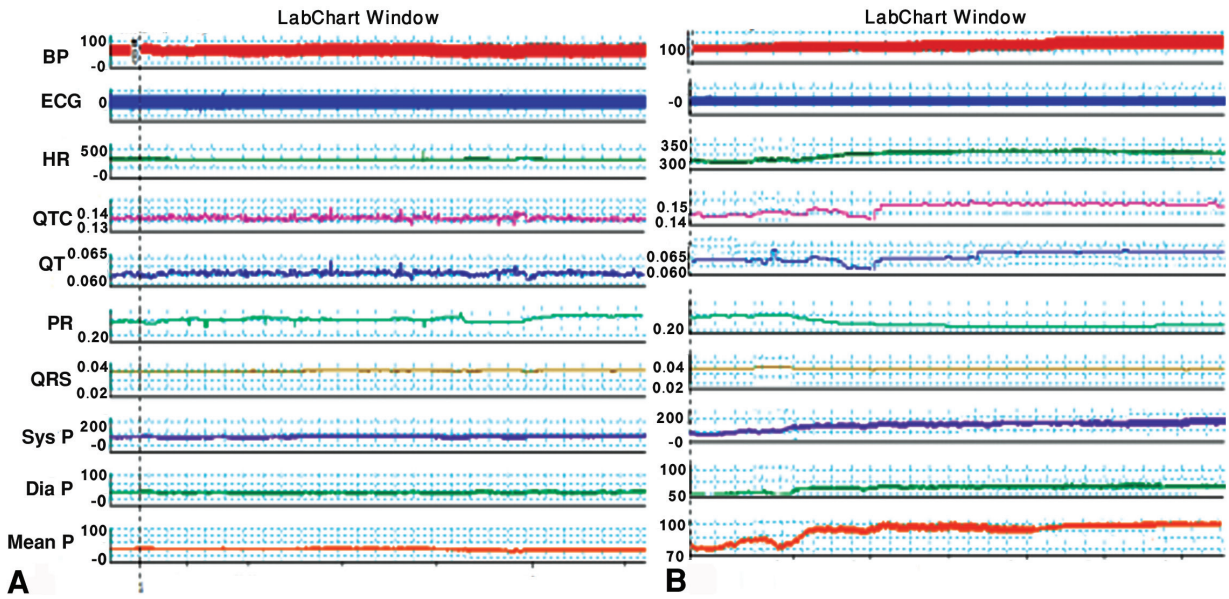

Figure 1 - Recording of blood pressure (BP) (channel 1) and electrocardiogram (ECG) (channel2) from the control group (**A**) and Khat treated group (**B**). The heart rate (HR), QTc, QT, PR, QRS intervals (channel 3 - channel 7) in each group were derived from the ECG channel. Sys - systolic, Dia - diastolic, P- pressure

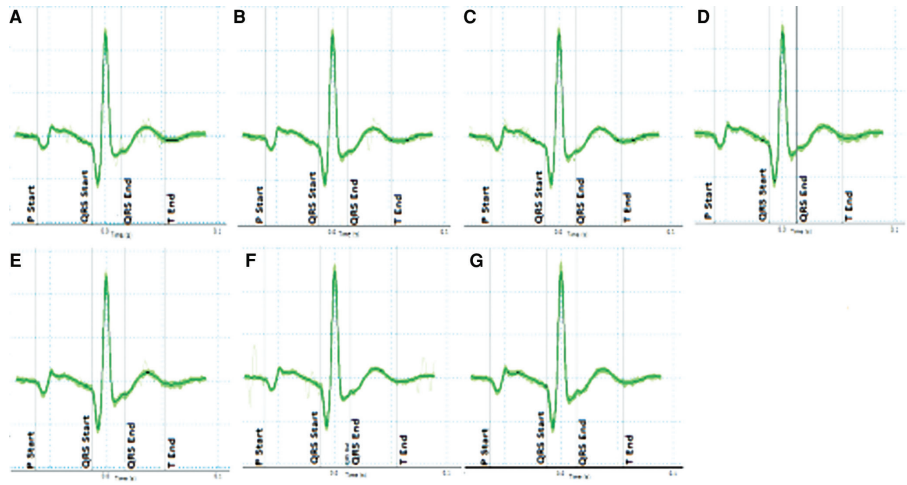

Figure 2 - Electrocardiogram tracings of control rats administered with normal saline recording at: **A**) 0.0 minutes; **B**) at 10 minutes; **C**) at 20 minutes; **D**) at 30 minutes; **E**) at 40 minutes; **F**) at 50 minutes; and **G**) at 60 minutes.

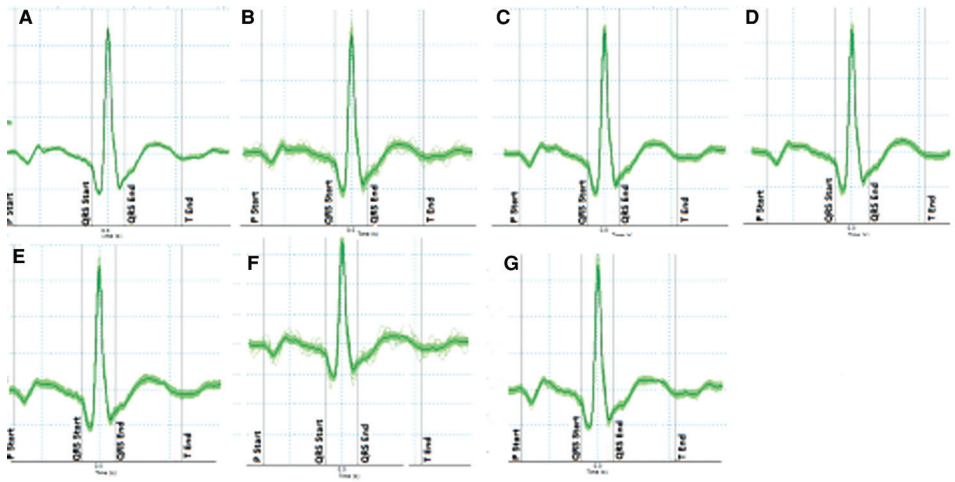

Figure 3 - Electrocardiogram tracings of Khat treated rats recording at: **A**) 0.0 minutes; **B**) 10 minutes; **C**) 20 minutes; **D**) 30 minutes; **E**) 40 minutes; **F**) 50 minutes; and **G**) 60 minutes.

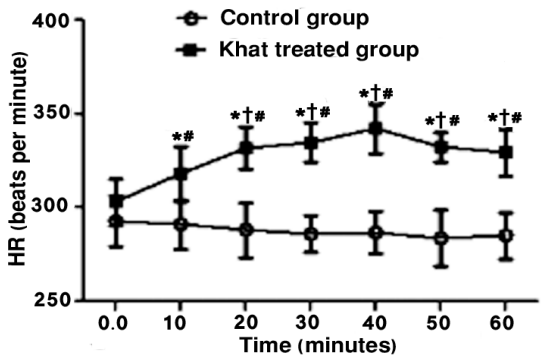

Figure 4 - Changes in heart rate (HR) in the control and Khat treated group. Values are expressed as mean ± SD for groups of 10 rats each. Values are statistically significant at $p<0.05$. *significantly different when compared to 0.0 minutes of the same group; †significantly different when compared to 10 minutes; and #significantly different when compared to the same period of the control group.

(10, 20, 30, 40, 50, and 60 minutes) with their specific baseline reading (0.0 minute), and between groups at the same corresponding time intervals. The raw data were recorded on the Powerlab software are shown in **Figure 1**. Notice the clarity of onset of the QRS complexes, and of the end of T waves (**Figures 2 & 3**). Plots of means HR, PR, QT and QTc versus time (minutes) in the control group administrated with normal saline, or in the experimental group treated with Khat hydroethanol extract are shown in **Figures 4-6** for groups of 10 rats each.

Blood pressure and ECG alteration in saline treated rats (Table 1, Figures 2, and Figures 4-6). Oral administration of normal saline did not affect the arterial BP, HR, RR, QRS, QT or QTc intervals during all the time intervals of the study. Furthermore,

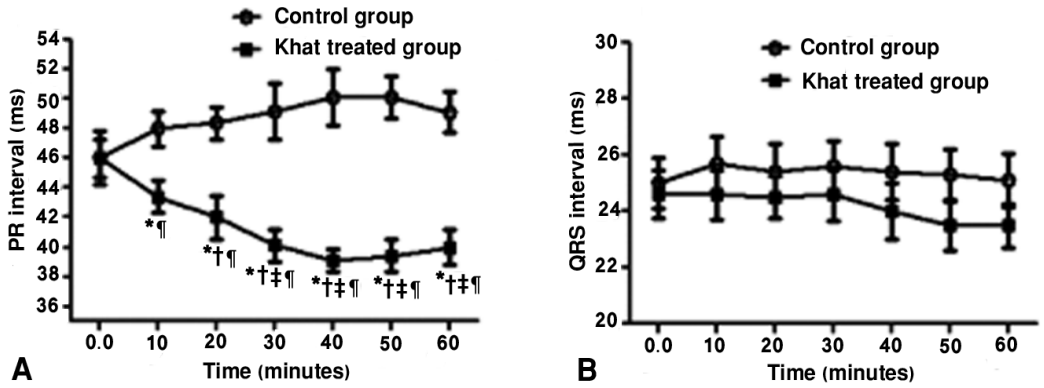

Figure 5 - Changes in PR intervals (**A**) and QRS durations (**B**) among the control and Khat group. Values are expressed as mean ± standard deviation for groups of 10 rats each. Values are statistically significant at $p<0.05$. *significantly different when compared to 0.0 minutes of same group; †significantly different when compared to 10 minutes; ‡significantly different when compared to 20 minutes; and ¶significantly different when compared to the same period of the control group.

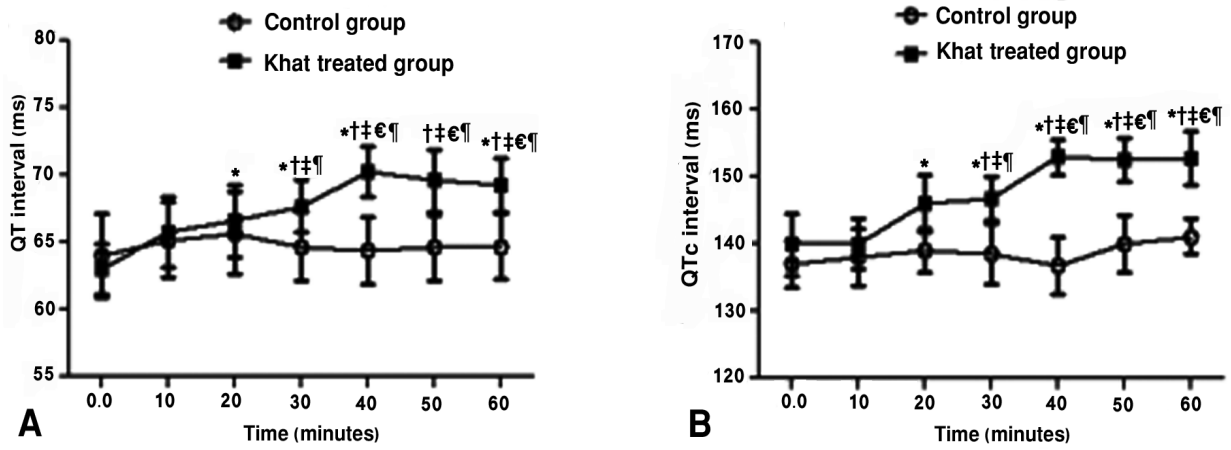

Figure 6 - Changes in QT (**A**) and QTc intervals (**B**) among the control and Khat treated group. Values are expressed as mean ± standard deviation for groups of 10 rats each. Values are statistically significant at $p<0.05$. *significantly different when compared to 0.0 minutes of the same group; †significantly different when compared to 10 minutes; ‡significantly different when compared to 20 minutes; €significantly different when compared to 30 minutes; and ¶significantly different when compared to the same period of the control group.

Table 1 - Changes in arterial blood pressure in the control and Khat treated Wistar rats included in a study performed at the Physiology Laboratory, Medical College of King Khalid University, Abha, Kingdom of Saudi Arabia.

Time, minutes	Control group			Khat treated group		
	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP
	mm Hg			mm Hg		
0.0	76.2 ± 3.54	50.3 ± 2.1	58.8 ± 2.13	75.2 ± 4.1	51.7 ± 3.17	60.01 ± 2.87
10	76.4 ± 3.02	48.6 ± 3.01	57.7 ± 1.23	82.6 ± 2.56*‡‡	59.3 ± 3.78	67.98 ± 3.01
20	78.5 ± 2.40	48.9 ± 4.53	57.6 ± 1.67	87.3 ± 3.34*†‡‡	64.8 ± 4.01	72.52 ± 2.34
30	79.5 ± 3.07	47.2 ± 4.67	59.0 ± 2.13	88.1 ± 3. 56*†‡‡	64.7 ± 2.67	72.25 ± 3.01
40	80.7 ± 2.98	48.9 ± 4.89	59.0 ± 2.32	89.5 ± 2.46*†§‡‡	65 ± 63.21	72.25 ± 2.98
50	80.1 ± 3.65	49.2 ± 3.12	59.2 ± 1.98	96.1 ± 1.98*†‡§¶‡‡	70.01 ± 3.21	78.81 ± 3.02
60	80.3 ± 1.12	49.3 ± 2.8	59.6 ± 1.96	101 ± 2.09*†‡§¶††‡‡	75.69 ± 2.45	84.01 ± 2.31

Values are expressed as mean ± standard deviation for groups of 10 rats each. Values are statistically significant at $p<0.05$. MAP - mean arterial pressure; *significant when compared to 0.0 minutes of same group; †significantly different when compared to 10 minutes; ‡significantly different when compared to 20 minutes; §significantly different when compared to 30 minutes; ¶significantly different when compared to 40 minutes; ††significantly different when compared to 50 minutes; ‡‡significantly different when compared to the same period of the control group

the baseline readings (zero readings) of the parameters studied among the rats administered with Khat were not significantly different compared to the rats administered with normal saline (**Figures 2, 4-6** and **Table 1**).

Effect of Khat on arterial BP (Table 1). The data of this study revealed that there was a time dependent significant increase in both systolic and diastolic BP over all the time intervals of the study as compared to their 0.0 minute's readings. The peak increases in both systolic and diastolic BP were observed at minute 60 after extract administration. The percents of increase in systolic BP after extract administration (in minutes) were: 9.8% (p=0.034) at 10; 16.1% (p=0.023) at 20; 17.5% (p=0.001) at 30; 19% (p=0.001) at 40; 27.8% (p=0.001) at 50; and 34.1 % (p=0.001) at 60 minutes, while the percent of increases in diastolic BP at the same time intervals were: 14.7% (p=0.006) at 10; 25.3% (p=0.001) at 20; 25.2% (p=0.001) at 30; 25.7% (p=0.001) at 40; 35.4%(p=0.001) at 50; and 46.2% (p=0.001) at 60. When compared to the control group treated with normal saline, the increases in systolic and diastolic BP in the Khat group were also significantly higher at all study time intervals (10-60 minutes) with a percent of increase at a corresponding time intervals: 8.1% (p=0.043) at 10; 11.2% (p=0.045) at 20; 10.8 (p=0.013) at 30; 11% (p=0.012) at 40; 19.9% (p=0.001) at 50; and 26.3% (p=0.001) at 60 in systolic BP; and 22% (p=0.011) at 10, 32.7% (p=0.001) at 20; 32.5%(p=0.001) at 30; 32.9% (p=0.001); 42.2% (p=0.001), and 53.5% (p=0.001) in diastolic BP.

Effect of Khat on HR (Figure 4). The HR increased progressively and significantly (p<0.05) among Khat treated group over all time intervals when compared to their baseline readings, with a maximum reading at 40 minutes. The percent of increases in HR at these time intervals were 5.0% (p=0.032), 9.0% (p=0.012), 11.2% (p=0.010), and 12.8% (p=0.006). Although the HR began to decline in a time dependent manner at 50 and 60 minutes after extract administration, it remained significantly higher than its baseline readings with a percent of change of approximately 9.6% (p=0.007), and 8.06% (p=0.002). The ANOVA test revealed that the increases in HR at all time intervals after extract administration were significantly higher (p<0.05), when compared individually to the corresponding time intervals in the control group with percent of increases in HR at 10-60 minutes of 9.2% (p=0.035); 15.2% (p=0.013); 17.1% (p=0.004); 19.1% (p=0.001); 16.9% (p=0.001); and 15.5% (p=0.001).

Effect of Khat on PR intervals and QRS durations (Figure 5). There was a progressive and significant decrease in the PR intervals among the rats treated with Khat (p<0.05) when compared with their baseline readings, and the control group in a time dependent manner during the whole period of the study with maximum decrease observed at 40 minutes. The percent of decrease of the PR intervals in the group of rats treated with Khat as compared to their base line readings are: -5% (p=0.034); -8.6% (p=0.018); -12.8% (p=0.013); -15.2% (p=0.001); -13.9% (p=0.001); and -12.8% (p=0.001); and when compared to their corresponding time intervals of the control group, the following values were obtained: -9.5% (p=0.006); -13.2% (p=0.002; -18.5% (p=0.001); -22% (p=0.001); -21% (p=0.001); and -18.5% (p=0.001). There was no significant change in the QRS durations among the rats treated with Khat throughout the study period when compared to its baseline readings, nor with that of rats in the control group.

Effect of Khat on QT and QTc intervals (Figure 6). In comparison to their baseline readings, the QT intervals at all minutes' intervals except at minute 10 were significantly prolonged. The maximum prolongation was observed at 40 minutes of Khat administration. The percents of increase in QT intervals (in minutes) were: 5.7% (p=0.041) at 20; 7.5% (p=0.032) at 30; 11.6% (p=0.01) at 40; 10.5% (p=0.001) at 50; and 10.0% (p=0.001) at 60. Similarly, the QTc intervals were also significantly prolonged at all time intervals except at 10 minutes as compared to their baseline reading with percents of increase in QTc after extract administration (in minutes) were: 4.3% (p=0.01) at 20; 4.8% (p=0.01) at 30; 9.3% (p=0.001) at 40; 8.9% (p=0.001) at 50; and 9.1% (p =0.001) at 60. When compared to the control group, the Khat treated rats showed no significant changes in both QT and QTc at 0.0, 10, and 20 minutes time intervals, while there was a significant increase in these parameters during the rest of the time intervals. The percent of increases in QT at different time intervals (in minutes) were: 5% (p=0.023) at 30; 9.1% (p=0.012) at 40; 7.7% (p=0.001) at 50; 7.1% (p=0.001) at 60; and for QTc: 6% (p=0.005) at 30; 12.4% (p=0.001) at 40; 8.9% (p=0.001) at 50; and 8.3% (p=0.001) at 60.

Discussion. In this study, BP and HR increased in Khat treated group at all time intervals (10-60 minutes) compared to their baseline (zero) readings, and to their corresponding time intervals of the control group administered normal saline. The effect of Khat chewing on HR and BP have been previously examined and reported by many investigators in an *in vivo* and *in vitro* studies.[11,12,16,18] Khat-chewers experience an increase in HR and BP. One possible cause of

elevated BP is assumed to be vasoconstriction.[16,19] Khat contains alkaloid cathinone, which mediate its sympathomimetic effects.[20] These substances stimulate the release serotonin and dopamine in the central nervous system, and noradrenaline from peripheral sympathetic neurons.[20] Cathinone has a similar action to amphetamine and cocaine causing an elevation in BP and HR proportional to blood levels, which peaks at 1.5 hour after chewing.[21] The later increases myocardial oxygen demand followed by catecholamine-mediated platelet aggregation and coronary vasospasm with subsequent myocardial ischemia and infarction.[19]

What is considered new and unique in our study is the ECG alteration of the rats after Khat extract administration. The major value of studying ECG in rat's heart is that it contains all of the tissues (that is, Purkinje, "M" fibers, endocardium, epicardium), receptors, and channels, on which a test compound might impact ventricular repolarization. Rat's heart is similar to that of a human, except it lacks the transient outward (ITO) channel.[22] The results of the present study have shown some differences in cardiac electrical activity with major alterations of PR, QT, and QTc interval after Khat administration. The PR interval is an index that correlates well with atrioventricular conduction, and an increase in this parameter indicates impairment in atrioventricular (AV) conduction, whereas a decrease in this parameter indicates an increase in the electrical conduction in the AV node. The present study showed that oral administration of Khat extract significantly reduced PR intervals in a time dependent manner with a maximum peak of decrease to occur at minute 40 indicating an increase in AV conduction, correlating well with the changes in HR. The significant increase in HR suggests that Khat has a positive direct effect on the rate of diastolic depolarization of the SA node.[1,2] This would indicate an effect on one of the 3 channels responsible for diastolic depolarization of the SA node: the inward rectifying K+ (IK1) 1998), 'funny' (If) and L-type Ca2+ (ICaL) channels.[23]

The QT interval, that is, the time elapsed for ventricular repolarization (ventricular refractory period) was also increased all through the 60 minute of the study with a peak increase occuring during the last 30 minutes where the data shows that the increases in QT intervals at 40, 50, and 60 minutes were insignificantly different to each other, but were significantly different when compared to the control group. A prolonged QT interval has been associated with cardiac arrhythmia and sudden death in humans.[2] At the cellular level, ventricular repolarization is prolonged in a number of cardiac disturbances such as myocardial hypertrophy, ischemia, and congestive heart failure.[24] Potassium channel sets the membrane potential, as well as the excitability of most livings cells. The K+ ions are predominantly responsible for the prolongation of QTc.[25] Lengthening of both QT and QTc indicate delayed ventricular repolarization, and may result from an effect of Khat on any, or all of the channels responsible for ventricular repolarization, such as rapidly activating K+ (IKr), and delayed rectifier K+ (IKs) channels.[26]

Although we did not observe any tachy-arrhythmia, which is expected to occur secondary to the long QT, this represent a limitation of this study, since the recording of the ECG and the whole study was short (60 minutes). However, long QT is a serious complication of Khat, and may contribute to the cardiac mortality associated with its consumption.

In conclusion, oral administration of Khat to rats caused an increase in BP and HR, and resulted in prolonged QT and QTc intervals, which must be added to the cardiac hazards of Khat chewing. Thus, further researches need to be carried out in human to clarify these findings.

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