Faculty of Veterinary Medicine
Department of Veterinary Hygiene and Management

Cairo University

Effect of Antioxidants on behavioural, biochemical and histopathological modifications (neuroinflammation, neurodegeneration) in Alzheimer's Disease Rat Model

A thesis presented by

Eman Hany Hassan Abdelnaby

(BVSc. Cairo University, 2010; MVSc. Cairo University, 2014)

For the degree of

Ph.D. in Veterinary Medicine Science

(Animal Behaviour and Management)

Under supervision of

Prof. Dr. Mervat Mahmoud Kamel

Professor of Animal and Poultry Behaviour and Management
Faculty of Veterinary Medicine
Cairo University

Prof. Dr. Heba Said Ellethey

Professor of Animal and Poultry Behaviour and Management
Faculty of Veterinary Medicine
Cairo University

Dr. Kassem Gabr Al-iraqi

Assistant Professor of Animal and Poultry Behaviour and Management
Faculty of Veterinary Medicine
Cairo University

(2018)

Cairo University
Faculty of Veterinary Medicine
Veterinary Hygiene and Management

Approval Sheet

The examination committee at 9 / 8 / 2018 approved the PhD Thesis (Veterinary Hygiene and Management) presented by Eman Hany Hassan after the required correction have been done .

Examination Committee **Signature**

Prof. Dr. Hosny H. Emeash
Professor of Animal Behaviour and Management
Fac. Vet. Med., Cairo University

Prof. Dr. Essam Moustafa Abd Elgawad
Professor of Animal Behaviour and Management
Fac. Vet. Med., Cairo University

Prof. Dr. Mervat Mahmoud Kamel
Professor of Animal Behaviour and Management
Fac. Vet. Med., Cairo University

Prof. Dr. Heba Saeed Ellethey
Professor of Animal Behaviour and Management
Fac. Vet. Med., Cairo University

Dr. Kassem Gabr El-Iraqi
Assistant Professor of Animal Behaviour and Management
Fac. Vet. Med., Cairo University

Supervision Sheet

Effect of Antioxidants on behavioural, biochemical and histopathological modifications (neuroinflammation, neurodegeneration) in Alzheimer's Disease Rat Model

A dissertation submitted

by

Eman Hany Hassan Abdelnaby

(BVSc. Cairo University, 2010; MVSc. Cairo University, 2014)

Under the supervision of

Prof. Dr. Mervat Mahmoud Kamel

Professor of Animal and Poultry
Behaviour and Management
Faculty of Veterinary Medicine
Cairo University

Prof. Dr. Heba Saied Ellethey

Professor of Animal and Poultry
Behaviour and Management
Faculty of Veterinary Medicine
Cairo University

Dr. Kassem Gabr Al-iraqi

Assistant Professor of Animal and Poultry
Behaviour and Management
Faculty of Veterinary Medicine
Cairo University

Cairo University
Faculty of Veterinary Medicine
Department of Veterinary Hygiene and Management

Name: Eman Hany Hassan Abdelnaby
Nationality: Egyptian.
Date of Birth: 25/03/1988.
Place of Birth: Egypt.
Degree: Ph.D. degree of Veterinary Medicine Sciences (Animal and Poultry Behaviour and Management).

Title: Effect of Antioxidants on behavioural, biochemical and histopathological modifications (neuroinflammation, neurodegeneration) in Alzheimer's Disease Rat Model**.**

Under supervision of:

- Prof. Dr. Mervat Mahmoud Kamel (Professor of Animal and Poultry Behaviour and Management, Department of Veterinary Hygiene and Management, Faculty of Veterinary Medicine, Cairo University).
- Prof. Dr. Heba Saied Ellethey (Professor of Animal and Poultry Behaviour and Management, Department of Veterinary Hygiene and Management, Faculty of Veterinary Medicine, Cairo University).
- Dr. Kassem Gabr Al-iraqi (Assistant Professor of Animal and Poultry Behaviour and Management, Department of Veterinary Hygiene and Management, Faculty of Veterinary Medicine, Cairo University).

Abstract

The present study was designed to evaluate the ameliorating and protective effect of caffeine (CF), Chia extract (CH) and *Lepidium Sativum* extract (LS) on aluminum chloride ($AlCl_3$) induced AD rat model. 128 adult Wistar male rats were allocated into 8 groups of 16 animals each, where control group (C) was supplied with normal tap water, while AD group was administered $AlCl_3$ in drinking water at 200 mg/kg body weight. AD ameliorated groups with caffeine (CF-AD), chia (AD-CH) and LS (AD-LS) were exposed to $AlCl_3$ alternatively with the ameliorating treatments in a day after day regime, while in CF, CH and LS groups rats were administered the different treatments alternatively with plan water. All groups received their respective treatments for 4 months after which behavioural analysis was performed including open field test (OFT) and elevated plus maze to assess anxiety-like behaviours, Y-maze test and novel object recognition test (NOR) to assess memory and learning abilities and forced swim test (FST) to evaluate the depression-like behaviour. After monitoring the behavioural activities, rats were decapitated, and their brains and hippocampus samples were collected for analysis of oxidative status (SOD, GSH, GSSG, MDA, 8OHdG, NO), metabolic dysfunction (ATP, PC, PS) and neurochemical profile (DA, DOPAC, HVA, 5-HT, 5-HIAA). Our obtained results revealed that chronic $AlCl_3$ exposure significantly increased cognitive dysfunction, anxiety like behaviours as well as depression in the AD group compared to control rats. Significant alterations were seen in oxidative profile and metabolic dysfunctions. A significant decline in levels of monoamines was also observed. Typical hallmarks of AD were noticeably found in the hippocampus tissue. Regarding the ameliorative treatments, our findings showed that the behavioural impairments caused by $AlCl_3$ were significantly attenuated but with various degrees according to the applied treatments, whereas LS was the dominant. Moreover, a potential antioxidant effect was observed in the biochemical assays. The microscopic findings showed enhancement in the histoarchitecture pattern of the hippocampus. For the protected groups, all results improved but were almost close to the control animals. Finally, it is concluded that medicinal herbs could be a potential strategy for AD management, with highlighting the promising effects of LS for further implementations.

Keywords: Alzheimer's disease- Antioxidants- Chia seeds- Oxidative stress- Caffeine- neurodegeneration – *Lepidium sativum* - animal model- Memory deficits- Medicinal herbs.

Dedication

To my mentors,

my dedicated husband,

& my family...

I couldn't have done this without you…

Thanks for all of your support along the way!

Acknowledgements

In the name of "ALLAH" most gracious, most merciful, I am extremely grateful and sincerely appreciated to ***Prof. Dr. Mervat Mahmoud Kamel,*** *Professor of Animal & Poultry Behaviour and Management, Faculty of Veterinary Medicine, Cairo University, for her scientific supervision, untiring help, valuable assistance, constant encouragement, valuable guidance, continuous interest, innovative ideas and fruitful opinions throughout the whole work.*

I would like to express my sincere appreciation and gratitude to ***Prof. Dr. Heba Saied Ellethey,*** *Professor of Animal & Poultry Behaviour and Management, Faculty of Veterinary Medicine, Cairo University, for her supervision, continuous support through my study and related research, as well as her patience, motivation, and immense knowledge. Her guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my Ph.D.*

I would like to express my sincere thanks to ***Dr. Kassem Gabr Al-iraqi,*** *Assistant Professor of Animal & Poultry Behaviour and Management, Faculty of Veterinary Medicine, Cairo University, for his supervision, guidance and sentimental support.*

Sincere gratitude is extended to ***Prof. Dr. Ciobica Alin,*** *Professor of Animal Physiology, Faculty of Biology, Alexandru Ioan Cuza University, Romania, for his generous help throughout the whole study and for providing all supplies and facilities needed for the execution of the pilot study that lasted from October 2016 till March 2017.*

Many thanks to ***Dr. Faten Fathy,*** *Assistant Professor at Pathology Department, Faculty of Veterinary Medicine, Cairo University, for doing the histopathological examination, and* ***Dr. Ramadan Sary,*** *Lecturer at Anatomy Department, Faculty of Veterinary Medicine, Cairo University, for his exerted efforts in the preparation of the herbal extracts. Same gratitude extended to* ***Dr. Omar Farid*** *at National Organization for Drug Control and Research, for conducting the biochemical analysis related to this work.*

I also acknowledge with thankfulness all of my colleagues at Faculty of Veterinary Medicine, Cairo University, and Faculty of Biology, Alexandru Ioan Cuza University, for their friendly cooperation, and support.

I would like to express my thanks to my parents, and my husband for their patience, support and continuous encouragement whom without their constant love and support I would not have been in the privileged position to undertake and complete my Ph.D. research, as well as achieve what I have so far in my life.

Table of Contents