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شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

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شبكة المعلومات الجامعية

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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بالرسالة صفحات لم ترد بالأصل

CLINICAL, BIOCHEMICAL AND EXPERIMENTAL STUDY ON THE ROLE OF FREE RADICALS AND ANTIOXIDANTS IN PRIMARY GENERALIZED TONIC CLONIC SEIZURES

Thesis
Submitted in Partial Fulfillment of the Requirements of
Doctorate degree
In
NEUROLOGY

BY

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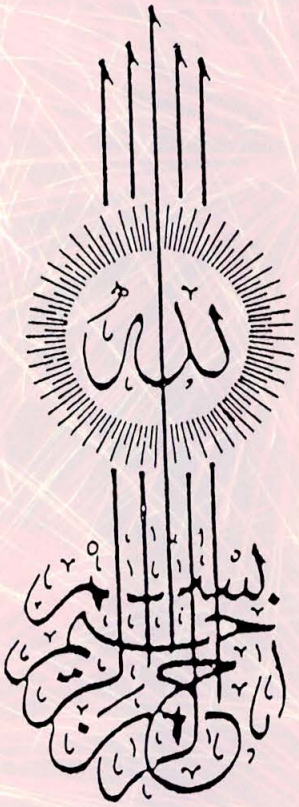

وما أوتيتم من العلم إلا قليلا

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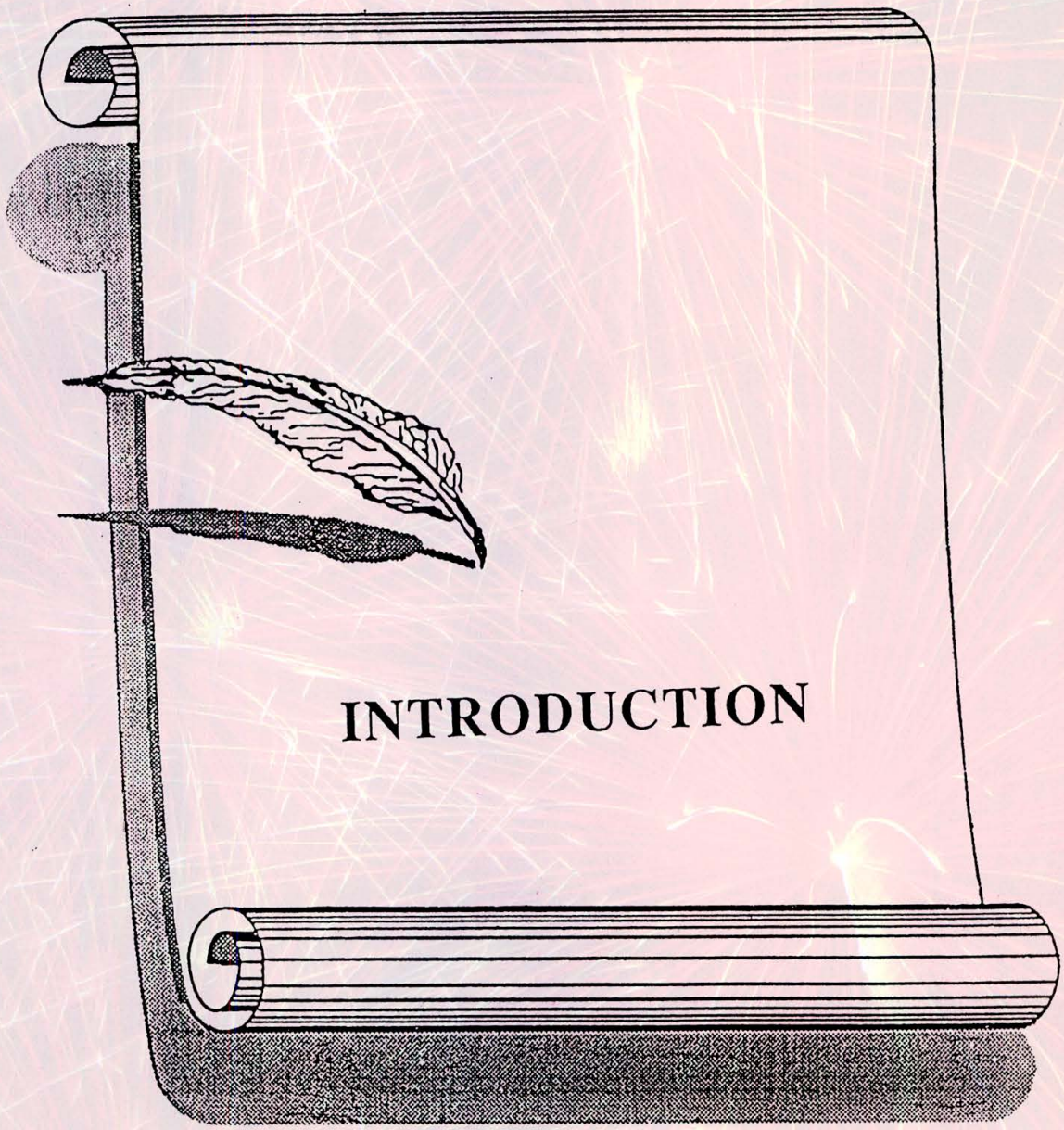
CONTENTS

ABBREVIATIONS

ACDs	=	Anticonvulsant drugs
AEDs	=	Antiepileptic drugs
CA	=	Catalase
CBZ	=	Carbamazepine
cGMP	=	Cyclic guanosine monophosphate
CNS	=	Central nervous system
Freq	=	Frequent
FRs	=	Free radicals
FRSEs	=	Free Radical Scavenging Enzymes
GABA	=	Gamma-aminobutyric acid
GPX	=	Glutathione peroxidase
GR	=	Glutathione reductase
GSH	=	Glutathione
GTCS	=	Generalized tonic clonic seizure
H_2O_2	=	Hydrogen peroxide
$HO^{\cdot}$	=	Hydroxyl radical
i.c.v.	=	Intracerebroventricular
Infreq	=	Infrequent
i.p.	=	Intraperitoneal
L- NAME	=	L-nitroamine mono-methyl ester
LPO	=	Lipid peroxidation
MDA	=	Malondaildehyde
NMDA	=	N-Methyl-D-Aspartate
NO	=	Nitric oxide
Mono	=	Monotherapy
NOS	=	Nitric oxide synthase
O_2^{-}	=	Superoxide
$ONOO^{-}$	=	Peroxynitrite
PB	=	Phenobarbitone
PHT	=	Phenytoin
Poly	=	Polytherapy
ROS	=	Reactive oxygen spices
SOD	=	Superoxide dismutase
Unmed	=	Unmedicated
VPA	=	Valproate



INTRODUCTION

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Epilepsy is, unquestionably, one of the commonest neurological disorders. The mechanism of epileptogenesis is not clearly established *(Kurekci et al., 1995).*

In 1988, *Davison et al.*, postulated that there is a role for free radicals in numerous neurological disorders. As the brain contains large amount of lipid in myelin sheaths, it is considered as a logical target of free radicals damage *(Choi, 1993).* Thus, the hypothesis that free radicals are involved in the pathogenesis of certain central nervous system (CNS) diseases, has gained increasing popularity in recent years *(Choi, 1993).*

Free radicals have been postulated to contribute in neuronal loss in cerebral ischemia *(Demopoulos et al., 1980),* seizures disorders *(Lange et al .,1980; Torbati et al., 1992),* schizophrenia *(Cadet, 1988),*aging *(Harmon, 1987; Pryor, 1987),* Parkinson's disease *(Yoshikawa ,1993 ;Youdim and Lavie ,1994),* and Alzheimer disease *(Richardson et al ., 1990).*

Free radicals are generated from the electromagnetic excitation of molecular oxygen, degradation of reactive oxygen species, atmospheric pollutants, such as nitric and nitrous oxide, and from non oxygen containing compounds, such as carbon tetrachloride or chloroform *(Bonorden and Pariza, 1994).*

Free radicals of oxygen are generated during many normal biochemical reactions in living tissues. The unpaired electron makes these compounds highly reactive. They can initiate disruptive peroxidation reactions with proteins, lipids and nucleic acid, which are important to the survival of cells. A fairly complex defense system has evolved to minimize

the damage that might occur *(Jesberger and Richardson, 1991; Bonorden and Pariza, 1994).*

Antioxidants play an important role in protecting the body from an oxidative insult by peroxides, hydroxyl radicals and superoxide anion radicals. The principle antioxidant present in human blood are urate, vitamins C and E, superoxide dismutase (SOD) and protein particularly ceruloplasmin, albumin and lactoferrin. Intracellularly there are in addition the enzymes SOD, glutathione peroxidase, catalase and methionine sulfoxide reductase *(Halliwell and Gutteridge, 1989).*

The lipid peroxidation of cell membrane, due to increase in free radicals or decrease in activities of antioxidant defense mechanisms, has been suggested to play a role in the pathogenesis of different types of epilepsy as well as in the increased incidence of recurrence of seizures *(Willmore, 1990; Abbott et al., 1990).*

It has been suggested that part of the effectiveness of antiepileptic drugs (AEDs) is due to influencing free radical generating systems. An excessive free radicals production was found in epileptic patients under treatment with AEDs. More complex changes were seen in polytherapeutic combination *(Maertens et al., 1995).*

Oxidative stress (free radical generation exceeds antioxidant defense) occur in many diseases. Phenytoin (PHT) is known to initiate oxidative damage to proteins and lipids in murine maternal hepatic and embryonic tissue organelles. There was a decrease in the total antioxidant capacity and elevation in lipid hydroperoxide concentration in sera of epileptic patients receiving PHT *(Mahie and Dasgugta, 1997).*

Glutathione peroxidase (GPX) and superoxide dismutase (SOD) are the most important members of antioxidant defense mechanisms.

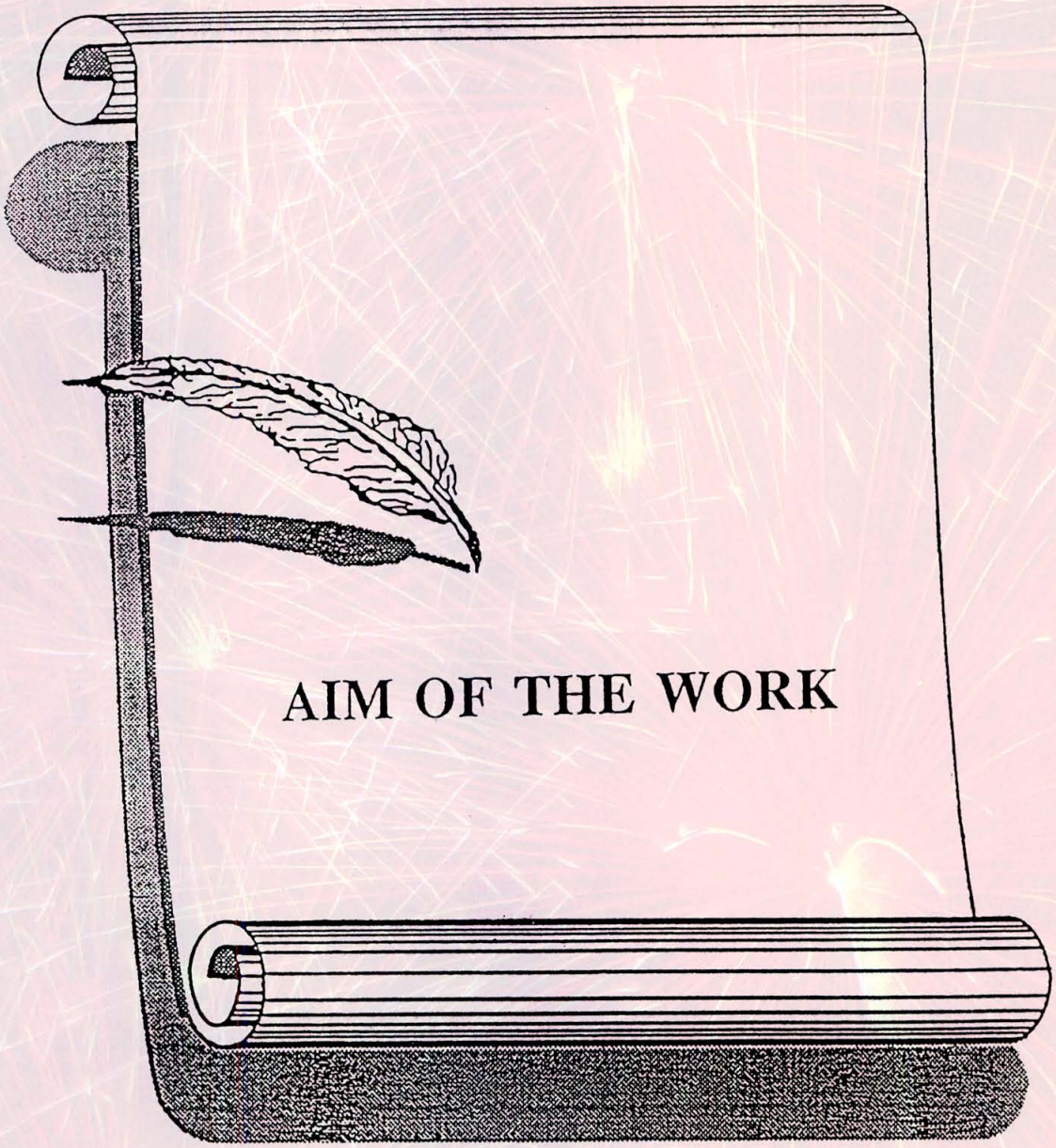
Glutathione peroxidase was found to be increased in valproate medicated patients, while its level did not significantly changed in carbamazepine medicated patients *(Kurekci et al., 1995)*.

Nitric oxide (NO) was found to play many roles in CNS as a messenger molecule, however when generated in excess, it can be neurotoxic. It is likely that most of the neurotoxic actions of NO are mediated by peroxynitrite, which is the reaction product of NO and superoxide anion *(Dawson and Dawson, 1996)*.

Nitric oxide is thought to be a transynaptic retrograde messenger involved in modulating neuronal activity, but its function in relation to N-Methyl-D-Aspertate (NMDA) receptor activation is controversial *(Theard et al., 1995)*. *De Sarro et al (1991)* showed that inhibition of NO has a protective effect against NMDA –induced seizure. On the other hand *Buissen et al (1993)*, reported that NO which is produced in response to NMDA receptor activation, leads to seizure activity termination.

There are some indications that the neuronal cell damage in human epilepsy may be caused by seizure *(Mouritzen, 1980)*, and is sometimes associated with functional impairment, such as memory loss *(Lenz et al., 1992)*. So the ideal antiepileptic drug is that which not only to prevent seizures, but also to protect against the neuronal damage possibly associated with appearance of seizures *(Pitkanen and Halonen, 1995)*.

Thompson et al (1996) concluded that NMDA receptor activation is not solely responsible for the neuronal pathology as a consequence of epileptiform discharge. On the other hand, *Glass and Dragunow (1995)* stated that no single chemical abnormality or morphological alteration is going to explain the clinically diverse disorder of epilepsy.



AIM OF THE WORK