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*Full Length Research Paper*

# Effect of single and daily khat (*Catha edulis*) extract on locomotor behaviour in CBA mice

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**It has been demonstrated that administration of cathinone is capable of increasing locomotor activity in animals. The present study was carried out with a psychostimulant *Catha edulis* extract. In this experiment, twenty CBA male mice, weighing 20 to 30 g, 5 to 6 weeks old were injected intraperitoneally with a single dose khat extract. Thereafter, they were continued to be injected daily with single daily khat extract for seventeen (17) days. The animals were divided into one controls group (injected 0.5 ml normal saline) and three experimental groups (injected 40, 120 and 360) mg/kg body weight khat extract, respectively. The animals were then submitted to open field task performance. Line crossings, centre square and rearing frequency were observed at 5 min block interval for 55 min. Single high dose (360 mg/kg) body weight khat extract significantly (P < 0.001) enhanced the line crossing in CBA mice. However, single low khat extract (40 and 120 mg/kg body weight) dose had no effect on the line crossing. On the other hand, single khat extract doses (40, 120 and 360 mg/kg) body weight significantly (P < 0.001) inhibited the centre square and rearing frequencies in CBA mice. Generally, single daily khat extract (40, 120 and 360 mg/kg) body weight treated CBA mice had significantly (P < 0.001) higher line crossings than control and single dose treated animals. The centre square and rearing frequencies were significantly higher (P < 0.05) in CBA mice injected with single daily doses of khat than the single dose treated group. However, mice treated with single daily doses (40, 120 and 360) mg/kg body weight khat extract had significantly (P < 0.05) lower rearing frequency than the control. Mice treated with 40 mg/kg b.wt single daily khat extract had higher (P < 0.05) centre square frequency than the control and mice injected with 120 and 360 mg/kg body weight khat extract. We demonstrate that repeated single daily khat causes behavioral sensitization, affecting both locomotor and anxiety behaviours.**

**Key words:** Locomotor activity, behavioural sensitization, khat, CBA mice, single and repeated daily dose, line crossing, centre square frequency, rearing frequency.

## INTRODUCTION

Khat, *Catha edulis* Forsk (family celestraceae) is a flowering evergreen shrub or small tree that either grows wild or cultivated in certain regions of East Africa and Southern Arabia. It has been known for centuries in East Africa, horn of Africa and the Middle East (Carlin, 2003; Connor et al., 2002). Khat is chewed for recreational purposes (Kennedy, 1987), and its valued psychostimulant effects (Baasher, 1980) is highest when fresh (Elmi, 1983). Fresh khat leaves mainly contains cathinone, an alkaloid thought to mediate the main psyc-hostimulant effects. This explains the khat users' preference for the fresh khat (Guantai and Maitai, 1982; Schorno et al., 1982). Cathinone is structurally similar to d-amphetamine, and because of their structural similarity, their psychological effects resemble and thus it has been referred to a natural amphetamine (Kalix, 1991). Khat also contains other alkaloids such as cathine and norephedrine, whose contribution to the physiological effects has not been elucidated. In the more economically developed countries, pure cathinone and methcathinone have been reported as substances of abuse but the compound

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are unknown in regions where khat chewing is a common practice (Sparago et al., 1996; Young and Glennon, 1998). This depicts the potential for artificial synthesis, use and abuse of this perceived social drug.

Cathinone one of the active ingredient of khat together with amphetamine acts by releasing catecholamines from presynaptic storage sites, inhibit re-uptake and stimulate release of dopamine in the central nervous system, thereby increasing the temporal and spatial presence of dopamine at the synaptic receptors (Krause et al., 2000; Safer and Krager, 1998). Studies carried out using laboratory animals, have reported increased locomotor activity in rats fed with *C. edulis* (Maitai, 1977). Similarly, other studies have presented evidence showing that (-) cathinone is capable of producing conditioned place-preference in rats at a dose (1.6 mg/kg) that produces increased locomotor activity (Calcagnetti and Schechter, 1992). Elsewhere, repeated oral administration of a standardised *C. edulis* extract (at a dose of 1 mg cathinone per kg body weight) or (-) cathinone (1.5 mg/kg) to rats, appeared to induce a strong locomotor sensitization (Banjaw, 2005).

Comparative studies of amphetamine and khat on physiological behaviours are numerous however, little is known on the effect of single and daily doses of methanol extracted khat extract administration on locomotor activity, exploration and anxiety. We have investigated the dose responses of line crossings, centre square and rearing frequencies as measures of locomotion and/or exploration and anxiety in CBA mice after single and daily khat extract administration.

## MATERIALS AND METHODS

### The experimental animals

Twenty male CBA mice, 5 to 6 weeks old and weighing 25 to 35 g, were bred in the Department of Medical Physiology, University of Nairobi. The animals were housed in groups of five in plastic wire meshed cages (30 x 15 x 12 cm) placed on a 0.75 m raised surface in the animal house. Wood shavings were used as beddings and were replaced every other day. The animals had access to standard rodent chow (Unga feeds, Nairobi) and fresh tap water *ad libitum*. The mice were kept under 10 h light: 14 h dark cycle (lights on: 0700 to 1700 h and lights off: 1700 to 0700 h). All experimental procedures on mice were conducted during the light cycle. The average room temperature and relative humidity were kept at 21± $^{1o}$C and 60%, respectively. The study was conducted in accordance with the internationally accepted principles for laboratory animal use and care (NIH publication # 85 – 23 revised 1985). In the subsequent days, the animals continued to be injected with the same dose of khat extract as above for seventeen (17) days. The animals were then subjected to another open field tests. The housing and other conditions resembled the conditions set above.

### Preparation of khat extract

Bundles of fresh khat were purchased from Westland, Nairobi local market. They were chopped on a glass plate, weighed (90.74 g) and then crushed with pestle and mortar. The crushed leaves were put into a flask and 800 ml of methanol was added to immerse the leaves completely. The mixture of khat material and methanol was stirred gently and then left to stand overnight. Filtration was done, first by use of gauze roll to separate the big particles, followed by Whatman No. 1 filter paper to remove the fine particles. Complete evaporation was achieved using Rotavac control evaporator (Heidolph, Germany) at 65$^0$C, 100 r.p.m and 240 pascal pressure.

The distillation took 2.5 h and was considered complete when all the methanol had evaporated with no drops coming out. The resultant extract weighed 32.47 g in a volume of 31.42 ml; this was used to prepare a working concentration of 1033.4 mg/ml. To determine the volume of the extract to be administered for example in a mouse weighing 26.5 g at a 40 mg/kg body weight, the weight of the mouse was multiplied by 40 mg/kg then divided by 1000 g and 1033.4 mg. Therefore, a mouse weighing 26.5 g was injected with a volume of 1.025, 3.075 and 9.225 µl at 40, 120 and 360 mg/kg body weight of khat extract, respectively. All the other doses and/or volumes for the animals were calculated based on weight and the formula above. The extract was administered by use of insulin syringes and accurate measurements of the extract were made possible using Finn pipettes. The dose of extract was adjusted to the final volume 0.5 ml using normal saline and administered intra-peritoneally. The extract containers were covered with aluminium foil to avoid light decomposition and were kept in a refrigerator. The doses were determined according to Al Meshal and colleagues (1991) who used 50 mg/kg body weight as their lowest khat extract dose in a 2n progression to investigate the toxicity of the plant.

### Experimental design

This was a randomized experimental study. Mice were handled for 5 min every day for the first two weeks prior to the experiment to habituate them to handling, the investigator and the experimental environment. The animals were allowed to acclimatize to the testing area for 15 to 30 min before the injection of khat or normal saline. All the experiments started at 0800 h and ended 1130 h every day. The animals were divided into 4 groups of 5 mice each. The controls were injected with 0.5 ml normal saline (0.9% solution of NaCl) and the treatment groups were injected with 40, 120 and 360 mg/kg body weight single dose of khat extract intraperitoneally (i.p) respectively. The final volume of the khat extract was made to 0.5 ml per injection for all the animals using normal saline.

The locomotor behaviours were observed during pre and post injection phases of khat extract. In the second experiment, CBA mice were divided into 4 groups of 5 animals. The controls were injected with 0.5 ml normal saline and the three treatment groups were injected with 40, 120 and 360 mg/kg body weight single daily dose of khat extract intraperitoneally (i.p) respectively for seventeen (17) days.

### Open field test

The open field test (Walsh and Cummins, 1976) is a locomotor behaviour assessment paradigm that provides simultaneous measures of locomotion, exploration and anxiety. The line crossings, rearing and centre square frequencies are used as measures of locomotor activity. However, the test also measures exploration and anxiety. A high frequency of the former behaviour indicates increased locomotion and exploration and/or a lower level of anxiety (Brown et al., 1999). The open field was constructed of white plywood; it measured 72 x 72 x 36 cm. One of the walls was clear plexiglass to allow viewing of mice. There were black lines drawn on the floor with a marker dividing the floor into a grind. The lines divided the floor into sixteen 18 x 18 cm squares (the squares are used because some mouse strains have high locomotor activity and cross the lines of the test chamber many times during a test

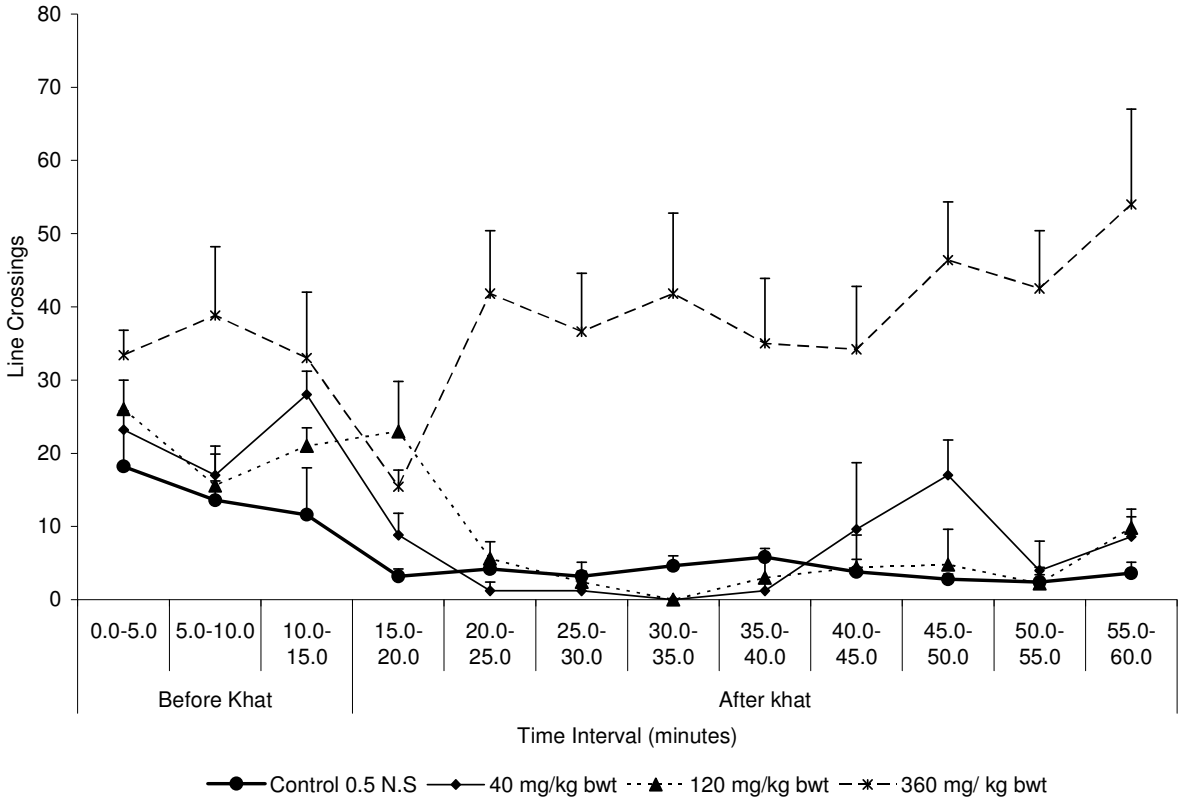


**Figure 1a**. Effect of single dose khat extract on line crossings in CBA mice. Data are presented as mean ± S.E.M. of line crossings between doses and over 60 min duration. Mice injected with 360 mg/kg b.wt khat extract had higher ($P < 0.001$) line crossings than mice treated with 40, 120 mg/kg b.wt and controls (n = 5 mice in each group).

session). The open field was located in 4.64 x 3.78 m test room with fluorescent lighting. Mice were placed individually in the centre of the open field and allowed to habituate and explore the apparatus for the first 15 min prior to administration of khat extract or normal saline.

Thereafter, the mouse was returned to the home cage and the open field box cleaned with 70% ethyl alcohol and permitted to dry between tests. Measures of line crossing, centre square and rearing frequencies (Brown et al., 1999) were scored at 5 min interval. The animals were then injected with khat at the predetermined doses and returned to the open field and scored for the locomotor measures at 5 min interval block for 40 to 55 min. Line crossings were scored manually by the investigator and an assistant. To maintain validity, mice activities were video taped with a video camera (image video camera (CAM) mounted 2 m above the field and connected to the VCR and TV. After the experiments, video tapes were replayed and the measures of locomotor activity were tallied and their means together with the manual tallies were determined and compared.

### Statistical analysis

Data for line crossings, centre square and rearing frequencies are expressed as mean ± S.E.M. Statistical analyses were carried out using the SPSS version 11. The differences in the mean among doses and time were analyzed using multivariate ANOVA followed by Bonferroni multiple comparison post hoc tests. The level of statistical significance was set at $P < 0.05$.

## RESULTS

Effect of single dose khat extract administration on locomotor activity in CBA mice. The results of the effect of singe dose khat extract on locomotor activity in CBA mice are presented in Figures 1a, 1b and 1c. The locomotor activity of all the mice were evaluated before and after injecting them with 0, 40, 120 and 360 mg/kg body weight doses of khat extract, respectively. The two phases (pre and post khat extract administration) were analysed together. Line crossings, centre square and rearing frequencies were scored. A multivariate analysis of variance test yielded a highly significant effect of doses ($F$ (3, 17) = 14.2; $P < 0.001$) and time ($F$ (11, 49) = 17.8; $P < 0.001$) on locomotor activity. The effect of interaction between doses and time on locomotor activity was also found to be significant ($F$ (47, 193) = 9.0; $P < 0.001$). A post hoc test with Bonferroni procedure revealed that the mean line crossing of mice treated with 360 mg/kg body weight khat extract was significantly higher ($P < 0.001$) than the control and mice treated with 40 and 120 mg/ kg body weight, respectively (Figure 1a). The results further showed that khat extract at 40 and 120 mg/kg body weight dose had no effect on line crossings. However, this parameter decreased ($P < 0.05$) over time in all the animals save for the animals treated with 360 mg/kg body

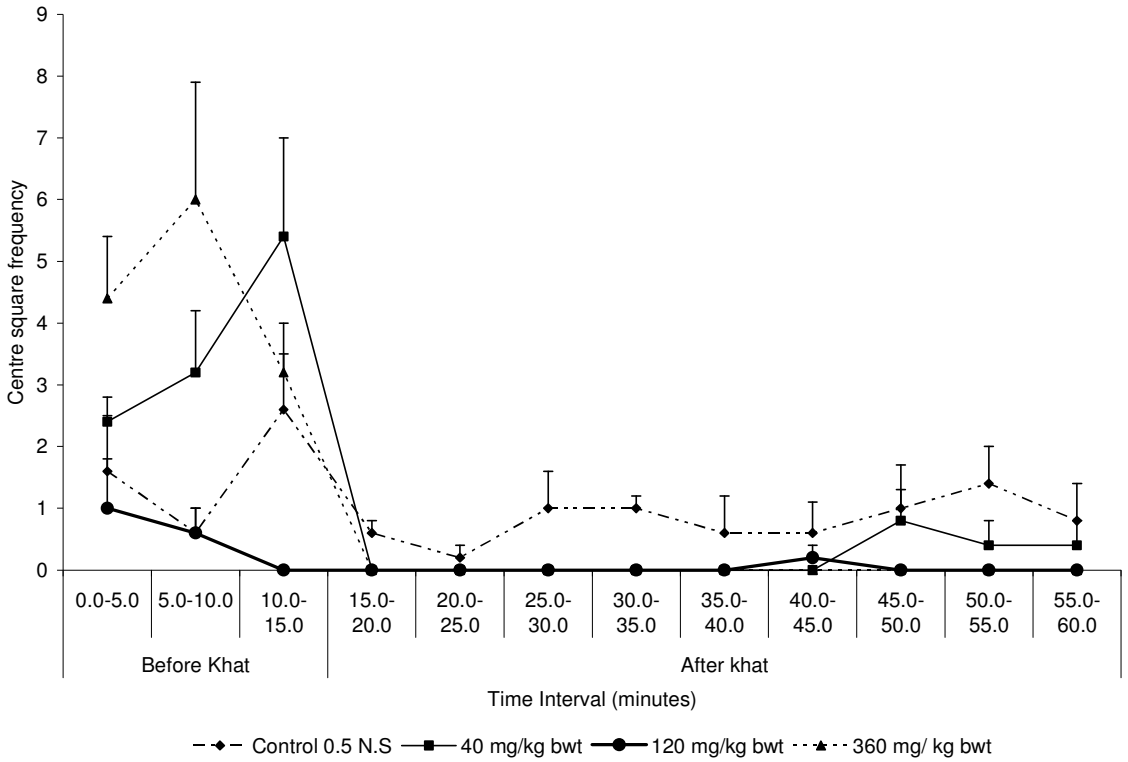


**Figure 1b.** Effects of single dose khat extract on centre square frequency in CBA mice. Data are presented as mean ± s.e.m. of centre square frequency. Mice treated with 40, 120 and 360 mg/kg b.wt khat extract had lower ($P < 0.05$) centre square frequency than the controls. The centre square frequency decreased significantly ($P < 0.05$) over time with significant ($P < 0.05$) decrease occurring between 15 to 35 minutes after injection (n = 5 mice in each group).

weight khat extract. A slight reduction in line crossings over the first 15 min (pre-injection) as the animal acclimatized to the test equipment was observed. This was followed by a reduction in the line crossings after 30 min following khat extract administration.

The centre square frequencies of CBA mice are shown in Figure 1b. The result show significant decrease in cenre square frequency across doses ($F$ (3, 17) = 13.9; $P < 0.001$) and time ($F$ (11, 49) = 6.8; $P < 0.001$), respecttively. The effect of dose and time interactions on centre square frequency was also found to be significant ($F$ (47, 193) = 3.5; $P < 0.001$). A post hoc test revealed that the mean centre square frequency of mice treated with 40, 120 and 360 mg/kg b.wt khat extract was significantly ($P < 0.05$) lower than the control. However, centre square frequency decreased significantly ($P < 0.05$) across time with significant ($P < 0.05$) decrease occurring between 15 and 35 min during post khat extract injection phase.

The results of rearing frequencies of the CBA mice are shown in Figure 1c. They show an increase in rearing frequency in the first 15 min, followed with 15 to 35 min interval of its absence and a subsequent gradual regain of this measure.

A multivariate analysis showed rearing frequency decreased significantly across doses ($F$ (3, 17) = 10.7; $P < 0.001$) and time ($F$ (11, 49) = 16.7; $P < 0.001$). The effect of interaction of dose and time on rearing was also found to be significant ($F$ (47, 193) = 8.3; $P < 0.001$). A post hoc test with Bonferroni procedure revealed that the rearing frequency of mice treated with 40, 120 and 360 mg/kg body weight was significantly ($P < 0.05$) lower compared to controls and the pre injection phase. The test also revealed that rearing frequency increased significantly ($P < 0.05$) during the first 10 min prior injection. The rearing frequency decreased between 15 and 45 min during khat extract administration phase, however, the decrease was not significant ($P > 0.05$). Thereafter, there was an increase in rearing frequency.

## Effect of single daily khat extract dose administration on locomotor activity in CBA mice

The results of the effect of repeated daily (17 days) khat extract dose administration on locomotor activity in CBA mice are shown in Figures 2a, 2b and 2c. The behaviours were evaluated before and after administration of 0.5 ml normal saline, 40, 120 and 360 mg/kg body weight khat extract, respectively. The two phases (pre- and post- khat extract injection phases) were analysed together. The line crossings, centre square and the rearing frequencies

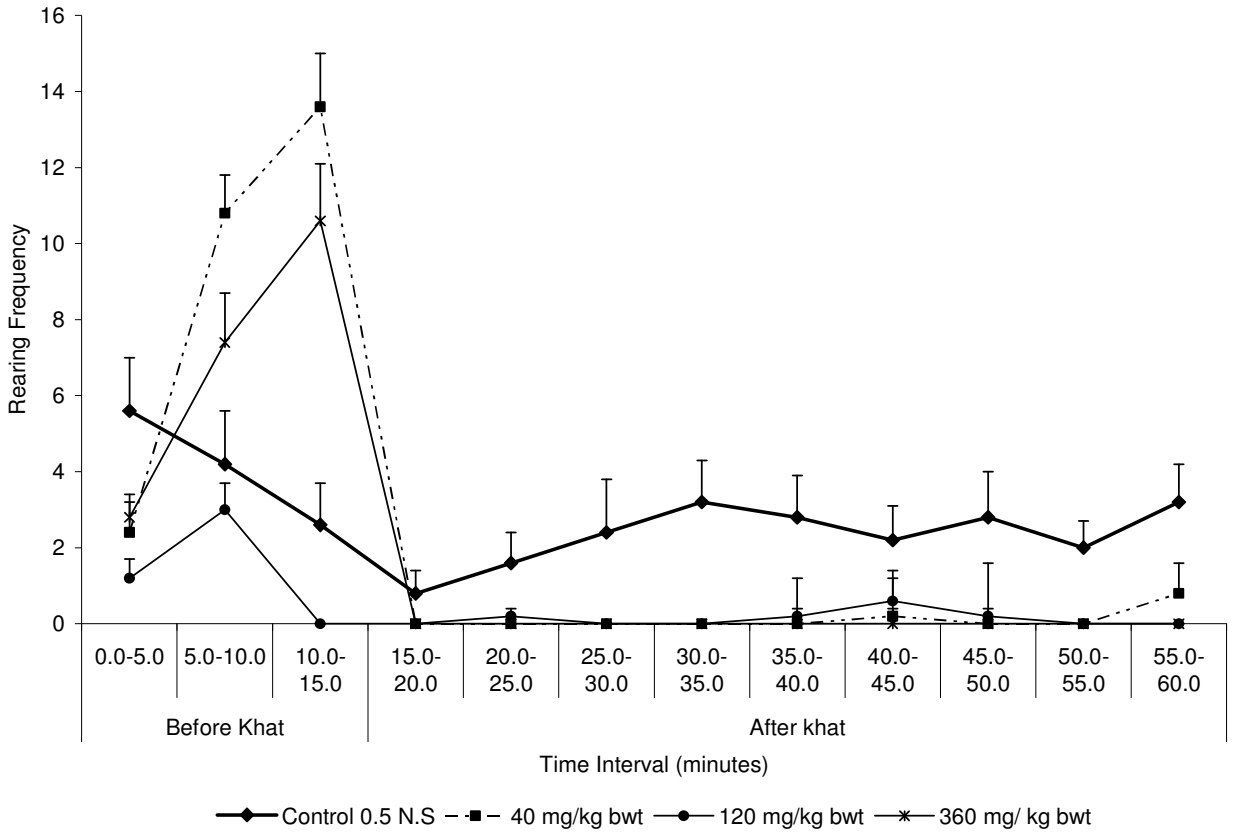


**Figure 1c.** Effect of single dose khat extract on rearing frequency in CBA mice. Data are presented as mean ± s.e.m. of rearing frequency. Mice treated with 40, 120 and 360, mg /kg b.wt khat extract had significantly ($P < 0.05$) lower rearing frequency compared to controls and pre-injection phase (n = 5 mice in each group).

were scored as the measure of locomotor activity. A multivariate analysis revealed highly significant effect of doses ($F$ (3, 17) = 18.82; $P < 0.001$) and time ($F$ (11, 49) = 3.17; $P < 0.05$) with no significant ($F$ (47, 193) = 0.94; P = 0.52) effect of the interaction of dose and time on locomotor activity.

A post hoc test revealed that the mean line crossings (17.08 ± 20.44), (34.68 ± 31.32), (50.32 ± 23.27) of mice treated with 40, 120 and 360 mg/kg body weight of khat extract were significantly ($P < 0.001$) higher than control group (5.64 ± 7.05) (Figure 2a). The effect of khat extract on line crossings appeared to be dose dependent. The mean line crossing decreased with time as the animal habituated prior and also during the first 20 min after khat injection phase. However, the decrease was not statistically significant.

The centre square frequency results are illustrated in Figure 2b. The figure shows a decrease in activity in a dose-related manner. The centre square frequency decreased significantly ($F$ (3, 17) = 5.74; $P < 0.05$) across doses but there was no significant change over time ($F$ (11, 49) = 0.52; P = 0.88) on this measure. The effect of interaction between dose and time on centre square frequency was not found to be significant ($F$ (47, 193) = 0.73; P = 0.74). A post hoc test revealed that the mean centre square frequency (2.8 ± 4.28) in mice treated with 40 mg/kg body weight of khat extract was significantly ($P < 0.05$) higher than control and mice treated with 120 and 360 mg/kg b.wt khat extract (1.61 ± 0.7) and (0.81 ± 1.22), (0.41 ± 0.68), respectively. In addition, the mean centre square frequency of mice treated with 360 mg/kg body weight was significantly ($P < 0.05$) lower than the controls and mice treated with 40 mg/kg body weight of khat extract.

The rearing frequency changed significantly across doses ($F$ (3, 17) = 23.89; $P < 0.001$) and time ($F$ (11, 49) = 2.64; $P < 0.05$). However, there was no significant effect ($F$ (47, 193) = 0.75; P = 0.76) of the interaction of dose and time on rearing frequency. A post hoc test showed that mice treated with 40, 120 and 360 mg/kg body weight of khat extract had significantly ($P < 0.05$) lower rearing frequency than the control (1.00 ± 1.77), (0.98 ± 2.75) and (1.3 ± 0.98) and (2.82 ± 3.5). In all animals, however, there were changes in rearing frequency across time but the changes were not significant. The results show that repeated single daily khat extract doses enhanced all the measures of locomotor activity in CBA mice in the 17 days period as compared to the mea-

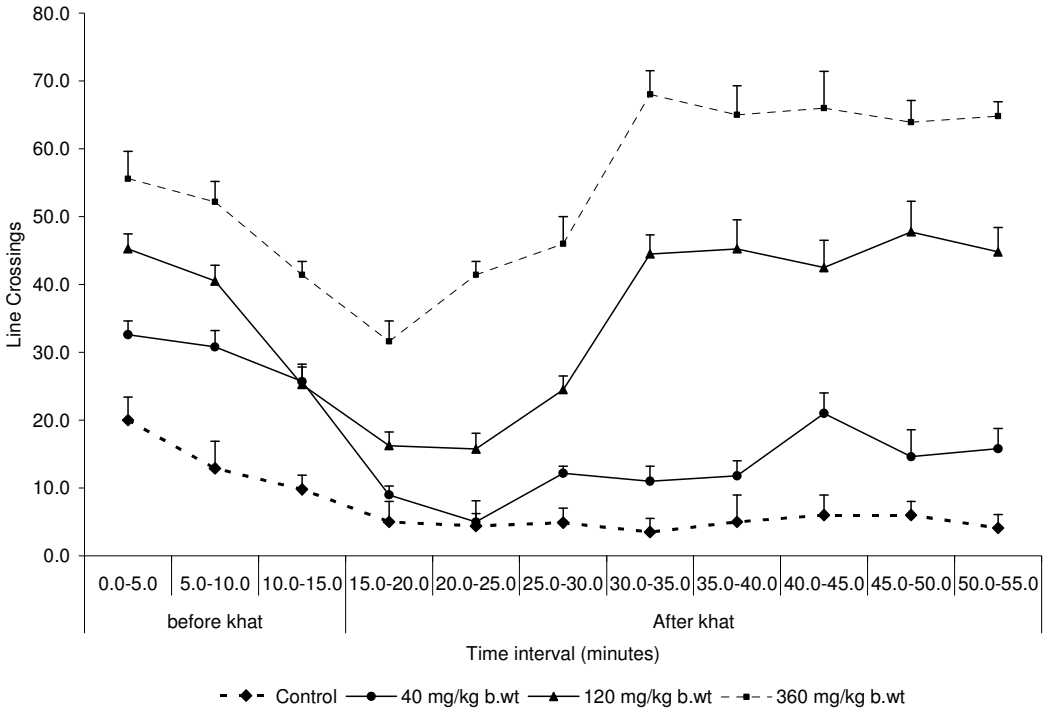


**Figure 2a**. Effects of single daily (17-days) khat extract doses on line crossings in CBA mice. Data are presented as mean ± s.e.m. of line crossings. Mice treated with 40, 120 and 360 mg/kg b.wt had significantly higher ($P < 0.001$) line crossings than the control (n = 5 mice in each group).

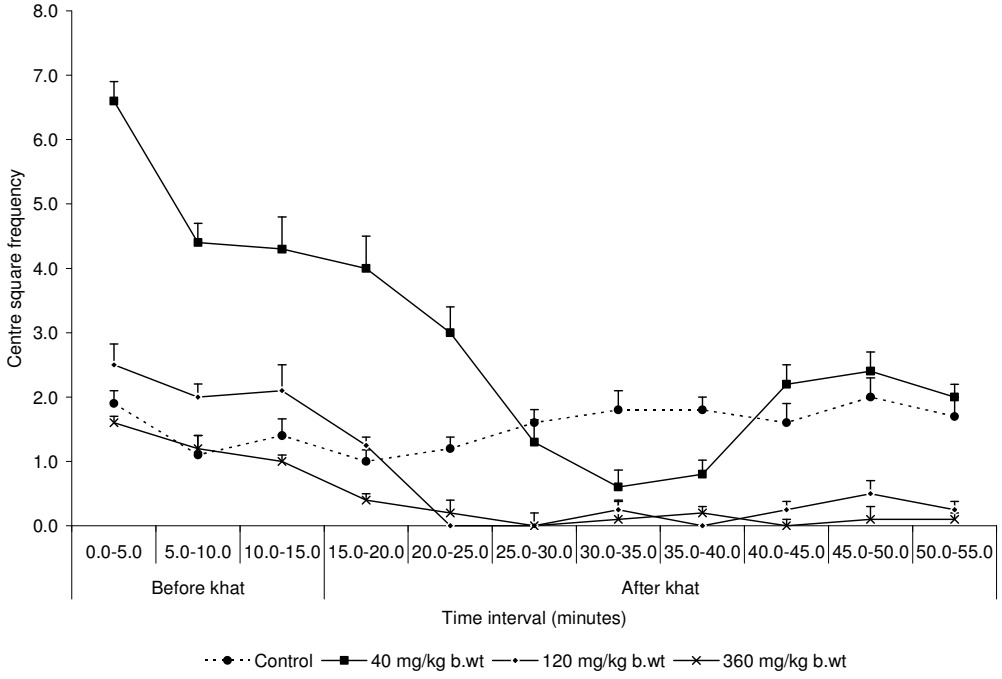


**Figure 2b.** The effects of single daily (17 days) khat extract dose administration on centre square frequency in CBA mice. Data are presented as mean ± s.e.m. of centre square frequency. Mice treated with 40 mg/kg b.wt khat extract had significantly ($P < 0.05$) higher centre square frequencies than controls and mice treated with 120 and 360 mg/kg b.wt of khat extract. The mean centre square frequency of mice treated with 360 mg/kg b.wt of khat extract was significantly ($P < 0.05$) lower than controls and mice treated with 40 mg/kg (n = 5 mice in each group).

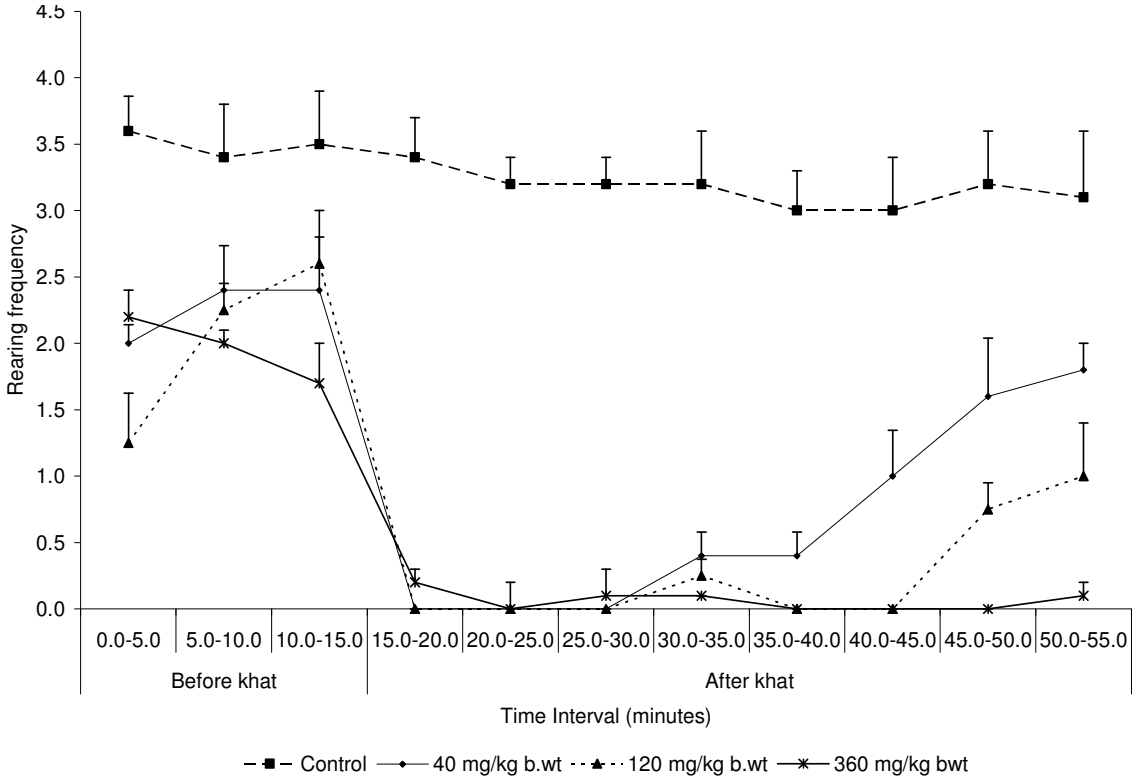


**Figure 2c.** The effects of single daily (17 days) khat extract dose on rearing frequency in CBA mice. Data are presented as mean ± s.e.m. rearing frequency. Mice treated with 40, 120 and 360 mg/kg b.wt khat extract had lower ($P < 0.05$) rearing frequency than the control (n = 5 mice in each group).

sures on the first day.

## DISCUSSION

The open field simultaneously provides measures of locomotion, exploration and anxiety (Walsh and Cummins, 1976). In the test, increased number of centre square frequencies and duration are indicative of low anxiety. On the other hand, increased line crossings and rearing frequencies are reflective of increased locomotion, exploration and/or a lower level of anxiety ((Brown et al., 1999; Podhorna and Brown, 2002). Defecation is another parameter often used as a measure of anxiety however; it has questionable validity (Lister, 1990). From the foregone, our results indicated that khat extract enhanced locomotion and exploration while it had mixed effects on the levels of anxiety depending on the parameter looked at. Based on line crossing the results are indicative of enhanced exploration and reduction of anxiety in CBA mice in a dose-dependent manner. On the other had, the result of the effect of khat extract on rearing and centre square frequencies are indicative of enhancement of anxiety levels, with high doses increasing it while low doses reducing the anxiety. The animals spent less time in the centre of the test arena than saline-injected mice indicating that their locomotor activity was thigmotactic rather than exploratory. In this regard, our findings are consistent with other numerous studies which have reported that khat induces hypomanic illness with grandiose delusions and paranoid or schizophrenic psychosis with persecutory delusions associated with mainly auditory hallucinations, fear and anxiety, resembling amphetamine psychosis (Tariq et al., 1983; Kalix, 1990; Pantelis et al., 1989; Yousef et al., 1995; Critchlow et al., 1987). The khat psychosis may be accompanied by depressive symptoms and sometimes by violent reactions (Pantelis et al., 1989). However, these symptoms rapidly abate when khat is withdrawn (Pantelis et al., 1989; Nielsen et al., 2004). In this study, however we did not investigate the effect of khat extract on defecation which could have confirmed the levels of anxiety in these animals.

Our results indicate that intraperitoneal administration of single dose of khat extract affected locomotor activity in a dose-dependent manner. Line crossings, were highest in mice injected with 360 mg/kg body weight khat extract but lower in doses less than 360 mg/kg body weight khat extract in a dose dependent manner. The khat used in this study did not show an inverted U-shape dose response curve, similar to the inverted U-shape response curve observed with amphetamines (Connor et al., 2002). However, animals injected with low doses of

khat extract exhibited locomotor activity similar to the control consistent with Connor and colleagues findings (2002). From the foregone, it appears the effects of the whole khat extract, with its many constituents, differ from amphetamines with regard to the production of locomotor activity and other behaviours.

The results on locomotor activity are consistent with a study carried out using methylphenidate hydrochloride (Ritalin), a non amphetamine psychostimulant (Penner et al., 2001), in which it increased the spontaneous locomotor activity of 7 to 11 day old CD-1 mouse pups, but the Ritalin treated pups spent less time in the centre of the test arena than saline-injected and non injected pups, indicating that their locomotor activities were thigmotactic rather than exploratory. Further, the results are also in agreement with the findings by Penner and colleagues that both low and high doses of methylphenidate hydrochloride administered chronically or acutely to CD-1 mice during infancy, increase locomotor activity on postnatal day 3 to 11 (Penner et al., 2001). In this manner, acute and chronic administration of khat have similar effects on locomotion as do other psychostimulants such as methamphetamine (Nazarian et al., 2000), cocaine (Kehoe and Boylan, 1992) and methylphenidate hydrochloride (Penner et al., 2001).

The maximum effect of khat extract was observed up-to $35^{th}$ minute; this observation is consistent with the fact that the maximum effect of cathinone is within 15 - 30 min upon intraperitoneal administration in rats reported by Schechter (1989). It has been documented that, the effect of cathinone occurs within 15 min under conditions that require 30 min for amphetamines (Cho and Segal, 1994). Recent studies have reported that, cathinone achieves a maximum plasma level within one hour following oral administration with a half life of approximately 3 h in humans (Zelger et al., 1980; Wilder, 1994; Toennes et al., 2003). Other studies have reported that psychostimulants have a shorter half life, and are more quickly metabolized in rodents compared to humans (Melega et al., 1995; Srinivas et al., 1992; Wargin et al., 1983). Indeed, peak plasma concentrations occurred at about 10 min following subcutaneous injection of cathinone in rats, compared to 15 to 30 min following oral administration (Cho et al., 1999; Wargin et al., 1983).

We also tested the effect of repeated daily khat extract administration on locomotor activity in CBA mice. The results demonstrate that single daily intraperitoneal administration of khat extract affected locomotor activity in a dose-related manner. The khat extract dose range used in this experiment spanned from 40 to 360 mg/kg body weight. The results showed an enhanced locomotor behaviour in a dose dependent manner. The daily doses of khat extract significantly enhanced line crossing in a dose dependent manner compared to the single dose effect. The centre square and rearing frequencies were enhanced at low khat extract doses and suppressed with increasing doses but the scores were higher than in mice injected with single dose khat extract. CBA mice treated repeatedly with khat extract, showed higher scores on all the measures compared to single dose khat treated CBA mice. The effect of both single and repeated daily khat extract doses on locomotor behaviour in CBA mice showed dose relationship. Low single dose khat extract had no effect on line crossings but enhanced this parameter in CBA mice when injected repeatedly for 17 days. Similarly, high single dose khat extract enhanced the line crossings in CBA mice if given repeatedly. The findings are the opposite of centre square frequency where low single dose khat extract showed higher centre square frequency than CBA mice treated repeatedly with low khat extract. The rearing frequency was inhibited by both high and low khat extract whether given as a single dose or as a repeated regime however, in the latter regime of khat extract administration, the scores of rearing frequency in CBA mice were higher.

Repeated daily doses of khat extract enhanced line crossings and rearing frequency in CBA mice than in a single dose regime; this is an indication of behavioural sensitisation. In this regard, our khat extract exhibited behavioural sensitization on locomotion and/or exploratory and anxiety behaviours. Behavioural sensitisation occurs when repeated treatment with psychostimulant drugs produces alteration in the behaviour that outlasts the initial neuropharmacological actions (Banjaw, 2005). This is usually illustrated by an increase in the magnitude of locomotor stimulatory effects (Robinson and Becker, 1986; Segal and Kuczenski, 1997). The progressive augmentation of behavioural responses to psychostimulants persists even after a long period of withdrawal and it develops rapidly even with relatively small doses of drug administered repeatedly in the same environment (Robinson and Becker, 1986; Stewart and Badiani, 1993). This phenolmenon is assumed to be due to mesoaccumbens dopamine projection embedded in the limbic circuit undergoing alteration. Investigations into the neural basis of behavioural sensitization has focused on mesoaccumbens projection because of vast literature implicating this dopamine pathways in the acute motor and reinforcing effects of amphetamine-like stimulants (Banjaw, 2005). The specific changes in the limbic circuit that promote behavioural sensitization are under control of experimental parameters such as the drug employed, dosage regimen, withdrawal period and the presence of conditioning cues (Robinson and Becker, 1986). The nature of persistent drug-induced neuro-behavioural adaptations is of interest because they are thought to contribute to the development of drug dependence, addiction and also psychopathologies, e.g. amphetamine psychosis (Robinson and Becker, 1986).

The locomotor activities are modulated by neurotransmitter dopamine and serotonin. Cathinone, the active compound of khat is associated directly and/or indirectly with dopamine or serotonin release, by its action on dopamine or serotonin transporter function (Banjaw et al.,

2003). In addition, cathinone is regarded as a dopamine releaser and acts through $D_1$, type dopamine receptors in mediating its reinforcing effects (Kalix, 1990). It has also been documented that cathinone and its close analogue amphetamine, increase the efflux of [$^3$H] dopamine from slices of rat striatum (Zelger and Carlin, 1983). Further, it has been demonstrated that the motor activities induced by S – (-) cathinone in experimental animals are associated with dopamine release (Glennon and Schowalter, 1981; Valterio and Kalix, 1982; Calcagnetti and Schecter, 1992). Recently it was reported that cathinone may act on nor adrenaline transporters (Rothman et al., 2003).

Quantifiable motor behaviours such as head twitches in mice and head shakes in rats are closely linked to brain serotonin mechanism whose release has been linked to S-(-) cathinone (Nielsen, 1985; Fleckenstein et al., 1999). However, in this study the head twitches and shakes were not studied in this experiment.

In conclusion, we demonstrate that single high dose khat extract causes increased locomotor behavior in CBA mice and repeated daily doses of khat extract increased locomotor behaviour and induced behavioural sensitization in CBA mice. In addition, the study indicates that Khat treatment results in mixed effects on anxiety related behaviours. Further studies should be carried out to investigate the effect of khat extract on exploration and anxiety using other behavioural paradigms such as elevated plus maze, light dark box and running wheel.

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