



Toxic effect of cathinone (an active principle of *Catha edulis*) on brain lipids in Swiss albino mice

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Abstract

The leaves of khat plant (*Catha edulis*) are widely consumed by people of East African countries and Arabian Peninsula for their pleasurable and stimulating effects. The consumption of khat is prohibited in the Kingdom of Saudi Arabia but it is being used by the people of Kingdom, especially in the region of Jazan, where it is easily available due to its cultivation in the neighbouring country Yemen. The objective of the study was to evaluate the effect of very low doses of cathinone on the brain lipids. Male Swiss albino mice were divided in 4 groups, one control and 3 experimental and each group having 6 animals. (-) Cathinone, 0.125, 0.25 and 0.5 mg/kg body weight was given intraperitoneal to animals for 10 days, once daily. Cathinone has elevated the level of triglyceride significantly and dose dependently as compared to control group. On the other hand, the content of ganglioside was depleted significantly and dose dependently in experimental groups as compared to control group. A significantly elevated level of cholesterol was observed with the doses of 0.25 and 0.5 mg/kg and phospholipids with the dose of 0.5 mg/kg of cathinone as compared to control group. No significant change on total lipids was observed in cathinone treated group as compared to control group. The study concludes that very low doses of cathinone were sufficient for the change on the brain lipid contents to provide excitement in khat chewers.

Keywords: Brain lipids (phospholipids, triglyceride, cholesterol, gangliosides), *Catha edulis*, Cathinone, Swiss albino mice

Introduction

Khat or Qat (*Catha edulis*, family Celastraceae) is a flowering evergreen tree or shrub native to regions of eastern Africa and the Arabian Peninsula. Khat can be grown in droughts where other crops have failed and also at high altitudes. It is harvested throughout the year. All parts of the fresh plant and leaves can be chewed, but the soft small top (crimson) and green leaves are preferred. Because of its social acceptability and euphoric effects, khat chewing often plays a dominant role in celebrations, meetings, marriages, and other gatherings. Khat chewing usually takes place in groups in a social setting. Only a minority frequently chew alone. In a khat chewing session, initially there is an atmosphere of cheerfulness,

optimism and a general sense of well being. A khat chewing session takes 2-10 hr and during this session 100 to 500 g of leaves and stems of the plants are chewed (Elmi, 1983; Nencini and Ahmed, 1989; Kalix, 1990; Matloob, 2003; Al-Hebshi and Skaug, 2005). Khat leaves have been used in traditional medicine for the treatment of depression, fatigue, hunger, obesity and gastric ulcers. Khat is stimulant and it is used to improve performance, stay alert and to increase work capacity (Kalix, 1984). Students have chewed khat in an attempt to improve mental performance before exams. In Saudi Arabia, the cultivation and consumption of khat are forbidden, and the ban is strictly enforced but there are so many cases of khat toxicity. The ban on khat is further supported by the clergy on the grounds that the Qur'an forbids anything that is harmful to the body. Most of the effect of chewing khat is thought to come from two phenylalkylamines, cathinone and cathine which are structurally related to amphetamine (Nencini *et al.*, 1984). The cathinone content was found to vary (0.74-3.3%) according to the country of origin of khat, Kenya having the highest cathinone contents

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(Dimba *et al.*, 2004; Geissshüsler and Brenneisen, 1987; Widler *et al.*, 1994). A minimum dose of khat leaves chewed by a person is 100 g accordingly a mice dose in 100 g of khat leave is 16.28 mg/kg body weight of cathinone. Qureshi *et al.* (1988) have given 5, 20 and 40 mg/kg body weight of cathinone orally to mice for a period of 6 weeks, while Schechler *et al.* (1984) have compared the effects of cathinone (0.6 mg/kg body weight i.p.), amphetamine and apomorphin on the behaviour activity of rats. The active principle of the khat, cathinone is in the list of narcotics as Schedule I drug. When khat leaves dry, the more potent chemical, cathinone decomposes within 48 hours leaving behind the milder chemical, cathin and norephedrine, a Schedule IV drug. Keeping the abuse of the khat, the University of Minnesota in 2009 launched an International Khat Research Program focusing its effects on the health and brain. The International Khat Research Program indicates the importance of the khat study.

Lipids are the important constituent of the nervous system. Lipid metabolism in central nervous system is of particular interest because of the high concentration of lipids. The importance of lipids in cell signalling and tissue physiology is demonstrated in many CNS disorders and injuries that involve deregulated metabolism. The imbalance of lipids is associated with neurological disorders (Alzheimer's disease, Parkinson's disease, Niemann-Pick disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, schizophrenia, bipolar disorders and epilepsy) and CNS injury (stroke, traumatic brain injury and spinal cord injury).

The limbic system is a complex set of brain structures that lies on both sides of thalamus right under the cerebrum and includes, hypothalamus, thalamus, amygdala, hippocampus, fornix, column of fornix, mammillary body, septum pellucidum, habenular commissure, cingulate gyrus, para hippocampal gyrus, uncus, limbic cortex, and limbic midbrain areas. The thalamus is known as the switchboard of the brain, as all incoming and outgoing calls pass through this area and it serve as the major relay station for sensory impulses on their way to the cerebral cortex. Hippocampus involved in long-term memories and implicated in maintenance of cognitive maps for navigation.

Amygdala involved in signalling the cortex of motivationally significant stimuli such as those

related to reward and fear in addition to social functions such as mating. Cingulate gyrus regulates the heart rate, blood pressure, cognitive and attention processing. To the best of our knowledge, no data of khat or cathinone toxicity is available on the brain lipids. This is the first report on the toxicity of cathinone on the lipids in limbic areas. The most of the available data of cathinone are at high doses. The objective of this study was to evaluate the effect of very low doses of cathinone on the brain lipids in limbic areas of Swiss albino mice.

Materials and Method

Materials: Most of the chemicals used in this experiment were purchased from Sigma-Aldrich Co., USA. Cathinone hydrochloride (5 mg vial) was the generous gift from the Poison Control & Medical Forensic Chemistry Center, Ministry of Health, Jazan, Kingdom of Saudi Arabia.

Animals: Male Swiss albino mice (25-30 g) obtained from the Animal House of the College of Pharmacy was used in this study. The animals were divided into four groups each having six animals. The group 1 was control and vehicle was given through intraperitoneally (i.p.). Groups 2-4 were the experimental and cathinone 0.125 mg, 0.25 mg and 0.5 mg/kg body wt were given i.p for a period of 10 days, once daily. On 10th day, 1 hr after the cathinone injection, the animals were sacrificed by decapitation and the brains were taken out quickly to dissect limbic area.

Dissection of the limbic areas: The brain portion between posterior optic chiasma and anterior brain stem was used as limbic area. Coronal sections of the brain were cut from the posterior of optic chiasma where fornix starts to anterior of the brain stem where hippocampus ends.

Extraction of brain lipids: Each limbic area was weight and homogenized in Ultra Turrex homogenizer (T-25) in 5 ml chloroform: methanol (2:1, v/v) according to the method of Folch *et al.* (1951) as modified by Islam *et al.* (1980). The homogenates were placed at 40 °C for an hr and shaken periodically. Thereafter, it was filtered through sintered glass funnel G4 and make up the volume to 10 ml. Normal saline solution 2.5 ml was added and mixed thoroughly. The test tubes were kept overnight at -20 °C for the complete separation of the layers. The upper layer was used for the



estimation of gangliosides and lower organic layer for the assays of total lipids, phospholipids, cholesterol and triglyceride.

Estimation of total lipids: Total lipids were estimated according to the method of Woodman and Price (1972). In brief, duplicate samples containing 0.1 ml of the lipid extract in 18 x 150 mm test tubes were taken. Concentrated H₂SO₄ (2.5 ml) was added to each test tube and heated in a boiling water for 10 min. After cooling, 5.0 ml of colouring reagent (potassium dihydrogen orthophosphate 6.0 g and vanillin 0.3 g in 100 ml Milli Q water) was added and absorbance was taken at 530 nm. A calibration curve with different concentrations (50 to 250 µg) of triolein was prepared adopting the same procedure as described above. The values of the standard curve were plotted and concentration of the total lipids was calculated from the calibration curve.

Estimation of cholesterol: The cholesterol was determined by the method of Henly (1957). Lipid extract (0.5 ml) was taken in test tubes and evaporated under the stream of nitrogen gas. Thereafter, 1.0 ml acetic acid and 3.0 ml ferric chloride acetic acid solution (50 mg ferric chloride in 100 ml acetic acid) were added followed by 1.0 ml of conc. H₂SO₄. Test tubes were vortexed at each addition and kept for 10-15 min at room temperature. The colour intensity was read at 560 nm against a reagent blank. A calibration curve with different conc. of cholesterol (50-400 µg) was drawn according to the same procedure as described above. The values were plotted and concentration of the cholesterol was calculated from the calibration curve.

Estimation of ganglioside: Ganglioside was estimated according to the method of Pollet *et al.* (1978) as modified by Islam *et al.* (1986). The 1.0 ml upper aqueous layer of the lipid extract was taken in test tubes. Thereafter, 2.0 ml of resorcinol reagent was added. The test tubes were heated in boiling water bath for 30 min. After cooling, 5 ml of a mixture of butylacetate: n- butanol (85:15, v/v) was added to each test tube, shaken thoroughly and stand for 15 min to separate the organic phase. About 3 ml of the organic phase was taken and absorbance was measured at 580 nm against reagent blank. A standard curve with different concentrations of N-acetylneuraminic acid (5-30 µg) having 1.0 ml final volume of water was prepared according to the same procedure as

described above. The values were plotted and concentrations of the gangliosides were calculated from the calibration curve.

Estimation of phosphorous: Phosphorus was estimated by the well known method of Fiske and Subbarow (1925) as described by Merinetti (1962). Lipid extract (0.1 ml) was taken in 18 x 150 mm glass test tubes and dried it at room temp. Thereafter, 1.0 perchloric acid (70%) was added to each test tube and digested till the acid become clear. Each test tube has 3-4 glass beads to avoid bumping during digestion. Then ammonium molybdate (2.5% in Milli Q water) 2.5 ml was added to each test tube and mixed thoroughly. Thereafter, reducing reagent (sodium sulphite 3.0 g, sodium meta-bisulfite 0.1 g and 1-amino-2-naphthol-4-sulfonic acid 0.05 g in 20.0 ml Milli Q water) 0.5 ml was added and volume was makeup to 5.0 ml with Milli Q water. After 10 min of heating in boiling water bath, the absorbance was read at 660 nm. A calibration curve with different concentration of phosphorous (1-8 µg) was prepared adopting the same procedure as described above. The values of the standard curve were plotted and concentration of the total lipids was calculated from the calibration curve. The phospholipids were calculated by multiplying the phosphorous values with a factor of 25.

Estimation of triglyceride: Organic layer 10 µl was taken in a test tube and dried under the stream of nitrogen gas. Thereafter, it was estimated according to the procedure of triglyceride kit of Human Diagnostic Worldwide, Germany as described by Kaur *et al.* (2003).

Statistics: Results were expressed as mean ± SEM of six animals. Differences between the means of experimental and control groups animals were analyzed by one-way ANOVA followed by Tukey–Kramer post hoc test. The p < 0.05 were considered statistically significant.

Results and Discussion

The brain is one of the richest in lipids among various body organs. It is essential components of all cellular structures in the brain. Lipids account for about half the dry weight of most of the structural architecture of the membranes in the brain (Ord and Kaack, 1975). These also constitute components of the ion channels, a portion of the neurotransmitter receptors, and a major constituent of myelin. The brain is enriched in highly



specialized membrane called myelin that accounts for its high lipid content (Zia and Islam, 2000) and is more prone to radical damage because of the high content of polyunsaturated fatty acids in the brain membrane and the low activity/level of enzymatic and non-enzymatic antioxidants (Halliwell, 1989). The total lipids in the brain make up to 65% of the dry weight of the white matter and 35–40% of the gray matter (Brante, 1949). The administration of various doses of cathinone has not altered the content of total lipids in the limbic areas of the mice as compared to the control group (Table-1). On the other hand, the content of triglyceride was increased significantly and dose dependently in cathinone treated groups as compared to the control group.

Table 1. Toxic effects of cathinone neon brain lipids contents in Swiss albino mice.

Doses of Cathinone (mg/kg b.w)	Total Lipids	Phospholipids
Control	88.92 ± 2.98	23.07 ± 1.79
0.125	88.69 ± 3.00 (-0.26 %)	22.47 ± 2.17 (-2.60 %)
0.25	88.29 ± 2.091 (-0.71 %)	20.51 ± 1.98 (-11.09 %)
0.50	87.11 ± 3.59 (-2.03 %)	17.95 ± 1.57* (-22.19 %)

The levels of total lipids and phospholipids were depleted dose dependently but the depletion on the contents of phospholipids was significant with the dose of 0.5 mg/kg body wt of cathinone. Values are expressed as mg/g fresh weight, as Mean ± SEM of 6 animals. *p < 0.05 cathinone vs control.

The primary function of lipids or TG is to provide energy to the cells. TG, as major components of very low density lipoproteins (VLDL) and chylomicrons, plays an important role in the body metabolism as energy sources. Initially the khat users feel euphoria, excitation, manic and energetic (Balint *et al.*, 2009). These actions of the khat may be due to the increased contents of the brain triglyceride which provide direct energy to the brain which makes them more energetic. Lipids are more palatable and storable to unlimited amount compared to carbohydrates. They have high energy value (25% of body needs) and provide more energy per gram than carbohydrates and proteins. There is a

contradiction on the alteration of serum triglycerides level by khat. Mahmood and Lindequist (2008) have reported significantly reduced level of triglyceride during khat feeding, but after cessation of khat feeding, its level was increased non-significantly to a level higher than that of corresponding control. No significant change in plasma triglyceride level in khat chewers was observed (Al-Zubairi, 2003). Also, a non significant reduction on the content of serum triglyceride was observed in healthy human khat chewers (Kalix, 1992; Hassan *et al.*, 2005). In rabbits, khat leaves reduced the concentration of triglyceride significantly (Al-Habori and Al-Mamary, 2004). Conversely, in the same species the content of triglyceride was increased significantly with the administration of khat (Al-Rajhi and Yousef, 2013).

Phospholipids are important components of all mammalian cells. It is an essential molecule that is important for optimal brain health. Phospholipids are found in high concentrations in the lining of practically every cell of the body, including brain cells. They help brain cells to communicate and influence how well receptors function. A cell in the human body cannot function normally without phospholipids and without a healthy cell membrane; we cannot have optimum memory and mental function.

Phospholipids play several roles in the brain. They not only determine which minerals, nutrients, and drugs go in and out of the cell, but also influence communication between the brain cells by influencing the shape of receptors and promoting the growth of dendrites. Since phospholipids help to form the cell membrane of the trillions of cells in the body, it makes sense that they would have an influence on not just the brain, but on a number of organs and tissues, including the heart, blood cells and the immune system. Phospholipids are embedded in the cell membrane. The decreased content of phospholipids with the dose of 0.5 mg of cathinone (Table-1) may increase the permeability of the membrane to penetrate more Ca^{2+} ion and stimulate the synapse to release more neurotransmitters which make excitement to the khat chewers. A further study with higher doses of cathinone, long duration and the fraction of phospholipids will be required to understand the membrane permeability, rerelease of Ca^{2+} ion,



mechanisms of action of cathinone and cell signaling.

Cholesterol is an important structural component of cellular membranes and myelin and a precursor of oxysterols, steroid hormones, and bile acids (Herz and Bock, 2002). Cholesterol is a major constituent of the human brain, containing about 20% of the body's total cholesterol. Cholesterol is tightly regulated between the major brain cells-neurons and glia, that is, astrocytes, microglia, and oligodendrocytes and is essential for normal brain development. Cholesterol is required for synapse and dendrite formation (Fester, *et al.*, 2009; Goritz, *et al.*, 2005) and for axonal guidance (Chaves *et al.*, 1997). Cholesterol depletion leads to synaptic and dendritic spine degeneration, failed neurotransmission, and decreased synaptic plasticity (Koudinov and Koudinova, 2005). A significant increased level of total cholesterol with the doses of 0.25 and 0.5 mg/kg body wt of cathinone was observed in the limbic areas of the mice as compared to control group (Fig. 1). Total plasma cholesterol was found to be affected in khat chewers (Al-Zubairi, 2003). While in rabbits, khat leaves reduced the total serum cholesterol level

significantly (AlRajhi and Yousef, 2013). Mahmood and Lindequist (2008) have reported a non-significant increment in the level of total serum cholesterol. Several neurodegenerative disorders such as Smith-Lemli-Opitz syndrome (De Barber, *et al.*, 2011), Huntington's disease (Block *et al.*, 2010) and Alzheimer's disease (Di Paolo and Kim 2011) are associated with impaired cholesterol homeostasis in the nervous system where cholesterol is known to play a role in modulating synaptic activity and stabilizing membrane microdomains. The result indicates that elevated level of cholesterol might have strengthened the synaptic plasticity which may cause the improve performance, stay alert and to increase work capacity in the khat chewers.

Gangliosides are the essential constituents of the cell membrane and are more concentrated and more complex in the central nervous system than any other organ (Warren, 1963; Rahmann, 1983). They are known to be involved in the synaptic transmission because they act as receptor sites for various neurotoxins (Irwin and Samson, 1971). The brain contains as much as 20 to 500 times more gangliosides than most non-neural tissues, and its content in grey matter is three times more than in

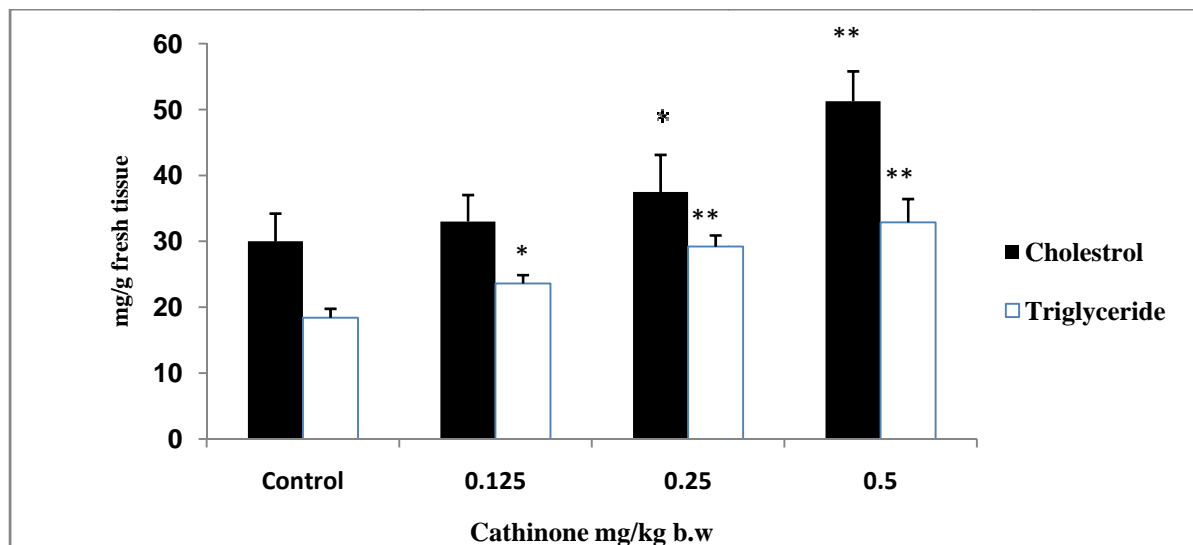


Fig.1 Shows the effect of cathinone on the contents of cholesterol and triglycerides in limbic areas of Swiss albino mice. The levels of cholesterol and triglyceride were increased dose dependently. Cathinone 0.25 and 0.5 mg/kg body wt has significantly elevated the level of cholesterol while all doses of cathinone have increased triglyceride level significantly. Values are expressed as mg/g fresh weight, as Mean \pm SEM of 6 animals. * $p < .05$, ** $p < .01$ cathinone vs control.

white matter. Changes in ganglioside composition can be induced by nerve stimulation, environmental factors or drug treatments. The gangliosides are believed to be functional ligands for maintenance of myelin stability and the control of nerve regeneration by binding to a specific myelin-associated glycoprotein. The occurrence of gangliosides in cell nuclei suggests a possible involvement of gangliosides in the expression of genes relevant to neuronal function. Irwin and

Samson, (1971) have shown that certain types of behavioural stimulation (stress, exercise, sensory stimulation, learning) seem to be accompanied by alteration of gangliosides metabolism, compared to corresponding control. In the present study, the content of gangliosides was depleted significantly and dose dependently in the cathinone treated group as compared to the control group (Fig.2). The gangliosides play a protective role in the CNS and its depletion may induce neurotoxicity.

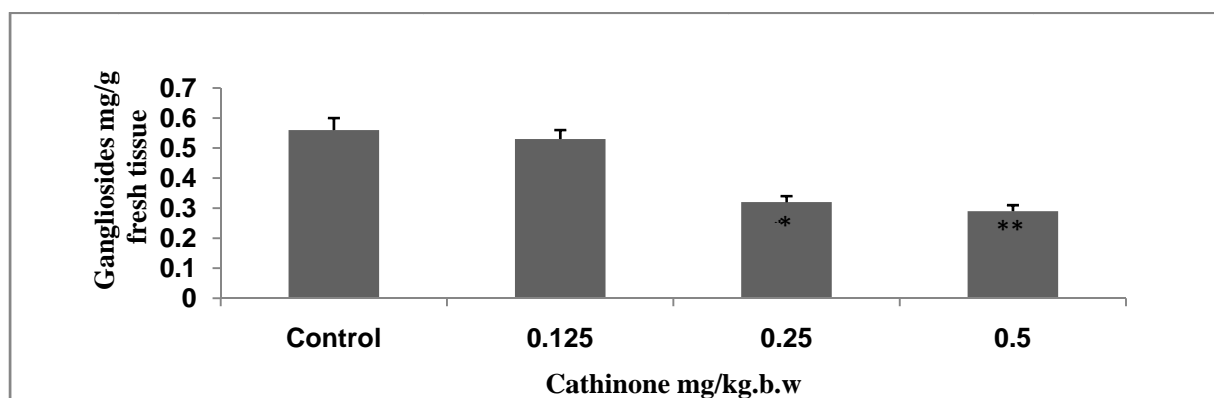


Fig. 2. Effect of cathinone on the content of gangliosides in limbic areas of Swiss albino mice. The level of gangliosides was decreased significantly and dose dependently (0.125, 0.25 and 0.5 mg/kg body wt of cathinone) as compared to control group. Values are expressed as mg/g fresh weight, as Mean \pm SEM of 6 animals. * $p < .05$, ** $p < .01$ cathinone vs control.

A further study with the higher doses and long duration of cathinone will be required to evaluate the effect of cathinone on total lipids, phospholipids and the fractions of phospholipids, its role in membrane permeability, Ca^{2+} ions release and cell signalling.

Conclusion

It is evident that very low doses of cathinone have significantly altered the contents of triglycerides, cholesterol, phospholipids and gangliosides in limbic areas caused synapse to release more neurotransmitters by penetrating more Ca^{2+} ions due to loose tightness of the membrane junction and cause the excitements in the khat chewers.

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