Effect of khat extract on young rat's memory

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ABSTRACT

Consumption of khat is still pressing issue in Jazan region. The present study was imperative to know the effect of khat use on memory of young rats. The current study used rats in age comparable to adult humans that mimic the stages of education and grouped in four groups. 1-control normal, 2-scopolamine, 3-khat extract administered group for four weeks, 4- khat withdrawal group administered khat extract for four weeks then left for one week without khat administration. All groups of rats were trained using Morris water maze task before treatment then the behavioral test was performed after treatments and cortex acetylcholinesterase (AChE) enzyme activities were determined in all groups. The body weights were detected weekly. The study showed that khat extract impaired performance in the water maze test, increased cortical AChE activity and reduced the body weight in a time related manner, meanwhile khat withdrawals showed partial retention of the maze performance, reduction in AChE activity and body weight gain. The study knocks alarm on cognitive impairment due to khat consumption especially on youth.

Key words: Khat; memory; Morris water maze; Acetylcholinesterase; body weight, rats.

INTRODUCTION

Khat (Catha edulis) is a flowering evergreen shrub or small tree that either grows wild or cultivated in countries bordering the Red Sea, along the east coast of Africa and in west Asia (Cox and Rampes 2003; Balint et al., 2009). In the Kingdom of Saudi Arabia, it has been reported that khat trees grown in the southern region, adjacent to the Yemen border. Chewers from Jazan region, located in the southwestern Saudi Arabia, use khat cultivated in Saudi Arabia or from Yemen. Chewing is still increasing at an alarming rate, especially among the younger population in high schools and institutions of higher learning (McClave et al., 2009; Alsanosy et al., 2013). The prevalence of khat chewing among male high school students and university students in Jazan province was estimated at 21% and 38%, respectively (Elsanosi et al., 2011). To manage this problem, the Saudi government has been trying to

control the expansion of chewing, cultivation, and trade of khat. In this regard, the Saudi government has enacted many policies and rules on the prohibition of khat chewing. However, even these strict government policies have failed to eradicate the chewing of khat in Jazan province (Ageely, 2009).

Khat chewing induces a state of euphoria and elation with feelings of increased alertness and arousal, which followed by a stage of vivid discussions, loquacity and an excited mood. Thinking characterized by a flight of ideas but without the ability to concentrate. Khat depressive users experience mood. irritability, anorexia and difficulty to sleep at the end of use (Nencini and Ahmed, 1989; Al Motarreb et al., 2002). In a study on adult healthy volunteers at Yemen, mood disturbances functional were reported during khat sessions (Hospital Anxiety and Depression scale). The effect on anxiety and depression was temporary

and had disappeared the next day (Hassan *et al.*, 2002a). Many Yemenite users, however, believe that khat chewing improves their sexual desire and excitement (Al Motarreb *et al.*, 2002). Khat chewing induced anorexia and insomnia (delayed bedtime) resulting in late wake-up next morning and low work performance the next day (Hassan *et al.*, 2002).

The present study aimed to evaluate the effect of khat extract on young rat's memory through behavioral assessment using Morris water maze task and determination of the acetylcholineesterase activity in brain cortex. Also, to evaluate the recovery occurred after stopping khat consumption as compared to rat model of memory dysfunction by scopolamine.

MATERIALS AND METHODS Experimental animals:

Forty animals of male young albino rats 3 months old equivalent, as adult socially mature, to the transition period between adolescence and adulthood in humans because the experimental period extended for more than 7 weeks later. Rats housed in plastic cages, kept under controlled temperature of 25±2 °C and 12h light/12h dark cycle throughout the experiment. A commercial rodent pellets diet were used during the experiment. The animals allowed adapting to the laboratory conditions for two weeks before the beginning of the experiment. Food and water were available ad libitum.

Test substances:

Scopolamine hydrobromide $(C_{17}H_{21}NO_4$. HBr) was supplied as a pure white powder from Sigma, St. Louis, Missouri, US. Khat methanolic extract.

Preparation of khat extract:

Khat extract was prepared according to the method described in Kimani and Nyongesa, (2008). Bundles of fresh khat were chopped on a glass plate, weighed (150 g) and then crushed with pestle and mortar. The crushed leaves put into a flask and 1000 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 Filtration overnight. was done bv Whatman No. 1 filter paper to remove the fine particles. Complete evaporation was achieved using evaporator and considered complete when the entire methanol had evaporated with no drops coming out. The resultant extract weighed. The animals were subjected to oral daily dose of 100 mg/kg body weight by oral gavage suspended CMC in (0.5)g/100ml carboxymethyl cellulose). Dose selection based on the average amount of khat leaves chewed daily by khat chewers (500 mg/kg of dry plant) (Al-Hashem et al., 2011)

Morris Water maze training

All rats used in this study received the training trials before treatments using modified Morris water maze (MWM) task, one of the most extensively used tools in behavioral neuroscience, to investigate spatial learning and memory (Morris, 1984; Choi et al., 2006). A black circular plastic pool (height 45 cm, diameter (120 cm) filled with water and kept at 22-25°C. An escape platform (diameter 14x14 cm) was submerged (0.5-1cm) below the surface of water. Pool was located in a room with varied distal room cues (such as posters, lamps), which are visible from the pool and can be used by rodents for spatial orientation. These extra-maze cues kept constant throughout the testing period. On training trials, the rats were placed in the pool of water (placed in a different quadrant at each trial), and allowed to remain on the platform for 10 s and then returned to the home cage. Rats that did not find the platform within 60 s were placed on the platform for 10 s. All rats received eight training trials as two times

per day for four consecutive days. During each trial session, the time taken to find the hidden platform (latency) was recorded.

Experimental design:

The trained male rats were divided into four groups :

- Control group received 1ml 0.5g/100ml carboxymethyl cellulose (CMC) for each 100 g body weight orally.
- 2. Scopolamine group treated as control and at 27th day received intraperitoneal single dose of scopolamine 2mg/kg.
- 3. Khat group received daily 100 mg/kg khat extract orally.
- 4. Khat withdrawal group, which treated as group 3, then left for one week without any treatment. Treatments extended for four weeks and body weight was recorded weekly. On the 28^{th} day, the test of the Morris water maze was performed then decapitated and brain samples were dissected immediately on ice. Morris water maze performed in khat one week withdrawal group then decapitated and brain samples dissection was done for separation of cortex area.

Acetylcholinesterase (AChE) activity assay:

AChE activity was determined by Ellman et al. (1961) method as described by Gorun et al. (1978). The principle of the method is the measurement of the rate of production of thiocholine produced because of acetylthiocholine hydrolysis. samples Brain cortex weighed and homogenized in saline (0.9% NaCl). The following reagents were pipettes in a cuvette: 0.15 ml phosphate buffer 20 mmol (pH 7.6). 0.05 ml of 5 mmol acetylthiocholine iodide and 0.01 ml of tissue homogenate. After 10 min of incubation at 38 °C, the reaction stopped with 1.8 ml of DTNB – phosphate ethanol reagent. The color was read immediately at 412 nm using Shimadzu spectrophotometer UV -2450. Omitting the enzyme from the incubation mixture made the control samples. The cholinesterase activity was determined as μ mol SH/min/g.

Statistical analysis:

Data were represented as means of escape latency times (sec) \pm SD using Statistical Processor System Support "SPSS" for Windows software, Release 20.0 (SPSS, Chicago, IL). Percentage change in body weight (PC-BW) from the initial body weight (BW) was estimated according to the equation:

PC-BW = ((test group mean BW- initial mean BW)/ initial mean BW) x 100.

In addition, the percentage change in acetylcholinesterase activities in tested groups (PC-AChE) was calculated according to the equation:

PC-AChE = ((test group mean AChE activity- control mean AChE activity)/ control mean AChE activity)x 100.

RESULTS

Assessment of the location of the escape platform in normal animals on the task before water maze treatment (pretreatment training session) was represented in Figure (1). It was obvious that there was a reduction in the latency time in seconds to find the platform from (59.70 \pm 0.67) in the 1st trial to (5.50 \pm 1.27) in the 8th trial confirming training. Data represented in Figure (2) about scopolamine group recording reversal of learning i.e the latency time to find the platform was increased significantly as compared to the training session in normal before treatment, recording (47.30 ± 4.80) in the 8th trial. Behavioral data about khat treated group represented in Figure (3) showed also impaired performance in the water maze test in the pre-trained rats due to the increased latency time to find the platform to be (48.70 \pm 5.31) and (41.10 \pm 4.83) in the 7^{th} and 8^{th} trials., respectively in the 4th day of training. The results declared the impairment of the spatial memory in the pre-trained animals

As data represented in Figure (4) about khat withdrawals showed retention of the location of the escape platform assessed in animals treated with khat recording decreased latency time to find the platform as compared to that recorded in khat group to be (17.20 ± 4.21) and (11.81 ± 4.81) in the 7th and 8th trials., respectively, in the 4th day of training. The aforementioned data were represented collectively in Figure (5).

The results of AChE activity measurement in cortex presented in Figure (6 A), showed significant increase in the enzyme activities in scopolamine, khat and khat withdrawal groups compared with the control value (p<0.05) recording 125.37%, 159.17% and 70.11%, respectively, as changes from control. percentage Meanwhile, khat withdrawal group exhibited significant decrease (p<0.05) in the recorded enzyme activity as compared to scopolamine or khat group's value.

(6B), Figure represents the percentage change in body weight of khat treated animals throughout the four weeks of the experimental periods and that for khat one week withdrawal which showed the time related reduction in body weight recording 4.62%, 15.71%, 18.92% and 22.08% in the 1^{st} , 2^{nd} , 3^{rd} and 4^{th} week, respectively, as percentage changes from control. Khat withdrawal group retained the loss in body weight significantly increased compared to the recorded values in khat group and recorded 1.30% percentage change from control.

DISCUSSION

The Morris water maze (MWM) is very useful for the evaluation of spatial learning and memory. The main advantage of this task allows the simultaneous evaluation of learning, spatial memory. The protocol describe, using a hidden platform, better evaluates the spatial learning and memory since animals must

build a spatial map to locate the submerged platform in the pool (Russig et al., 2003; Choi et al., 2006). Lesions in distinct brain regions like hippocampus, striatum, basal forebrain, cerebellum and cerebral cortex impair MWM performance (Chou et al., 2001; D'Hooge and De Deyn, 2001). In a modeling of stroke-induced seizures in animals memory impairments strategy. related to abnormal search suggesting that the spatial learning impairment resulted from corticostriatal rather than hippocampal damage. This was supported by the normal cytoarchitecture of the hippocampus (Karhunen et al., 2003). The results indicated that scopolamine injection induced impaired performance in the water maze test increased acetylcholinesterase activity. Scopolamine was used to induce memory deficits in animal models (Klinkenberg and Blokland, 2010). Acetylcholinesterase (AChE) is an important enzyme that rapidly hydrolyses acetylcholine (ACh), regulating the levels of this neurotransmitter in the synaptic cleft, thus terminating its action. Scopolamine, a nonselective muscarinic cholinergic receptor antagonist, was used widely to investigate cholinergic influence on learning ability in experimental animals (Jeong et al., 2008). Scopolamine pretrial administration memory impairment in caused the behavioral tests, and it was reported to be associated with dysfunction in central cholinergic system that plays an important role in the learning and memory (Bartus, 2000; Hasselmo, 2006) and blocking of muscarinic cholinergic receptors in the prefrontal cortex affects memory performance (Boix-Trelis et al., 2007). The present results is in line with previous studies (Ali and Arafa, 2011: Al Hazmi et al., 2013; Arafa et al., 2013). Therefore, AChE could use as an index of cholinergic function and changes in enzyme activity which may indicate alterations in the availability of Ach at the level of its receptors. Acetylcholine plays the most important neurotransmitter involved in the regulation of cognitive functions and acetylcholine hydrolysis occurs through the enzyme AChE. Hence, the increased enzyme activity is responsible for degradation of acetylcholine. This degradation of the neurotransmitter was reflected in the impairment in the behavioral performed memory test (MWM).

Results about khat administration revealed impaired performance in the water maze test, increased cortical AChE activity and reduced body weight throughout experimental period the meanwhile khat withdrawals showed partial retention of the maze performance. reduced AChE activity and significant body weight gain.

The active ingredients of Khat are (norpseudoephedrine) cathine and (Benzovlethanamine): cathinone these alkaloids are similar in structure and pharmacological activity to amphetamines (Wagner et al., 1982). The acute effects of cathinone and cathine on neurotransmitters comparable to amphetamines effects: both stimulate the CNS and suppress appetite. However, cathinone has a more rapid onset and a shorter half-life than amphetamine. Cathinone is the main the stimulant effect of khat and is an unstable molecule that rapidly converted into the less powerful stimulant cathine. Fresh leaves of khat have greater ratio of cathinone to cathine than dried ones (Chappell and Lee, 2010). Colzato et al (2011) study suggested that khat use is associated with impairments in working memory and cognitive flexibility consequences of long-term as amphetamine and methamphetamine use due to similarity between cathinone and amphetamine. Also, the possibility that long-term use of cathinone, the active ingredient of khat, is associated with dysfunctions in prefrontal cortex. The chronic khat use is likely to be associated with reduced functioning of Dopamine D2 (DAD2) receptors in the striatum and dysfunctions in prefrontal cortex and

orbitofrontal cortex-areas that have been shown to play major roles in cognitive control (Miller 2000). Banjaw et al., (2005) demonstrated significant elevation of dopamine and significant decrease in metabolite, 5-hydroxyindole serotonin acetic acid (5-HIAA) in the prefrontal cortex of rats administered khat extract, or commercial cathinone. Recent study on adult male khat chewers from Jazan region in southwest Saudi Arabia revealed that khat chewers showed neuropsychological learning. motor decreases in speed/coordination, and set-shifting/ response inhibition functions reflecting effect on their mental and neurological health (Ismail et al., 2014) and associated with lower quality of life and lower socioeconomic status (Sheikh et al., 2014). There is accumulating evidence indicating the existence of khat withdrawal syndrome and a low level of tolerance. Withdrawal symptoms usually include inertia. nightmares. trembling, depression, sedation and hypotension (Cox and Rampes, 2003).

The present study suggested the impact of khat extract administration on the induction of memory impairment in young rats. This study gave alarm on cognitive impairment due to khat consumption especially on youth. Adult young people are the mainstay of the nation and its future builders and maintain their physical and mental health is a duty. Islam religion educates his followers to keep away from everything that hurts their bodies, their lives and their souls and encourage them to do the good work.

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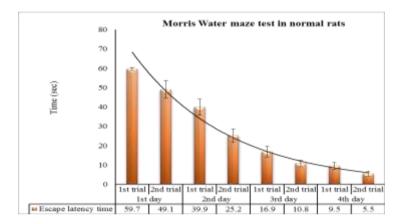


Fig. 1: The escape latencies time recorded in normal rats during four consecutive days. Values are means± SD.

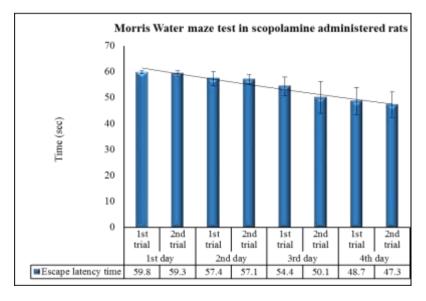


Fig. 2: The escape latencies time recorded in scopolamine group during four consecutive days. Values are means± SD.

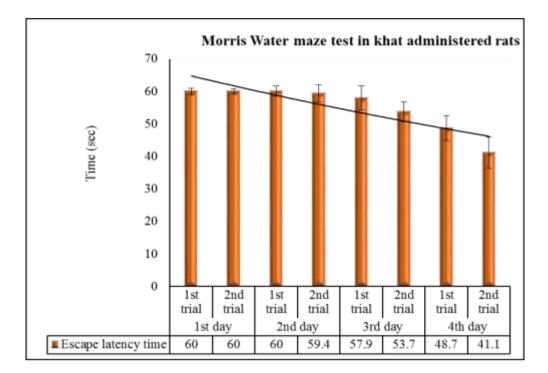


Fig. 3: The escape latencies time recorded in khat group during four consecutive days. Values are means± SD.

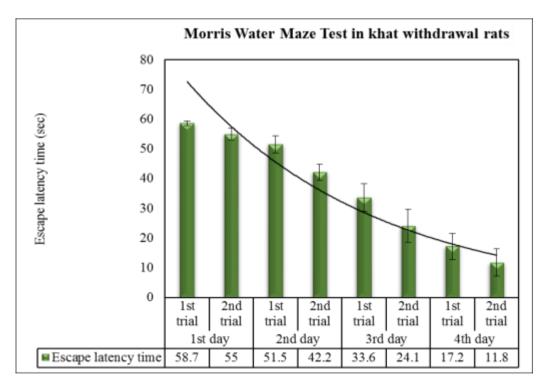


Fig. 4: The escape latencies time recorded in khat withdrawal group during four consecutive days. Values are means± SD.

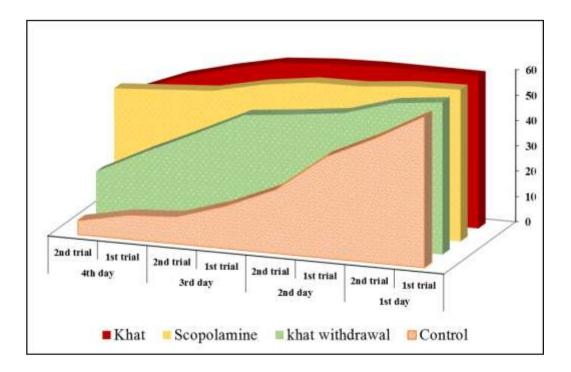


Fig. 5: Cumulative figure showing escape latencies time recorded in control, scopolamine, khat and khat withdrawal groups during four consecutive days. Values are means.

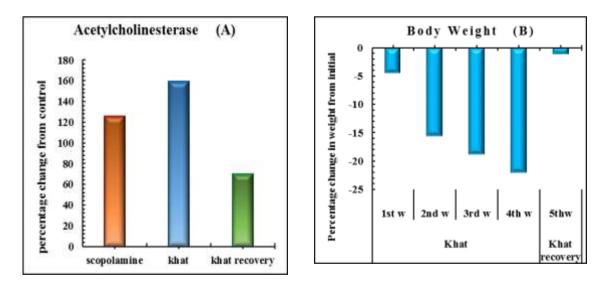


Fig. 6 (A&B): Effect of khat and khat withdrawal on percentage change from corresponding control values on acetylcholinesterase enzyme activities in brain cortices (A) and body weight (B).

تأثير مستخلص القات على ذاكرة الجرذان الصغيرة

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المستخلص

لقد كان وما زال تعاطي القات من القضايا الملحة في جازان. وقد أظهرت الدراسات السابقة انتشاره بين طلاب المدارس الثانوية والجامعات مما يشكل خطرا يهدد مستقبلهم ومستقبل امتهم. فكان لزاما الدراسة لمعرفة تأثير تعاطى القات في القدرة على الذاكرة والادراك في هذه المرحلة العمرية فاستخدمت الدراسة الحالية الجرذان البالغة الصغيرة السن والتي تحاكى مراحل التعليم في الانسان في أربع مجموعات الأولى ضابطة والثانية حقنت بريتونيا سكوبو لامين مرة واحدة والمجموعة الثالثة تعاطت في منا القات لمدة أربعة أسابيع و الهجموعة الرابعة تعاطت مستخلص القات المعامية من عالي والمجموعة الثالثة تعاطت فميا مستخلص القات لمدة أربعة أسابيع و الهجموعة الرابعة تعاطت مستخلص القات لمدة أربعة أسابيع ثم توقف تعاطى القات لمدة أسبوع واحد. تم تدريب جميع المجموعات باستخدام الاختبار السلوكي متاهة موريس المائية قبل بدء المعاملات وبعدها. وتم تقدير نشاط انزيم الأسيتال كولين استيراز في قشرة المخ بالأضافة لتقدير وزن

أظهرت نتائج الدراسة ضعف الأداء في اختبار المتاهة المائية لدى تعاطى مستخلص القات ، وزيادة نشاط انزيم الأسيتل كولين استيراز في قشرة المخ وانخفاض وزن الجسم بطريقة عكسية مع استمرار فترة التعاطى، كما أظهرت الدراسة ان انسحاب القات أدى الى استعادة جزئية لأداء المتاهة، وانخفاض في نشاط الأسيتل كولين استيراز وزيادة في وزن الجسم. الدراسة تدق ناقوس الخطر في ضعف الادراك نتيجة استخدام القات وخاصة على الشباب.