UNIVERSITI PUTRA MALAYSIA

BIOCHEMICAL AND MUTAGENIC EFFECTS OF 'KHAT' (CATHA EDULIS) IN RATS

ADEL SHARAF AL-ZUBAIRI

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By

ADEL SHARAF AL-ZUBAIRI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

June 2007
DEDICATION

TO MY FAMILY
Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

BIOCHEMICAL AND MUTAGENIC EFFECTS OF 'KHAT' (CATHA EDULIS) IN RATS

By

ADEL SHARAF AL-ZUBAIRI

June 2007

Chairman: Associate Professor Patimah Ismail, PhD

Faculty: Medicine and Health Sciences

Khat leaves were originally used as a stimulant and a remedy against diseases and khat chewing became a widespread habit that has a deep-rooted sociocultural tradition in Africa and the Middle East. The present study was undertaken to evaluate the biochemical and toxicological effects of crude Catha edulis extract sub-acute (7 weeks) administration and to investigate the biochemical, toxicological and mutagenic effects of Catha edulis crude extract sub-chronic (13 weeks) administration in rats. Seventy four Sprague-Dawley male rats were used in this study. The sub-acute treatment group (38 rats) was further divided into 4 groups (control group and 500, 1000 and 2000 mg/kg body weight treatment groups), while the sub-chronic treatment study group (36 rats) was subdivided into three further groups (control group and 1000 and 2000 mg/kg body weight treatment...
groups). For genotoxicity assessment we used chromosomal aberrations assay (CAs) and single cell gel electrophoresis assay (SCGE), the comet assay.

Body weight changes and food consumption were found to be not significantly different among all treatment groups when compared to the corresponding controls. We estimated the lipid peroxidation products, as a biomarker of oxidative stress and free radical activity, malondialdehyde, MDA (measured as plasma TBARS) and the results in the sub-acute (7 weeks) treatment group were found to be non-significantly different compared to the control group, while in the 13 weeks treatment groups, MDA levels in the 1000 and 2000 mg/kg body weight treatment groups were found to be significantly (P < 0.05) lower, by 28% and 30% respectively, compared to the control group.

Lipid profiles, uric acid, albumin, liver enzymes activities and total and prostatic acid phosphatase (ACP) results in the sub-acute treatment groups were found to be non-significantly affected compared to the control group. In contrast testosterone was found to be 2.8 and 2.4 folds significantly higher (P< 0.01) in the 1000 and 2000 mg/kg body weight treatment groups respectively, compared to the control group. These levels were also found to be increased in the 500 mg/kg body weight treatment by 54% compared to the control group although the increase was not significant.
Results of serum total cholesterol and HDL cholesterol concentrations after 13 weeks treatment with *Catha edulis* crude extract were found to be significantly higher by 18% and 15% respectively (P< 0.05), in the 1000 mg/kg body weight treatment group compared to the control group. For the genotoxicity assessment tests we observed conflicting results between the CAs and comet assay. The results of CAs assay in the 2000 mg/kg body weight treatment group were found to be significantly higher (7.38%) compared to the control group (2.2%) (P< 0.05), while in the 1000 mg/kg body weight treatment group 2.5% aberrated metaphases were observed. On the other hand results of DNA damage in the comet assay were observed to show no significant difference between treatment and control groups. However the predominant chromosomal aberrations scored in the CAs were chromatoid gaps followed by chromatoid breaks. We can conclude that *Catha edulis* leaves contribute antioxidant properties due to its polyphenolic constituents as well as testosterone up-regulation. Further investigations are recommended to elucidate the effects of fresh leaves of *Catha edulis* on chromosomes and other biomolecules using molecular techniques.
Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagaimemenuhi keperluan untuk ijazah Doktor Falsafah

KESAN BIOKIMIA DAN MUTAGENIK ‘KHAT’ (*CATHA EDULIS*) DALAM TIKUS

Oleh

ADEL SHARAF AL-ZUBAIRI

Jun 2007

Pengerusi: Profesor Madya Patimah Ismail, PhD

Fakulti: Perubatan dan Sains Kesihatan

Daun Khat (*Catha edulis*) asalnya digunakan sebagai stimulasi dan penawar terhadap penyakit dan kunyahan daun khat telah menjadi amalan yang meluas yang juga merupakan amalan tradisi di Afrika dan Timur Tengah. Pada kajian yang telah dijalankan ke atas tikus bagi menentu kesan biokimia dan toksik terhadap pengambilan ekstrak *Catha edulis* dalam masa 7 minggu untuk rawatan sub-akut dan kesan biokimia dan kesan ketoksikan dan mutagenik terhadap pengambilan ekstrak *Catha edulis* dalam masa 13 minggu untuk rawatan sub-kronik. Sebanyak 74 tikus jantan jenis Sprague-Dawley telah digunakan di dalam kajian ini. Bagi kumpulan rawatan sub-akut (38 ekor tikus), ianya dibahagikan kepada 4 kumpulan iaitu (kumpulan kawalan dan kumpulan rawatan bagi kepekatan 500, 1000 dan 2000mg/kg
jisim badan). Manakala bagi kumpulan kajian rawatan sub-kronik (36 ekor tikus) kemudian dibahagikan kepada 3 lagi kumpulan (kumpulan kawalan dan kumpulan rawatan bagi kepekatan 100 dan 2000mg/kg jisim badan). Bagi penilaian genotoxsisiti teknik Asai Aberasi Kromosom (CAs) dan Gel Elektroforesis Sel Tunggal (Pengasaian Komet) telah digunakan. Terdapat perbezaan yang tidak signifikan bagi perubahan jisim badan dan pengambilan makanan jika dibandingkan dengan kumpulan kawalan. Produk peroksida lipid telah diukur sebagai biomarker kepada stress oksidatif dan aktiviti radikal bebas, malanodialdehid, MDA (diukur sebagai TBRAS plasma) dan keputusan untuk kumpulan rawatan sub-akut (7 minggu) didapati terdapat perbezaan yang tidak signifikan jika dibandingkan dengan kumpulan kawalan. Manakala bagi kumpulan rawatan untuk 13 minggu pula, paras MDA untuk 1000 dan 2000 mg/kg jisim badan pula didapati signifikan (P<0.05) sebanyak 28 peratus dan 30 peratus berbanding dengan kumpulan kawalan.

Bagi keputusan profil lipid, asid urik, albumin, aktiviti enzim hati dan total dan prostatik asid fosfat (ACP) ke atas rawatan sub-akut didapati tidak signifikan jika dibandingkan dengan kumpulan kawalan. Walau bagaimanapun, testosterone didapati signifikan sebanyak 2.8 dan 2.4 lebih tinggi (p<0.01) bagi 1000 dan 2000 mg/kg jisim badan berbanding dengan
kumpulan kawalan. Paras ini juga didapati meningkat sebanyak 54 peratus bagi 500 mg/kg jisim badan jika dibandingkan dengan kumpulan kawalan walaupun peningkatan itu tidak signifikan.

Bagi keputusan total kolesterol dan HDL kolesterol, selepas 13 minggu rawatan menggunakan Catha edulis didapati signifikan sebanyak 18 peratus dan 15 peratus lebih tinggi, (p<0.05) untuk 1000 mg/kg jisim badan jika dibandingkan dengan kumpulan kawalan. Bagi ujian penilaian genotoksisiti terdapat perbezaan keputusan antara CAs dan pengasaian komet. Keputusan pengasaian CAs dalam 2000 mg/kg jisim badan kumpulan rawatan didapati mempunyai signifikan yang tinggi (7.38 peratus) jika dibandingkan dengan kumpulan kawalan (2.2 peratus) (P<0.05), manakala bagi kumpulan rawatan untuk 1000 mg/kg jisim badan didapati sebanyak 2.5 peratus aberasi metafasa. Sementara itu, keputusan untuk kerosakan DNA dalam pengasaian komet, mendapati tiada perbezaan yang signifikan di antara kumpulan rawatan dan kumpulan kawalan. Bagaimanapun, predominasi untuk aberasi kromosom di dalam CAs ialah ruang chromatoid diikuti dengan perpecahan chromatoid. Kesimpulannya, Catha edulis mungkin menyumbang sebagai bahan antioksidan berdasarkan kandungan polifenolik juga sebagai regulasi testosteron. Kajian yang lebih mendalam dicadangkan untuk memastikan kesan daun Catha edulis ke atas kromosom dan biomolekul yang lain menggunakan teknik molekul.
ACKNOWLEDGEMENTS

In the Name of ALLAH, the Beneficent, the Merciful

I owe first and foremost my profound gratitude to almighty ALLAH, the source of all inspiration and help, and without whose assistance, this study would not have come into the existence.

Deepest gratitude to my supervisor Associate Professor Dr Patimah Ismail for her continuous wise guidance during all stages of my research work and her constructive criticism and patience and for her willingness to help, listen and assist in every way in the midst of her heavy responsibilities. I also record my sincere appreciation to the committee members; Dr Chong Pei Pei and Associate Professor Dr Asmah Rahmat, for their wise guidance, valuable advice, suggestions and precious evaluation and valuable comments during the supervision of this thesis.

I sincerely appreciate and acknowledge all staff members and technicians who gave me a hand during the preparation of this work. Sincere thanks to Mr Nasir, Safarina, Zam and Ita for their help.
I certify that an Examination Committee has met on 1st June 2007 to conduct the final examination of Adel Sharaf Moh. Al-Zubairi on his Doctor of Philosophy thesis entitled “Biochemical and Mutagenic Effects of ‘Khat’ (Catha edulis) in Rats” in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the candidate be awarded the relevant degree. Members of the Examination Committee are as follows:

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Date: 3 AUGUST 2007
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This thesis submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee are as follows:

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School of Graduate Studies  
Universiti Putra Malaysia  

Date: 9 August 2007
DECLARATION

I hereby declare that the thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at UPM or other institutions.

ADEL SHARAF MOHAMMED AL-ZUBAIRI

Date: 15 July 2007
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The Sub-Chronic (13 weeks) Effects Study Group
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LIST OF ABBREVIATIONS

ACP Acid Phosphatase
ACTH Adrenocorticotrophic Hormone
ALP Alkaline Phosphatase
ALT Alanine aminotransferase
AMI Acute Myocardial Infarction
c-AMP cyclic-Adenosine Monophosphate
ANOVA Analysis of Variance
AST Aspartate aminotransferase
CAs Chromosomal Aberrations
CAT Catalase
CB Cytochalasin B
CCD Charge-coupled Device
CDKs Cyclin-Dependent Kinases
CGH Comparative Genomic Hybridization
CHO Chinese Hamster Ovary
CNS Central Nervous System
COL Cholchicine
DMSO Dimethylsulphoxide
DNA Deoxyribonucleic Acid
DSB Double Strand Breaks
<table>
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<th>Abbreviation</th>
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<tr>
<td>EDTA</td>
<td>Ethylenediamine Tetracetate</td>
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<tr>
<td>FBS</td>
<td>Fetal Bovine Serum</td>
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<td>GGT</td>
<td>Gamma Glutamyl Transpeptidase</td>
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<td>GK</td>
<td>Glycerol Kinase</td>
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<tr>
<td>GPO</td>
<td>Glycerol Phosphate Oxidase</td>
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<tr>
<td>GPx</td>
<td>Glutathione Peroxidase</td>
</tr>
<tr>
<td>GST</td>
<td>Glutathione-S Transferase</td>
</tr>
<tr>
<td>H₂O₂</td>
<td>Hydrogenperoxide</td>
</tr>
<tr>
<td>HDL-chol</td>
<td>High Denisty Lipoprotein cholesterol</td>
</tr>
<tr>
<td>IFCC</td>
<td>International Federation for Clinical Chemistry</td>
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<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
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<td>LDL-chol</td>
<td>Low Density Lipoprotein cholesterol</td>
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<td>LPL</td>
<td>Lipoprotein Lipase</td>
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<td>MDA</td>
<td>Malonydialdehyde</td>
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<td>M-FISH</td>
<td>Multiplex Fluorescent Hybridization</td>
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<tr>
<td>MN</td>
<td>Micronucleus</td>
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<tr>
<td>NaOH</td>
<td>Sodium Hydroxide</td>
</tr>
<tr>
<td>OECD</td>
<td>Organization for European Cooperation and Development</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate Buffered Saline</td>
</tr>
<tr>
<td>PCE</td>
<td>Polychromatic Erythrocyte</td>
</tr>
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<td>PEG</td>
<td>Polyethylene Glycol</td>
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<td>PHA</td>
<td>Phytohaemagglutinin</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>PSA</td>
<td>Prostatic Specific Antigen</td>
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<td>RNA</td>
<td>Ribonucleic Acid</td>
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<td>ROS</td>
<td>Reactive Oxygen Species</td>
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<tr>
<td>SCE</td>
<td>Sister Chromatid Exchange</td>
</tr>
<tr>
<td>SCGE</td>
<td>Single Cell Gel Electrophoresis</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SKY</td>
<td>Spectral Karyotyping</td>
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<td>SOD</td>
<td>Superoxide Desmutase</td>
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<td>Thiobarbituric Acid Reactive Substances</td>
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<td>Unscheduled DNA Synthesis</td>
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<tr>
<td>UV</td>
<td>Ultraviolet</td>
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<tr>
<td>VLDL</td>
<td>Very Low Density Lipoprotein</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
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CHAPTER 1

INTRODUCTION

Khat is the common name for the plant *Catha edulis* Forskal (Family: Celastraceae), a tree or large shrub growing in many countries of East and Central Africa and the Arabian Peninsula (Watt and Breger, 1962; Kalix, 1988). The young leaves and shoots (Khat) are chewed for their stimulating effects due to the plant's phenylalkylamines (Khatamines) particularly cathinone (Kalix and Braenden, 1985).

Khat grows wild in countries bordering the Red Sea and along the east coast of Africa. The people of these countries have chewed khat for centuries. There are several names for the plant, depending on its origin: chat, qat, qaad, jaad, miraa, mairungi, cat and catha. In most of the Western literature, it is referred to as khat. The leaves have an aromatic odour. The taste is astringent and slightly sweet. The plant is seedless and hardy, growing in a variety of climates and soils. Khat can be grown in drought areas where other crops have failed and also at high altitudes. Khat is harvested throughout the year. Planting is staggered to obtain a continuous supply.
(Luqman & Danowski, 1976). Khat is mainly grown in Ethiopia, Kenya, Yemen, Somalia, Sudan, South Africa and Madagascar. It has also been found in Afghanistan and Turkestan.

Previously, khat leaves were available only near to where they were grown. Recently, improved roads and air transport have allowed a much wider distribution. Khat is harvested in the early hours of the morning and sold in markets in late morning. It is presented as a bundle of twigs, stems and leaves, wrapped in banana leaves to preserve freshness (Luqman & Danowski, 1976).

Khat is a drug of natural origin (Kalix et al., 1991) that man has found for inducing pleasurable feelings and has become known and used worldwide, whereas the use of other drugs of natural origin having these properties remained more or less confined to the areas of their origin. The stimulating properties of the leaves of khat were probably known before those of coffee (El-Mahi, 1962). It was used in Yemen even before coffee (Lewin, 1931). Khat grows as an evergreen bush or tree, usually about 1-6 meters and even 25 meters high in favorable climates and soil conditions and frequently classified into several categories by the color of the branches and leaves.