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Original Article

Effect of the Ethanolic Extract of *Catha edulis* Leaves on the Electrical Activity of Some Brain Centers of Male Rabbits

Mohammed Sadeg Abdullah Al-Awar*, Mohammed Abdullah Yahya Al-Eryan

Department of Biology, Faculty of Education, Amran University, Yemen.

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Catha edulis is an evergreen tree with psychotropic effects. The present work was conducted to evaluate the possible effects of the ethanolic extracts of *Catha edulis* leaves (ECE) on the electrical activity of 4 areas in the brain of male rabbits. Forty male rabbits weighting 2200-2500 g were divided into 4 groups. The electrical activity of motor, somato–sensory, occipital, and auditory areas were measured after 60, 120 and 180 min of intraperitoneal administration of doses of 0, 5, 10, and 15 g of *Catha edulis* leaves in 10 % ethanolic extract, using electroencephalography. Results showed that ECE had a significant ($P < 0.001$) pathological effects on the electrical activity of the studied areas of the brain, except the auditory area. Further cellular and molecular studies should reveal the mechanism of action of *Catha edulis* in the brain.

Keywords: *Catha edulis*, brain, electrical activity

Khat is a common name given to the plant (*Catha edulis* Forssk.); it is an evergreen tree or large shrub with glabrous leaves. Peter Forsskal, (1736-1763) was the first to notice Khat.This Swedish scientific botanist who died in Yemen, described the plant and classified it *Catha edulis*, family Celastraceae (1).

Khat is widely cultivated in East Africa and Southern Arabia (Yemen); it grows wild at altitudes of 1500-2000 meters above sea level. Khat is more than a psychotropic plant, as it is the basis of a life style and plays a dominant role in celebrations, especially at birth, marriage, funeral services and political meetings (2).

Several pharmacological and chemical investigations have been carried out on the isolation and identification of the active constituents of the Khat. Many authors isolated some alkaloids identified as cathine, cathinine and cathidine components (3). Wolfes isolated cathine in a crystalline form and identified cathine as being norpseudoephedrine (4). This alkaloid was considered to be responsible for the effects of Khat (5-6). Latter studies revealed the presence of another alkaloid in the leaves of Khat, identified as cathinone and was suspected to be a labile precursor of cathine, and converted into cathine during the drying process (6-7). The pharmacological aspects of Khat are now well understood. Khat effects are mainly due to the cathinone, which is more potent than cathine (8-10). In addition to alkaloids, the leaves of Khat contain a variety of substances, including tannins, inorganic ions (K^+, Mg^{++}, Ca^{++}, Na^+) and amino acids (6, 11). The study of United Nations narcotics laboratory (UNNL), found that the leaves of Khat contained not only cathine and its diastereomer norephedrine [R, S (-) phenylpropanolamine], but also revealed the presence of important amount of a further alkaloid named cathinone [S (-) α – aminopropiophenone], with a

*Correspondence: Department of Biology, Faculty of Education, Amran University, Yemen. E-mail: momed.sadeg@gmail.com, dr.msadeg@auye.ac

structure closely related to that of cathine (norpseudoephedrine) as well as to that of amphetamine (7, 12).

Since 1956 the United Nation commission of narcotics and drugs prohibited Khat's sale and cultivation due to its addictive effects and danger on man's life. World health organization (WHO), classified Khat as a drug of abuse, which can produce mild to moderate psychic dependence but not physical dependence and tolerances (13-14). The present work is the first study designed to determine the possible effects of the ethanolic extract of *catha edulis* leaves on the electrical activity of 4 areas in the brain of male rabbits.

Materials and methods

Plant extracts preparation

Catha adulis leaves were obtained from city of Dalih, Dalih governorate, Yemen. Under shade – dried powdered leaves were Soxhlet extracted with 10% Ethanol, to afford a gummy residue (ECE 10 %). Three doses were prepared: 10 % of ethanolic extract of 5, 10, and 15 g of *Catha edulis* leaves. For physiological testing the extracts, were dissolved in 5 ml propylene glycol (PG).

Animals

Forty male rabbits (2200-2500 g) were used. They were adapted to condition of experiment for 5 days in a standard environmental condition and kept under standard commercial diet with water *ad libitum* according to the institutional guide for the care and use of laboratory animals.

The animals were divided into 4 groups of 10 animals each and received the extracts intra peritoneally (ip). Group 1 (control) were given propylene glycol (PG) 5 ml/kg. Group 2 (ECE1 were treated with 5 g ethanolic extract/. Group 3 (ECE2) were treated with 10 g/kg extract.

Group 4 (ECE3) were treated with 15 g/kg of extract.

Electroencephalography (EEG)

The electrical activity of rabbits brain was recorded using electroencephalograph (EEG), (Siemens ES1200, Germany), after 60, 120, and 180 minutes of administration of the ethanolic extracts of *Catha edulis*. The fur of the animals above the skull was shaved; four punctures in the skull above the studied areas were cautiously made, and the connecting to the EEG electrodes was inserted in the punctures. The electrical activity of motor, somato-sensory, occipital visual, and auditory areas, were recorded.

Statistical analysis

The statistical analysis was performed by statistical analysis system (SAS) software. Continuous data are expressed as mean ± SE. Data were compared using one– way ANOVA. P value <0.001 was considered to be statistically significant.

Results

Tables 1-3 show the electrical activity of motor, somato-sensory, occipital visual, and auditory areas,in the brain after 60, 120, and 180 min, respectively, of ip administration of 10% ethanolic extracts of *Catha edulis*.

Results showed that in the motor area, the alpha wave values were significantly (P< 0.001) increased in all treated animals after 60 min of ECE administration (Table1). The increase of alpha wave values continued after 120 min (Table 2), but was less than after 60 min. The alpha wave values returned to the normal after 180 min of ECE administration (Table 3).

The beta wave values significantly (P< 0.001) decreased in the motor area in all treated animals. This decrease continued even after 180 min of ECE administration (Table 3).

Regarding the somato-sensory area, the alpha and beta waves values significantly increased after 60 min in ECE2 and ECE3 groups (P< 0.001) (Table 1). Both alpha and beta waves values significantly increased after 120 min of ECE administration in all treated animals (P< 0.001) (Table 2). The increase in alpha wave values continued in animals in ECE2 and ECE3 after 180 min, whereas the beta waves values returned to the normal except

in ECE3 animals (Table 3).

In occipital area, after 60 min the alpha wave values increased in ECE2 and ECE3 animals, the values of beta wave also increased in ECE1 and ECE2 groups (Table 1). The increase of alpha wave values continued (Table 2) after 120 min in ECE1 and ECE2, whereas the beta wave values of ECE1 and ECE2 groups were decreased. After 180 min the alpha wave values continuedto be high but to a lesser extent than after 60 and 120 min, whereas the beta wave values returned to the normal (Table 3).

No electrical activity change was recorded in the auditory region.

Table 1. The electrical activity of 4 areas in brain after 60 min of Catha edulis extracts administration

Treatments	Dose g/Kg	Motor area Mc.V	Somato- sensory area Mc.V	Occipital visual area Mc.V	Auditory area Mc.V
Control 5 ml PG/Kg	–	$\alpha - 10 \pm 0.70$ $\beta - 40 \pm 1.52$	$\alpha - 5 \pm 0.95$ $\beta - 40 \pm 1.90$	$\alpha - 10 \pm 1.00$ $\beta - 50 \pm 1.25$	$\alpha - 10 \pm 1.20$ $\beta - 50 \pm 1.0$
ECE 1	5	$\alpha - 13 \pm 0.70$ $\beta - 30 \pm 0.45$	$\alpha - 5 \pm 0.70$ $\beta - 40 \pm 0.10$	$\alpha - 10 \pm 0.90$ $\beta - 60 \pm 1.10$	$\alpha - 10 \pm 0.10$ $\beta - 50 \pm 0.40$
ECE 2	10	$\alpha - 13 \pm 0.20$ $\beta - 30 \pm 1.01$	$\alpha - 7 \pm 1.2$ $\beta - 60 \pm 1.10$	$\alpha - 12 \pm 0.75$ $\beta - 60 \pm 1.55$	$\alpha - 10 \pm 1.01$ $\beta - 50 \pm 0.70$
ECE 3	15	$\alpha - 12 \pm 0.75$ $\beta - 20 \pm 1.20$	$\alpha - 7 \pm 0.01$ $\beta - 60 \pm 1.01$	$\alpha - 12 \pm 0.45$ $\beta - 50 \pm 0.75$	$\alpha - 10 \pm 1.00$ $\beta - 50 \pm 0.95$

Values are: mean of 10 animals ±SE; PG: Propylene glycol, Mc.V: microvolt; α: alpha wave; β: beta wave.

Table 2. The electrical activity of 4 areas in brain after 120 min of Catha edulis extracts administration

Treatments	Dose g/Kg	Motor area Mc.V	Somato-sensory area Mc.V	Occipital visual area Mc.V	Auditory area Mc.V
Control 5 ml PG/Kg	–	$\alpha - 10 \pm 0.70$ $\beta - 40 \pm 0.10$	$\alpha - 5 \pm 0.55$ $\beta - 40 \pm 1.30$	$\alpha - 10 \pm 0.70$ $\beta - 50 \pm 1.60$	$\alpha - 10 \pm 0.90$ $\beta - 50 \pm 0.75$
ECE 1	5	$\alpha - 11 \pm 1.00$ $\beta - 20 \pm 0.40$	$\alpha - 7 \pm 1.10$ $\beta - 50 \pm 1.10$	$\alpha - 12 \pm 0.10$ $\beta - 40 \pm 1.45$	$\alpha - 10 \pm 1.20$ $\beta - 50 \pm 0.50$
ECE 2	10	$\alpha - 11 \pm 1.70$ $\beta - 20 \pm 0.40$	$\alpha - 9 \pm 0.01$ $\beta - 50 \pm 1.01$	$\alpha - 12 \pm 0.75$ $\beta - 40 \pm 1.10$	$\alpha - 10 \pm 1.20$ $\beta - 50 \pm 0.45$
ECE 3	15	$\alpha - 11 \pm 0.30$ $\beta - 20 \pm 0.90$	$\alpha - 9 \pm 1.01$ $\beta - 50 \pm 1.10$	$\alpha - 10 \pm 1.00$ $\beta - 50 \pm 1.10$	$\alpha - 10 \pm 0.01$ $\beta - 50 \pm 0.30$

Values are: mean of 10 animals ±SE; PG: Propylene glycol, Mc.V: microvolt; α: alpha wave; β: beta wave.

Table 3. The electrical activity of 4 areas in brain after 180 min of Catha edulis extracts administration

Treatments	Dose g/Kg	Motor area Mc.V	Somato-sensory area Mc.V	Occipital visual area Mc.V	Auditory area Mc.V
Control 5 ml PG/Kg	–	$\alpha - 10 \pm 0.01$ $\beta - 40 \pm 0.10$	$\alpha - 5 \pm 0.10$ $\beta - 40 \pm 0.10$	$\alpha - 10 \pm 1.70$ $\beta - 50 \pm 1.10$	$\alpha - 10 \pm 1.05$ $\beta - 50 \pm 1.20$
ECE 1	5	$\alpha - 10 \pm 1.70$ $\beta - 20 \pm 0.50$	$\alpha - 5 \pm 1.45$ $\beta - 40 \pm 1.10$	$\alpha - 11 \pm 0.01$ $\beta - 50 \pm 0.01$	$\alpha - 10 \pm 0.01$ $\beta - 50 \pm 0.75$
ECE 2	10	$\alpha - 10 \pm 1.20$ $\beta - 30 \pm 0.70$	$\alpha - 7 \pm 1.10$ $\beta - 40 \pm 1.10$	$\alpha - 11 \pm 0.50$ $\beta - 50 \pm 0.95$	$\alpha - 10 \pm 1.45$ $\beta - 50 \pm 0.01$
ECE 3	15	$\alpha - 10 \pm 1.00$ $\beta - 30 \pm 1.00$	$\alpha - 7 \pm 0.10$ $\beta - 50 \pm 0.45$	$\alpha - 10 \pm 1.05$ $\beta - 50 \pm 1.01$	$\alpha - 10 \pm 1.00$ $\beta - 50 \pm 0.10$

Values are: mean of 10 animals ±SE; PG: Propylene glycol, Mc.V: microvolt; α: alpha wave; β: beta wave.

Discussion

The electroencephalography is not only a method of determining the functional state of the nervous cells, but in some cases it helps to establish the character of the diseases and the localization of the pathological process in the brain (15).

The above mentioned changes in the electrical activity of nervous cells can occur only if the Na^+ pumps in the cells membrane are temporary blocked and/or if the enzymatic system of brain is damaged (16). Therefore, it can be assumed that one or more compounds in *Catha edulis* have the ability to temporary block the Na^+ pumps in cells membrane, and /or, the ability to affect the enzymatic system of the brain. Farag and Al-Qirbi reported that *Catha edulis* affects the enzymatic system of rabbit's brain (17).

The frequency changes in EEG values could be due also to the acute change in the level of gamma amino butyric acid (GABA) in the brain (16). The ability of the constituents of *Catha edulis* to decrease the levels of 5- hydroxytryptophane (5-HTP) and GABA in the brain of rabbits, was previously reported (Kennedy *et al.*, 1983). However, the change in the electrical activity of nervous cells may lead to many pathological disorders in peoples with long– term Khat chewing, and at the end, to the death of nervous cells. The frequency changes in the values of EEG recorded in our experiment, (i.e. abnormal ($P < 0.001$) increase and decrease in the electrical activity of brain in the treated animals compared with the control animals), are similar to that recorded in patients with psycho-neurological disorders dependent on narcotics (18). The frequency change in the electrical activity of the brain can lead to a withdrawal phenomenon (e.g. restlessness, agitation, tremor, rarely convulsions) (18). Some of Khat constituents were reported to cause similar symptoms (6). The changes in EEG values in our experiments were similar to the EEG changes recorded in patients with paradoxical reactions such as restlessness, hallucinations, aggressiveness, agitation, unusual behavior, psychosis, anxiety, nightmares, irritability and delusions (18). Jeger and Sireling, also reported that Khat caused some of the above mentioned disorders (19).

Other adverse effects such as confusion, depression, increase or decrease in libido may also occur in the case of frequency change in brain electrical activity (16). Some of khat contents cause similar effects (6).

Tiredness (drowsiness, lethargy, dopiness, prolonged reaction time) tremor, dizziness, head-

ache, ataxia, clouding of consciousness, and reduced alertness, dysarthria, anterograade, amnesia, and tension can develop in case of frequency change in electrical activity of brain (18). Similar disorders were also reported as the effects of Khat consumption (20).

Further deep studies are needed to better understand the mechanism of action of Khat in the brain.

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Conflict of interest

The authors declared no conflict of interest.

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