“Study on the effects of Naringin and Clozapine combination in an experimental model of Schizophrenia in rats“

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First and foremost, no words can be ever said expressing my deep thanks to ***GOD*** *for helping, supporting, encouraging, providing me the ability to complete this work and blessing me with generous professors while carrying out my research.*

I would like to express my great appreciation and thanks to ***Prof. Ebtehal El-demerash Zaki****, Professor of Pharmacology and Toxicology, Head of department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, who has helped me to make this work possible by her great effort, support and endless help from the scratch start till the end. I would like also to thank her for the great effort she did towards our department.*

Most heartfelt thanks are due to ***Prof. Marianne George Tadros,*** *Professor of Pharmacology and Toxicology, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, for her support, effort, encouragement, guidance and indispensable help. Her precious advices were always pushing me forward.*

I would like to express my appreciation and gratitude to ***Dr. Ahmed Esmat Abdel-razik,*** *Associate professor of Pharmacology and Toxicology, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, for his support and encouragement. I would like to thank him too for his continuous guidance and indispensable help throughout thesis writing and revision.*

*Foremost, I would like to express my sincere gratitude to **Dr. Esther Tharwat Menze**, Associate professor of Pharmacology and Toxicology, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, for the continuous support of my PhD study, for her patience, motivation, enthusiasm, and immense knowledge. Her guidance helped me in all the time of research starting from the research question to writing of this thesis. In fact, she was more than a supervisor, she never stopped supporting and encouraging me.*

It is my great pleasure to thank all members of Pharmacology and Toxicology Department, Faculty of Pharmacy, Ain Shams University, each one by name, for their continuous support and help. Really I enjoyed and still enjoying being a member of this department.

*Finally, but of great importance, I wish to express my deep gratefulness and thanks to my father **Prof. Youssif George Youssif** and my brother **Eng. Michael Youssif George** for their support, continuous prayers for which my mere expression of thanks likewise does not suffice and for all what they endured to tolerate and uphold me in finishing this thesis.*

Mina Youssif George

Schizophrenia is a chronic, disabling and one of the major neurological illnesses affecting nearly 1% of the global population. Currently available antipsychotic medications possess several side effects. The current research aimed at investigating potential therapeutic add-on benefit to enhance the effect and cease the side effects of clozapine anti-schizophrenic. In this study, naringin was given to Wistar rats at a dose of 100 mg/kg orally, alone or in combination with clozapine 5 mg/kg i.p. To induce schizophrenia, ketamine was administered at a dose of 25 mg/kg i.p. for 14 consecutive days. Ketamine induced positive, negative and cognitive schizophrenia symptoms together with neurotransmitters' imbalance. In addition, ketamine administration caused significant glutathione depletion, lipid peroxidation and reduction in catalase activity. Naringin and/or clozapine treatment significantly attenuated ketamine-induced schizophrenic symptoms and oxidative injury. Additionally, ketamine provoked apoptosis via increasing Bax/Bcl2 expression, caspase-3 activity, and cytochrome-c and Akt protein expression while naringin/clozapine treatment significantly inhibited this apoptotic effect. Moreover, naringin activated the neurodevelopmental wnt/β-catenin signaling pathway evidenced by increasing pGSK-3β and reducing pβ-catenin protein expression. Furthermore, naringin was able to reduce main clozapine side effects including agranulocytosis, dyslipidemia, weight gain and hyperglycemia when added to clozapine treatment. Collectively, these findings may suggest that naringin possesses a potential therapeutic add-on effect against ketamine-induced schizophrenia.

Keywords: Naringin; ketamine-induced schizophrenia; clozapine side effects; antioxidant; apoptosis; Wnt/β-catenin.

4-AAP	4-amino-antipyrine
ACh	Acetylcholine
AChE	Acetylcholinesterase
Akt	Protein Kinase B
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
APC	Adenomatous Polyposis Coli
BAX	BCl-2 Associated X
BCA	Bicinchoninic acid
BCl-2	B-cell lymphoma-2
BDNF	Brain-derived Neurotrophic Factor
BVA	Bovine Serum Albumin
cAMP	Cyclic Adenosine Monophosphate
CAT	Catalase
CE	Cholesterol Esterase
CK1α	Casein Kinase 1α
CMC	Carboxy Methyl cellulose
CO	Cholesterol Oxidase
CPT-1	Carnitine Palmitoyltransferase-1
D2 Receptots	Dopamine Receptors
DAT	Dopamine Transporter
DCHBS	3,5-dichloro-2-hydroxy benzene sulfonic acid
DTNB	5,5’ dithiobis (2-nitrobenzoic acid)
DTT	Dithiotheritol
Dvl	Disheveled
ECD	Electrochemical Detector
FZ	Frizzled
GABA	Gamma Amino Barbituric Acid
GluR	Glutamate Receptors
GlyT1	Glycine Transporter 1
GP_X	Glutathione Peroxidase
GR	Glutathione Reductase
GSH	Reduced Glutathione
GSK-3β	Glycogen Synthase Kinase -3 β
H_2O_2	Hydrogen peroxide

HRP	Horseradish Peroxidase
IAP	Inhibitors of Apoptosis Protein
IL-6	Interleukin-6
iNOS	Inducible Nitric Oxide Synthase
IκB	Inhibitor of kappa B
K_2HPO_4	Dipotassium hydrogen phosphate
KH_2PO_4	Anhydrous potassium dihydrogen phosphate
Lrp5/6	Low Density Lipoprotein 5/6
mAChRs	Muscarinic Acetylcholine Receptors
MAO	Monoamine Oxidase
MDA	Malondialdehyde
mTORC2	mammalian target of rapamycin complex 2
nAChRs	Nicotinic Acetylcholine Receptors
NF-κB	Nuclear Factor kappa B
NMDA	N-Methyl D- Aspartate
OD	Optical Density
PDK1	3-phosphoinoitide-dependent protein kinase 1
PI3K	Phosphatidylinositol 3-kinase
PI3P	Phosphatidylinositol 3,4,5 trisphosphate
pNA	p-nitroaniline
PPI	PrePulse Inhibition
PVDF	Polyvinylidine Fluoride
ROS	Reactive Oxygen Species
SDS	Sodium dodecyl sulfate
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SP	Sucrose Preference
SREBP	Sterol Regulatory Element-binding Proteins
SOD	Superoxide Dismutase
TBA	Thiobarbituric acid
TBS	Tris Buffered Saline
TBARS	Thiobarbituric Acid Reactive Substances
TBS	Tris Buffered Saline
TCA	Trichloroacetic Acid
TCF/LEF	T-cell-specific transcription factor/lymphoid

	enhancer-binding factor
TEMED	Tetramethylethylenediamine
TGs	Triglycerides
TNF-α	Tumor Necrosis Factor-α
UCP-2	uncoupling protein-2