

### Effect of khat on ovarian oxidative stress in female rats

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#### ABSTRACT

Oxidative stress (OS) greatly influences the reproductive health in female mammalian animals. The study used female Wistar rats weighing  $200 \pm 10$  g grouped and administered orally as, control groups (1ml CMC), (0.5 g/100ml carboxy methyl cellulose)) and Khat groups (1ml khat extract) (150mg/kg) each for 3 and 6 weeks. Ovaries from each group at the two experimental periods used for the determination of ovarian OS markers. Results showed significant decrease in superoxide dismutase (SOD) enzyme activities and nitric oxide (NO) levels and reduced glutathione/oxidized glutathione (GSH/GSSG) levels as well as significant increase in malondialdehyde (MDA) contents in khat groups after 3 and 6 weeks of treatment as compared to their corresponding control values. Results overt that ovaries from rats subjected to khat extract were under OS due to the imbalance between ROS production and anti-oxidants.

**Key words:** Khat; Rat; Superoxide Dismutase; Nitric Oxide; Glutathione; Malondialdehyde.

#### INTRODUCTION

Khat (*Catha edulis* Forsk) is an evergreen bush that can grow to the height of an oak tree in the wild. The leaves are shiny and leathery, with serrated edges; the young leaves are light green and turning dark reddish green with age (Balint *et al.*, 2009; Cox and Rampes 2003; Getahun and Krikorian, 1971). Millions of people use fresh leaves of Khat as a recreational drug on daily bases for its euphoric and psychostimulant effect. Khat leaves are chewed slowly over several hours, and the juice of the masticated leaves is swallowed as part of deep-rooted socio-cultural tradition of the indigenous population living in East Africa and the Arabian Peninsula (Al-Hebshi and Skaug, 2005; Belew *et al.*, 2000; Patel, 2015). The active stimulant ingredients of fresh khat leaves are cathinone and cathin and when its leaves dry, cathinone, the more potent converts to cathin, the less potent substance (Belewe *et al.*, 2000; Al-Motarreb *et al.*, 2002).

Jazan region of Saudi Arabia lies at the far southwestern corner of the country

and is adjacent to Yemen, where many types of khat trees are grown and where the prevalence of khat chewing is high (82% among men and 43% among women) (Numan, 2004).

Detailed studies on the effects of khat on female reproductive activity are limited. The available data reveal that chewing of khat has a negative impact during pregnancy and on fetal growth or lactation (Bedada and Engidawork, 2010; kedir *et al.*, 2013; Mwenda *et al.*, 2003). In addition to previous studies that addressed the adverse effects of khat consumption or its active ingredient cathinone on male reproductive performance (Al-Habori, 2005, Dalu, 2000; El-Shoura *et al.*, 1995; Islam *et al.*, 1990; Mwenda *et al.*, 2003). Many cross sectional studies performed to elucidate the prevalence of khat chewing among Jazani people and recorded the starting chewing khat during the age range 14-24 years, without neglecting that started less than 15 years old. They recorded chewing motivation was for fun (Ageely, 2009; Al-Sanasy, 2009; Alsanasy *et al.*, 2013; Ayano *et al.*, 2019; Mahfouz

*et al.*, 2015; Sheikh *et al.*, 2014). They recorded use of Khat trend is increasing among higher education students in Jazan region. The prevalence of khat chewing was 33.2% and was significantly higher for males 42.2% than for females 11.3% (Mahfouz *et al.*, 2015). The prevalence of chewing khat in this sensitive age range that characterized by the construction of personality and good health as well a period of fertility and giving future healthy generation. Islam religion educates his followers to keep away from everything that hurts their bodies, their lives and their souls and encourage them for benefits. Hence the use of khat through females with regard to the previously recorded health deleterious effects encourage research on the field of effect of chewing khat on female reproductive system to investigate.

Oxidative stress exerted by imbalance between productions of reactive oxygen species (ROS) and the biological system's capacity to detoxify the reactive intermediates or repair damage. This imbalance leads to the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. (Deavall *et al.*, 2012). Oxidative stress and production of ROS was identified to play a key role in the pathogenesis of subfertility in both males and females (Agarwal *et al.*, 2012). The role for antioxidants and ROS in the ovarian environment and female fertility and subfertility is an area deserving research (Ruder *et al.*, 2008).

This study designed to investigate the effect of oral Khat extract administration for 3 and 6 weeks on the oxidative stress status in rat's ovaries through the determination of the ovarian OS markers, MDA, GSH/GSSG, NO (nitrite/nitrate) in addition to SOD enzyme activity.

## MATERIALS AND METHODS

### Extraction of Khat (*Catha edulis* Forsk):

Extraction carried out by modification to the method (Harbone, 1984). One kg of Khat (*Catha edulis* Forsk) leaves was minced and macerated in 2.5 liter of 80 % (v/v) aqueous ethanol for 48 hours at room temperature with shaking. The supernatant was filtrated through a filter paper (0.45µm). This process was repeated two times in the same conditions. The extracts were collected, filtered and dried at room temperature. It was then weighed and the yield percentage (% of dry weigh) was determined to be 10%. The plate extract was then be refrigerated until use.

### Experimental animals:

The study used twenty-four female albino rats (*Rattus norvegicus*), weighing  $200 \pm 10$  g and housed in plastic cages, kept under controlled temperature of  $25 \pm 2$  °C and 12 h light / 12 h dark cycle throughout the experiment. The animals allowed adapting to the laboratory conditions for one week before the beginning of the experiment. Commercial rodent pellet diet and water were available *ad libitum*. Animals divided into two equal groups as follows:

- 1- Control groups (C3w and C6w): administered 1ml CMC (0.5 g/100ml carboxymethylcellulose) P.O. daily for 3 and 6 weeks.
- 2- Khat groups (Khat 3w and Khat 6 w): administered 1ml P.O. daily dose of 150 mg/kg khat extract suspended in CMC for 3 and 6 weeks. Dose selection based on overdose of the average daily khat chewers (500 mg/kg of dry plant) (Al-Hashem *et al.*, 2011).

### Tissue samples preparation and biochemical assays

Animals from control and treated groups the day after completion of each period of treatment sacrificed and the

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ovaries excised from each animal, cleaned, dried and weighed. Each ovary homogenized in 1/10 weight/volume of 75% aqueous HPLC grade methanol. The homogenate was centrifuged at 4000 rpm for 10 min and the supernatant used for application to High-Performance Liquid Chromatography (HPLC) analysis in sample volume application 20  $\mu$ l. Each ovary sample will use for determination of the ovarian OS markers, malondialdehyde (MDA), reduced glutathione (GSH), oxidized glutathione (GSSG), nitric oxide (nitrite/nitrate) by HPLC as described in our previous studies and the chromatographic separation of reference standard and sample example illustrated in Figure (1)(Arafa et al., 2010, Rawi *et al.*, 2011). In addition to superoxide dismutase (SOD) enzyme activity using spectrophotometric kits according to Nishikimi *et al.* (1972).

#### Statistical analysis:

Data expressed as means  $\pm$  SE. Statistical analysis evaluation by one-way analysis of variance (ANOVA) with LSD post hoc test and comparisons performed

to assess the significance of differences among various groups at  $p < 0.05$  using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

### RESULTS

Data recorded in Table (1) showed very high significant effect between means of all groups for each recorded parameter, SOD, MDA, NO and GSH/GSSG. In addition to data represented in Figure (2) revealed significant decrease in SOD enzyme activities, NO and GSH/GSSG in treated groups for 3 and 6 weeks periods as compared with their corresponding normal control values. They recorded percentage changes from control values, (-26.86 and -20.30) for SOD, (-45.15 and -53.36) for NO and -22.22 and 23.53) for GSH/GSSG at 3 and 6 weeks intervals, respectively. On the contrary, data about MDA showed significant increase in treated groups throughout the experimental periods as compared with the corresponding control values and verified percentage changes from control values, (42.11 and 75.47) after 3 and 6 weeks of treatment, respectively.

**Table (1): Effect of khat extract administration for 3 and 6 weeks in female albino rats on the ovarian OS markers.**

Groups Parameter	SOD (U/g)	MDA (ng/g)	NO ( $\mu$ g/g)	GSH/GSSG ( $\mu$ g/g)
<b>C3w</b>	188.67 $\pm$ 6.54 <sup>a</sup>	0.57 $\pm$ 0.03 <sup>a</sup>	6.60 $\pm$ 0.28 <sup>a</sup>	0.18 $\pm$ 0.005 <sup>a</sup>
<b>Khat 3w</b>	138.00 $\pm$ 7.28 <sup>b</sup>	0.81 $\pm$ 0.05 <sup>b</sup>	3.62 $\pm$ 0.16 <sup>b</sup>	0.14 $\pm$ 0.001 <sup>b</sup>
<b>C6w</b>	167.50 $\pm$ 5.44 <sup>c</sup>	0.53 $\pm$ 0.03 <sup>a</sup>	6.84 $\pm$ 0.35 <sup>a</sup>	0.17 $\pm$ 0.01 <sup>a</sup>
<b>Khat 6w</b>	133.50 $\pm$ 7.45 <sup>b</sup>	0.93 $\pm$ 0.07 <sup>b</sup>	3.19 $\pm$ 0.18 <sup>b</sup>	0.13 $\pm$ 0.01 <sup>b</sup>
<b>F (p)</b>	14.94* ( $<0.001^*$ )	15.790* ( $<0.001^*$ )	57.440* ( $<0.001^*$ )	15.548* ( $<0.001^*$ )

Data expressed in mean  $\pm$  SE (N=6) and compared by F test (ANOVA) using Post Hoc Test (LSD) for comparison between groups. The different superscripts are significant\* at  $p \leq 0.05$ .

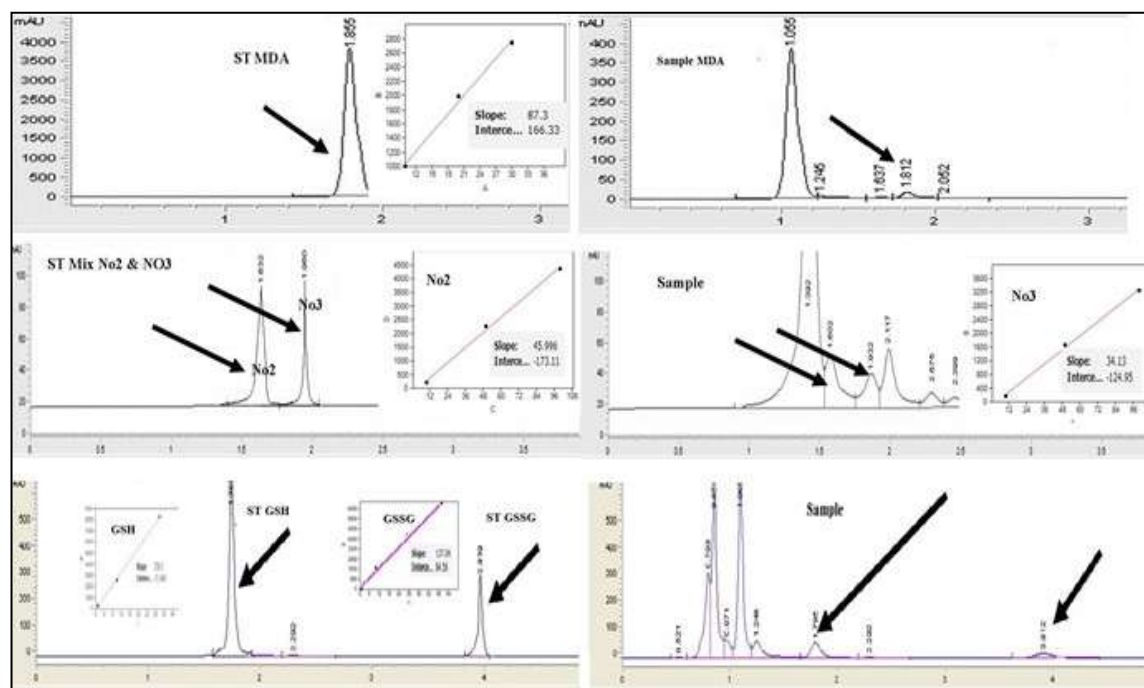


Fig. (1): HPLC Chromatogram of MDA, Nitrit, Nitrate, GSH and GSSG reference standards and sample examples.

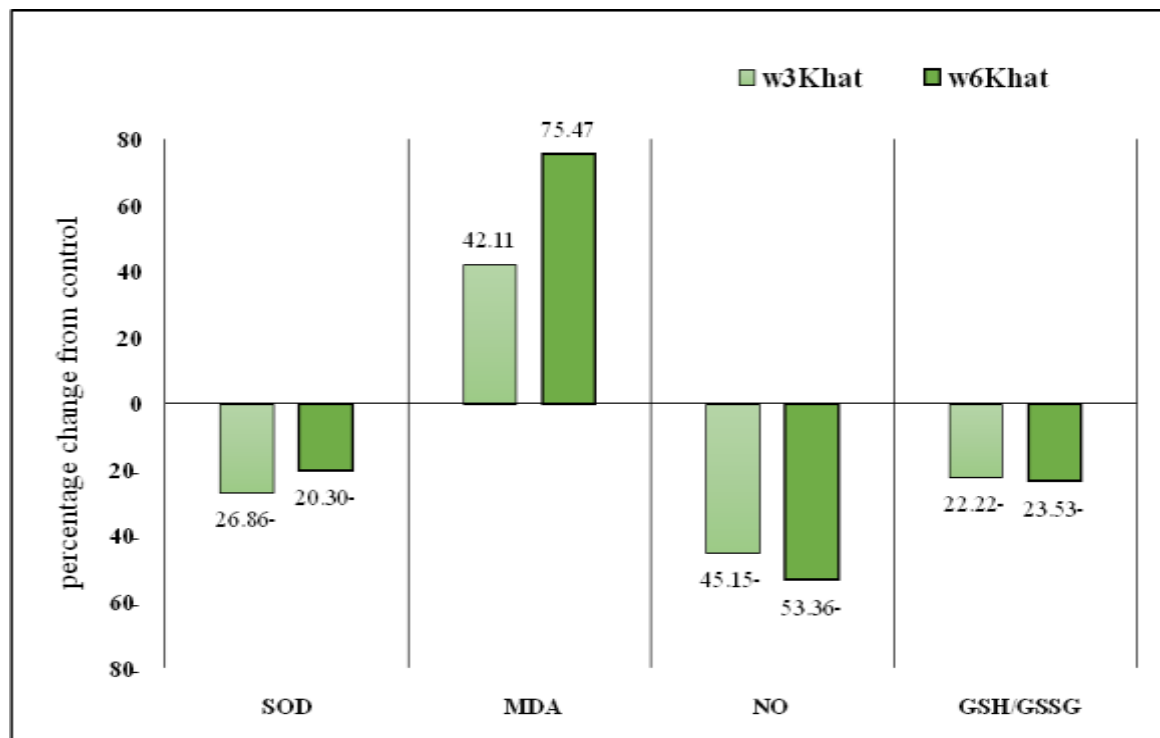


Fig. (2): Effect of khat extract administration for 3 and 6 weeks on the percentage changes from control value of the recorded OS markers, SOD, MDA, NO and GSH/GSSG ratio in rat ovarian tissue.

## DISCUSSION

Oxidative stress and production of ROS as pro-oxidant molecules may cause reduction in the antioxidant defense mechanisms of the body and identified to play a key role in the pathogenesis of subfertility in both males and females (Agarwal *et al.*, 2012).

In the present study, results revealed significantly decreased SOD enzyme activity throughout the experimental periods, indicating the consumption of this antioxidant enzyme against the overproduction of the free radicals, and catalyzed the dismutation of superoxide radical into hydrogen peroxide ( $H_2O_2$ ) and molecular oxygen ( $O_2$ ) (Ighodaro and Akinloye, 2018). In addition, Sabatini *et al.* (2000) demonstrated that the SOD activity in follicular fluid from polycystic ovarian syndrome infertile women is significantly lower than that in proven fertility; suggested the role of SOD in the pathophysiology of the ovary. On the other hand, previous studies using micromodels with deletions of antioxidant genes reported that ovaries of adult female mice had reduced numbers of preovulatory follicles and corpora lutea and they were subfertile because of a defect in late follicular development or ovulation (Matzuk *et al.*, 1998; Devine *et al.*, 2011; Arianmanesh *et al.*, 2011).

Moreover, MDA is the final degradation product of membrane proteins during OS and only index for lipid peroxidation but its interaction with DNA and proteins has often been referred to as potentially mutagenic (Del Rio *et al.*, 2005) and reflects the degree of cell injury (Sharma 2004) as observed in ovarian elevated level of MDA in epithelial ovarian cancer (Caglayan *et al.*, 2017). As regard to MDA in our study there were significant increases in MDA contents of 3 and 6 weeks treatment compared with the corresponding control. In addition, ovarian NO level showed significant decreases in

Khat treated groups as compared to the corresponding control. Nitric oxide is one of intraovarian mediators with possible effects in the ovulatory process and in the regulation of corpus luteum function (Zackrisson *et al.*, 1996). Ovulation involves several biochemical pathways, which induce breakdown of extracellular matrix in the follicle wall with changes in the vasculature with evidenced role of NO in follicular rupture (Shukovski and Tsafrin, 1994; Bonello *et al.*, 1996). Besides, direct effect of NO in ovulation at the ovarian level predicted by NO inhibitor reduced ovulation rate in *in vitro* rat ovary (Bonello *et al.*, 1996). In addition to the demonstrated NOS mRNA in the rat ovary with maximal amounts of eNOS mRNA were present in the ovary at a time just prior to ovulation (Van Voorhuis *et al.*, 1995). In addition, many sensory neurons projecting to the ovary contain NOS and release NO that, may participate in modulation of ovarian function in human, rats, and the circulating NO metabolites (nitrite and nitrate) observed to increase during follicular development (Rosselli *et al.*, 1994).

Glutathione referred to as scavenging antioxidants from the second line defense antioxidants, which scavenge or neutralize free radicals to inhibit chain initiation and break chain propagation reactions (Ighodaro and Akinloye, 2018). The ratio of reduced glutathione (GSH) with oxidized glutathione (GSSG) (GSH/GSSG) often used as a marker of OS within cells (Locigno and Castronovo, 2001; Townsend *et al.*, 2003). Our results indicated the significant decrease of the redox status showed by the ratio GSH/GSSG in ovarian tissues in Khat extract administered rats throughout the experimental periods. Normally the GSH/GSSG ratio exceeds 100/1, while in several models of OS this ratio decreased to values of 10:1 and even 1:1 (Chai *et al.*, 1994). Glutathione levels change rapidly during progression of meiosis and early

embryonic development of oocytes, and its high content at the time of fertilization is essential for male pronucleus formation and for embryonic development to the blastocyst stage. Previous study by Devine *et al.* (2011) suggested that OS had significant negative impacts on female fertility and gamete health. Recently, Ramadan *et al.* (2017) reported that ROS and antioxidant enzyme systems involved in the regulation of reproductive processes, including ovarian follicular development, luteal steroidogenesis, endometrial receptivity and shedding, embryonic development and implantation, in addition to the role of oxidant–antioxidant status in epithelial ovarian cancer (Caglayan *et al.*, 2017).

Khat toxicity recorded decreased activity of antioxidant enzymes due to ROs and OS in rats (Al- Qirim *et al.*, 2002; Al-Zubairi *et al.*, 2003), implicated by generation of free radicals despite of its present antioxidants as active ingredients (Al- Qirim *et al.*, 2002; Al-Akwa *et al.*, 2009; Aleryani *et al.*, 2011; Al-Hashem *et al.*, 2011) and depleted antioxidant defense mechanisms in cells required for its optimal activity causing oxidative damage (shewamene and Engidawork, 2014).

On the other hand, Khat extract prolonged exposure in mice induced total and partial sterility in male and post-implantation loss in female and reduced the percent pregnancy rates (Tariq *et al.*, 1986) and interacts with DNA metabolism as a potent genotoxic agent. (Abderrahman and Modallal, 2008).

### Conclusion:

Results of this study suggested that khat extract experienced ovarian OS status in rats.

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### تأثير القات على الإجهاد التأكسدي للمبيض في إناث الجرذان

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### المستخلص

يؤثر الإجهاد التأكسدي بشكل كبير على الصحة الانجابية في إناث الثدييات. استخدمت هذه الدراسة مجموعتين من إناث الجرذان الويستر وزن  $10 \pm 200$  جم والتي تم تجريعها فمياً. مجموعة ضابطة تم تجريعها (1 مل CMC) (0.5 جم/100 مل كاربوكسي ميثيل سيليلوز) ومجموعة القات تم تجريعها (1 مل مستخلص القات) (150 مجم/كج)، كل منهما لفترة 3 و 6 أسابيع. استخدمت أنسجة المبيض من كل مجموعة بعد فترتي التجربة لتقدير مؤشرات الإجهاد التأكسدي.

أظهرت النتائج نقصاً معنوياً في أنشطة أنزيم سوبر أكسيد ديسميوتاز ومستويات أكسيد النيتريك ونقصاً معنوياً لمستوي نسبة الجلوتاثيون المختزل إلى الجلوتاثيون المؤكسد (GSH/GSSG) بالإضافة إلى الزيادة المعنوية في محتوى المالونالدهايد وذلك في مجموعتي القات بعد 3 و 6 أسابيع مقارنة بقيم المجموعتين الضابنتين المناظرتين. كما أوضحت النتائج أن مبايض الفئران المجرعة بمستخلص القات في حالة إجهاد تأكسدي بسبب عدم التوازن بين إنتاج الشوارد الحرة ومضادات الأكسدة.