Effect of Some Medicinal Plant Extracts on The Oxidative Stress Status in Alzheimer's Disease Induced in Rats

Thesis

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BY

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Abstract

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder. Increased oxidative stress has been shown to be a prominent and early feature of vulnerable neurons in AD. Exposure to oxidative stress induces the accumulation of intracellular reactive oxygen species (ROS), which in turn causes cell damage in the form of protein, lipid, and DNA oxidations.

Our aim is to study the effect of salvia triloba and piper nigrum plant extracts on the oxidative stress status in Alzheimer’s disease induced in rats.

Fifty rats were enrolled in this study and were classified into five groups (ten each). Group 1: control group, group 2: AD group; group 3: AD group treated with Rivastigmine in a dose of 0.3 mg/kg b. wt. as a reference drug daily for three months; group 4: AD group treated with total extract of the aerial part of *Salvia triloba* in a dose calculated according to result of chronic toxicity Study (750 mg/kg b. wt. /day) daily for three months; group 5: AD group treated with total extract of seeds of *Piper nigrum* in a dose calculated according to result chronic toxicity Study (187.5 mg/kg b. wt. /day) daily for three months.

Induction of Alzheimer’s disease (AD) was induced by oral administration of aluminum chloride in a dose of 17 mg/kg b. wt. daily for one month. After three months animals' sera were collected and used to determine serum malondialdehyde, nitric oxide, total antioxidant capacity and erythrocyte superoxide dismutase.

The results indicated that extracts of Salvia & Piper as well as rivastigmine improved serum antioxidants profile compared to AD group.

In conclusion, the used extracts have free radical scavenging antioxidants which protect brain tissue from oxidative damage, and help to improve AD.

Key words: Alzheimer’s disease; oxidative stress; salvia triloba ; piper nigrum .

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List of abbreviations

12/15LOX	12/15lipoxygenase
5-OHC	5-hydroxycytosine
8-OHA	8-hydroxyadenine
8-OHG	8-hydroxyguanine
ACH	Acetylcholine
AD	Alzheimer's disease
AGES	Advanced glycation endproducts
ALCL3	Aluminium chloride
ALP	Alkaline phsphatase
ALT	Alanine amino-transferase
APOE	Apolipoprotein e
APP	Amyloid precursor protein
AST	Aspartate amino-transferase
Aβ	B-amyloid
BACE	Beta-amyloid cleaving enzyme
CAT	Catalase
CCl4	Carbon tetrachloride
ChEls	Cholinesterase inhibitors
CNS	Central nervous system
Cu Zn-SOD	Copper, zinc superoxide dismutase
DNA	Deoxy ribonuclic acid
EC-SOD	Extracellular form of superoxide dismutase
EDTA	Ethylene diamine tetra acetic acid
GPX	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
GSSG	Disulfideoxidized glutathione
H_2o_2	hydrogen peroxide
LDL	Low density lipoprotein
LO^-	Alkoxyl radical
LO^{-2}	Peroxy radical
LOH	Lipid aldehyde
LOOH	Lipid hydroperoxide
MAPT	Microtubule-associated protein tau
MDA	Malondialdehyde
Mn-SOD	Manganese superoxide dismutase
mtDNA	Mitochondrial deoxy ribonucleic acid
NaCl	Sodium chloride
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	nicotin amide adenine dinucleotide phosphate hydrogenase

NBT	Nitroblue tetrazolium
NF-KB	Nuclear transcription factor kappa b
NMDA	N-methyl-d-aspartate
NO	Nitric oxide
NO^{-}_{2}	Nitrogen dioxide
O2	Singelet oxygen
O^{-2}	Superoxide anion radical
ODFR	Oxygen derived free radical
OH^{-}	Hydroxyl radical
$ONOO^{-}$	Peroxynitrite
PMS	Phenazine methosulphate
PON1	Paraoxonase 1
PSEN1	Presenilin-1
PSEN2	Presenilin-2
RAGE	Advanced glycation endproduct receptor
ROS	Reactive oxygen species
SE	Selenium
SOD	Superoxide dismutase
SORL1	Sortilin-related receptor
TAC	Total antioxidant capacity
TBA	Thiobarbituric acid
TFR	transferrin

Introduction and Aim of the work

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Introduction :

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that primarily affects the elderly population and is considered to be responsible for the majority of dementia cases in people aged 65 or older. This disease is characterized by numerous symptoms such as memory and language impairment, cognitive dysfunction and behavioural disturbances (i.e., depression, agitation and psychosis), which become progressively more severe. Due to its debilitating nature, an enormous social and economic burden is placed on society **(Brookmeyer et al., 2007)**.

Neuroimaging of the patient with AD or other dementias may reveal atrophy of the brain, such as enlarged ventricles and sulci and narrowed gyri, although these features are not always present **(Geldmacher and Whitehouse, 1997**). Neuronal loss is the main neuropathologic feature underlying the symptoms of AD. Microscopically, AD is characterized by the presence of senile plaques and neurofibrillary tangles (NFTs). Plaques are extracellular deposits of filamentous β-amyloid, a protease cleavage product of amyloid precursor protein **(Lue et al., 1999)**.

Several mechanisms have been postulated to explain AD pathogenesis, A beta toxicity, cholinergic dysfunction, tau protein hyperphosphorylation , oxidative damage , synaptic dysfunction, inflammation secondary to senile plaques **(Von Bernhardi, 2007)**.

Increased oxidative stress has been shown to be a prominent and early feature of vulnerable neurons in AD. Exposure to oxidative stress induces the accumulation of intracellular reactive oxygen species (ROS), which in turn causes cell damage in the form of protein, lipid, and DNA oxidations. Elevated ROS levels are also associated with increased deposition of amyloid-β and formation of senile plaques, a hallmark of the AD brain. If enhanced ROS exceeds the basal level of cellular protective mechanisms, oxidative damage and cell death will result. Therefore, substances that can reduce oxidative stress are sought as potential drug candidates for treatment or preventative therapy of neurodegenerative diseases such as AD **(Nelson et al., 2009)**.

Medicinal plants have been traditionally used in the treatment of several human diseases and their pharmacological and therapeutic properties have been attributed to different chemical constituents isolated from their crude extracts. Of particular importance, chemical constituents with antioxidant activity can be found at high concentrations in plants and can be responsible for their preventive effects in various degenerative diseases, including cancer, neurological and cardiovascular diseases **(Mentreddy, 2007).** Thus, the antioxidant properties of plants have a full range of perspective applications in human healthcare **(Silva et al., 2005)**.

Salvia is an important genus in the family Laminaceae (**Imanshahidi and Hosseinzadeh, 2006**). The East Mediterranean Sage (*Salvia Triloba*) is a native plant of the Mediterranean, which has been used in traditional medicine by many Asian and Middle Eastern countries to treat several ailments. The leaves of the plant are boiled as an herbal

tea for the relief of headaches, stomachaches, abdominal pain and many other disorders. The aqueous and oil extracts of sage have been shown to possess antioxidant, anti-inflammatory, anticancer and antimicrobial activities (**Gali-Muhtasib, 2006**). Its high antioxidant activity could be also considered to depend on the phenolic compounds detected in this herb such as hydroxybenzoic acid derivatives, caffeic acid derivatives (e.g.,rosmarinic acid), ferulic acid as well as flavonoid derivatives; luteolin and quercetin **(Proestos et al., 2006).**

Black pepper (*Piper nigrum*) is a flowering vine in the family Piperaceae (**Quijano et al., 2006**). Piperine is a major plant alkaloid present in black pepper (*Piper nigrum*) and long pepper (Piper longum), which are among the most common spices consumed by a large number of people worldwide. This compound is known to possess several pharmacological actions, such as antimicrobial, antifungal, anti-inflammatory and antioxidant effects **(Selvendiran et al., 2003)**. Piperine has been demonstrated in in vitro studies to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species, lower lipid peroxidation in vivo and beneficially influence cellular thiol status, antioxidant molecules and antioxidant enzymes in a number of experimental situations of oxidative stress **(Srinivasan K , 2007)**.

Aim of the work:

The aim of this thesis is to study the effect of ethanolic extracts of salvia triloba and piper nigrum plant on the oxidative stress status in Alzheimer's disease induced in rats.

Review of Literature

Chapter 1