Pharmacological study on the potential effect of antidepressant(s) on ovariectomized-induced osteoporotic rats

A thesis submitted for partial fulfillment of the requirements of the master degree in pharmaceutical sciences (Pharmacology and Toxicology)

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2019

دراسة دوائيه لتأثير مضادات الاكتئاب علي هشاشة العظام المحدثة تجريبيا في الجرذان بواسطه استئصال المبايض

رسالة مقدمة لاكمال متطلبات درجة الماجستير في العلوم الصيدلية (علم الادوية والسموم)

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2019

بسم الله الرحمن الرحيم

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صدق الله العظيم

سورة المجادلة آية ١١

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Acknowledgement

Firstly, I would like to express my sincere gratitude to Dr. Samar Saad Azab, Associate Professor in Pharmacology and Toxicology Department, Faculty of Pharmacy, Ain Shams University, for her continuous support and encouragement. I would like to thank her for her patience, motivation, and immense knowledge. Her guidance helped me in all the time of my research steps. She steered me in the right direction whenever she thought I needed it.

I would like to express my sincerest appreciation and gratitude to Dr. Hebatalla Ibrahim Ahmed, Associate Professor in Pharmacology and Toxicology Department, Faculty of Pharmacy (Girls), Al-Azhar University. I would like to thank her for her advice, guidance, generous help, kindness and continuous support. Her supervision and support truly helped me through the progression and smoothness of this work.

I would like to express my deepest appreciation to Dr. Ahmed Esmat Abdelrazek, Associate Professor in Pharmacology and Toxicology Department, Faculty of Pharmacy, Ain Shams University. The door to Dr. Ahmed office was always open whenever I had a question about my research or writing. Without his assistance and dedicated involvement in every step throughout the process, this thesis would have never been accomplished.

Finally, I must express my very profound gratitude to my beloved daughter Mona and my dearest Hani as they were the reason for my success in every step in my life. I would also like to thank my Sister Amany, my Father and my Brother for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

Nora Zakaria Mahmoud

Abstract

The interrelationship between osteoporosis and depression has been demonstrated in several but contradictory studies. The present study aimed to investigate the potential effect of antidepressants Imipramine& Fluoxetine on ovariectomized-induced osteoporosis in rats, thus re-positioning their therapeutic indications as anti-osteoporotic drugs. Two weeks following bilateral ovariectomy, rats were treated with Estradiol, Imipramine and Fluoxetine for two weeks. At the end of 6 weeks, depression studies were conducted i.e. open field and forced swimming tests. Bone turnover biomarkers (serum calcium (Ca), serum alkaline phosphatase (ALP), serum osteocalcin, femur osteoprotegrin (OPG) and femur receptor activator of nuclear factor κB ligand (RANKL) were determined. Histopathological examination and Electron Microscope examination of trabecular femoral bone were performed and the trabecular morphological parameters were determined by computed tomography CT. Regarding bone histopathology, imipramine exerted a partial restoration of bone structure while estradiol and fluoxetine completely restored bone mass compared to the corresponding osteoporosis group. Besides, Electron Microscope examination revealed that imipramine demonstrated a partial restoration of bone structure while estradiol and fluoxetine completely restored bone mass compared to the corresponding osteoporosis group. In bone morphometric parameters, treatments significantly improved trabecular density by about 70%, 66% and

63% respectively. Trabecular thickness was significantly elevated by about 41%, 42% and 43% respectively compared to the osteoporosis group. Treatment with Estradiol, Imipramine and Fluoxetine decreased the values of serum ALP by about 70%, 58% and 59% respectively. They also reduced serum Osteocalcin by about 69%, 69% and 68% respectively. Furthermore, they reduced RANKL value by about 59%, 66% and 65% respectively. In contrast, they significantly elevated the values of OPG by about 581%, 586% and 629% respectively and increased OPG/RANKL ratio by about 583%, 1042% and 837% respectively compared to the corresponding osteoporosis groups. These treatments also reduced depressive features caused by ovariectomy in open field test and forced swimming test. Swimming score in forced swimming test and Ambulation frequency in open field test were found to be strongly correlated with ALP, osteocalcin, OPG, RANKL, trabecular density and trabecular thickness. In conclusion, Imipramine and Fluoxetine have shown potential osteoprotective effects on ovariectomized-induced osteoporosis in rats, which mediate re-positioning their therapeutic indications as anti-osteoporotic drugs.

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List of Abbreviations

A	Absorbance
AAS	Atomic absorption spectrometry
ALP	Serum alkaline phosphatase
AMP	2-amino-2-methyl-1-propanediol
ANOVA	Analysis of Variance
BMD	Bone mineral density
Ca	Serum calcium
cDNA	Complementary deoxyribonucleic acid
CT	Computed tomography
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FST	Forced swimming test
H & E	Hematoxylin and eosin
HE	Histopathological examination
HRP	Horseradish peroxidase
kV	kilovolt
MAB	Monoclonal antibodies
MAOIs	Monoamine oxidase inhibitors
MDD	Major Depressive Disorder
OC	Osteocalcin
OD	Optical density
OFT	Open field test
OPG	Osteoprotegrin
OPG/RANKL	OPG RANKL ratio
OVX	Ovariectomy
RANKL	Receptor activator of nuclear factor κB ligand
RNA	Ribonucleic acid
rpm	Rotation per minute
RT-PCR	Real time polymerase chain reaction
SEM	Standard error of the mean
SNRI	Serotonin noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
Tb	Trabecular
TB.TH	Trabecular thickness
TCA	Tricyclic antidepressants
TMB	Tetramethylbenzidine
TRI reagent	TRIzol reagent

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