Experimental Study of the Effects of Boswellia Serrata and Ginger (Zingiber officinale) on Alzheimer's Disease Induced in Rats

Thesis submitted for fulfillment of Medical Doctorate degree in Medical Pharmacology

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Abstract

Alzheimer's disease is now the most common cause of dementia. Increased oxidative stress, accumulation of oxidatively damaged nucleic acids, proteins, and lipids and inflammation induce deficits in cognitive and psychomotor performance and play an important role in development of Alzheimer's disease (AD). AD was induced in rats by giving AlCl₃ (17 mg / kg b.wt). Aqueous infusions of ginger (Zingiber officinale) (108 and 216 mg / kg b.wt), Boswellia serrata (45 and 90 mg / kg b.wt), rivastigmine (0.3 mg / kg b.wt) were given orally to study their protective as well as therapeutic effects on AlCl₃ induced AD in rats, which were evaluated by using behaviour stress tests as activity cage, rotarod and T-maze as well as by biochemical tests for detection of ACh and ACh E in brain homogenate and histopathologic examination.

Ginger and Boswellia serrata produced protective and therapeutic effects on AD.

Key words: Alzheimer's disease, oxidative, inflammation, cognitive, AlCl₃, Ginger, Boswellia serrata, activity cage, rotarod, T-maze, ACh, Ach E.
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Abbreviations

**A**
Ach: Acetylcholine
AchE: Acetylcholine esterase
AKPA: Acetyl-11-keto-β-boswellic acid
ADL: Activities of daily living
ATPase: Adenosine triphosphatase
ALA: Alpha lipoic acid
Al: Aluminum
Alcl₃: Aluminum chloride
ANOVA: One-way analysis of variance
AD: Alzheimer’s disease
APP: Amyloid precursor protein
AICD: Amyloid precursor protein intracellular domain

**B**
Aβ: Beta-amyloid peptide
BBA: Beta-boswellic acid
BSA: Bovine serum albumin
BDNF: Brain derived neurotorpic factor
BuChE: Butyrylcholinesterase
BHA: Butylated hydroxyanisole
b.wt: Body weight
BSD: Boswellia 45 mg /kg
BLD: Boswellia 90 mg /kg

**C**
Ca²⁺: Calcium
ChAT: Choline acetyl transferase
ChE: Cholinesterase
ChEI: Cholinesterase inhibitors
CuZnSOD: Copper zinc Super Oxide Dismutase
CA3: Cornu Ammonis3 area of hippocampus proper
COX: Cyclooxygenase

**D**
DPPH: 1,1-diphenyl-2-picrylhydrazyl
DMBA: 7, 12-dimethylbenz anthracene
DNA: Deoxy ribonucleic acid
Abbreviations

**E**
- ELISA: Enzyme linked immunosorbent assay
- E.S.R: Erythrocyte sedimentation rate
- EAA: Excitatory amino acid
- ERK: Extracellular signal-regulated kinases 1 and 2

**F**
- FAO: Food and Agriculture Organization of the United Nations
- FDA: Food and Drug Administration

**G**
- GABA: Gamma amino butyric acid
- GRAS: Generally Recognised as Safe
- GBE: Ginkgo biloba extract
- GSH-PX: Glutathione peroxidase
- gm: Gram
- GIT: Gastro intestinal tract
- GSD: Ginger 108 mg/kg
- GLD: Ginger 216 mg/kg

**H**
- 5-HETE: 5-hydroxyeicosatetraenoic acid
- H₂O₂: Hydrogen peroxide

**I**
- iNOS: Inducible nitric oxide synthetase
- IA: Incensole Acetate
- IL: Interleukins
- i.c.v: Intra-cerebroventricular

**J**
- JNK: c-Jun N-terminal kinase

**K**
- KBA: 11-keto boswellic acid
- Kg: Kilogram

**L**
- LTB4: Leukotriene B4
- LPS: Lipopolysaccarides
- LDL: Low density lipoproteins
**Abbreviations**

**M**
- MDA: Malondialdehyde
- Mepaco: Arab company for pharmaceutical and medicinal plants
- MTP: Microtubule proteins
- ml: Milliliter
- mg: Milligram
- mM: Millimolar
- MMSE: Mini mental state examination
- MAPKs: Mitogen-activated protein kinases

**N**
- NF-κB: Nuclear factor kappa B
- NGF: Nerve growth factor
- NFTs: Neurofibrillary tangles
- NO: Nitric oxide
- NMDA: N-methyl-D-aspartate
- NSAID: Non steroidal anti-inflammatory drugs

**P**
- PD: Parkinson’s disease
- pmol: Picomole
- PMN: Polymorphonuclear leucocytes
- PUFA: Polyunsaturated fatty acids
- pH: Power of hydrogen
- PGE2: Prostaglandin E2

**R**
- RNS: Reactive nitrogen species
- ROS: Reactive oxygen species
- RO•: Alkoxyl radical
- ROO•: Peroxyl radical
- rpm: Rotations per minute

**S**
- NaCl: Sodium chloride
- s APP: Soluble amyloid precursor protein
- S.E: Standard error
- O₂⁻: Superoxide anion
- SOD: Superoxide dismutase
**Abbreviations**

**T**
- TPA: 12-O-tetradecanoylphorbol-13-Acetate
- TBARS: Thiobarbituric acid reactive substance
- TRPV3: Transient receptor potential vanilloid3
- Tris-HCl: 2-Amino-2-hydroxymethyl-1,3-propanediol hydrochloride
- TNF-α: Tumour necrosis factor

**V**
- V717F: Valine at residue 717 substituted by phenylalanine
- VLDL: Very low density lipoproteins

**W**
- WBCs: White blood cells
- Wks: weeks
- WHO: World Health Organisation
1.1) Introduction

1.1.1) Alzheimer's Disease

Alzheimer's disease (AD), which represents one of the most economically costly diseases to society is a neurodegenerative disorder characterized by progressive degeneration of hippocampal and cortical neurons that leads to impairment of memory and cognitive ability. Impairment of short-term memory is usually the first clinical feature, whereas retrieval of distant memories is preserved relatively well into the course of the disease. When the condition progresses, additional cognitive abilities are impaired, as the ability to calculate, and use common objects and tools. The pathological hallmarks of AD are senile plaques, which are spherical accumulations of the protein β-amyloid accompanied by degenerating neuronal processes, and neurofibrillary tangles, composed of paired helical filaments and other proteins. This corresponds to the clinical features of marked impairment of memory and abstract reasoning, with preservation of vision and movement (Ryoichi & Masuo, 2009).

The selective deficiency of acetylcholine in AD, has given rise to the "cholinergic hypothesis," which proposes that a deficiency of acetylcholine is critical in the genesis of the symptoms of AD (Terry & Buccafusco, 2003). Therefore a major approach to the treatment of AD has involved attempts to augment the cholinergic function of the brain. This involves the use of inhibitors of acetyl cholinesterase as tacrine, donepezil, rivastigmine, and galantamine (Lon et al, 2008). Also other hypotheses state that inflammation plays a key role in the pathogenesis of AD. In addition excessive reactive oxygen species (ROS) levels are implicated in the aetiology of AD (Zhu et al, 2006).
1.1.2) Ginger (Zingiber officinale)

Ginger has been listed in “Generally Recognized as Safe” (GRAS) document of the United States Food and Drug Administration (FDA) (Ajith et al, 2008). Ginger extract has anti-oxidative properties and scavenges superoxide anion and hydroxyl radicals due to its high content of gingerol which is a polyphenolic compound. Ginger also has anti-inflammatory properties (Nirmala et al, 2008).

1.1.3) Boswellia serrata

Boswellia is a genus of trees known for their fragrant resin which has many pharmacological uses particularly as anti-inflammatory. The boswellic acids that are a component of the resin have shown some promise as a treatment for asthma and various inflammatory conditions (Gupta et al, 1998). Boswellia gum extraction from its resins is used to provide prevention and treatment of colitis, ulcerative colitis, Crohn’s disease, and ileitis, also boswellia shows satisfactory antioxidant activity in the cerebral-vascular system (Assimopoulou et al, 2005).

Hypothesis:

Ginger (Zingiber officinale) and Boswellia serrata would have an ameliorative effect on AD due to their anti-inflammatory and antioxidant properties. Ginger contains 6-gingerol and shogaols which are polyphenolic compounds known for their antioxidant properties. Boswellic acids which are the major components of boswellia are responsible for its anti-inflammatory properties.
1.2) Aim of work

The purpose of this experimental work is to investigate the possible prophylactic and curative effects of aqueous infusions of ginger (*Zingiber officinale*) and *Boswellia serrata*, in comparison to standard anticholinesterase rivastigmine on Alzheimer’s disease induced in rats by using aluminium chloride.

The prophylactic and therapeutic effects of ginger and boswellia on rats receiving AlCl₃ for induction of AD, will be evaluated by using behaviour stress tests, measuring acetylcholine and acetylcholinesterase in brain homogenates and Histopathologic examination of the hippocampus for all rats in all groups in this experimental study.
2.1) Alzheimer's Disease

The prevalence and incidence of Alzheimer's disease (AD) increases with age. The typical neuropathological changes in this degenerative disease were first described nearly one hundred years ago by Alois Alzheimer in a fifty-years-old woman called Auguste Deter. Alzheimer followed her until she died in 1906 (Maccioni et al, 2001). AD is now the most common cause of dementia (Hansson et al, 2006).

Fig1: Auguste Deter.
Photograph dated November 1902.
(Konrad et al, 1997)

2.1.1) Aetiology of Alzheimer's disease

Among several pathogenic mechanisms for AD, it seems that oxidative stress through inducing the formation of unusually high concentration of oxygen and nitrogen-reactive species and depletion of endogenous antioxidants plays a role in damaging and killing neurons. There is evidence of increased levels of markers of oxidative stress in brain tissue from AD patients (Maccioni et al, 2001). Neuronal degeneration and death in the neocortex and hippocampus are probably the causes of the striking behavioral and functional deficits of patients with AD (Miguel-Hidalgo et al, 2002). In addition, inflammation,
genetic and cerebro vascular diseases have important roles in development of AD (Vagnucci & Li, 2003).

Increased oxidative stress and accumulation of oxidatively damaged nucleic acids, proteins and lipids disrupt intracellular signal transduction systems and intercellular signaling molecules that are important for maintaining the cellular structure of the brain and its neuronal circuits and thus is thought to exacerbate brain aging and induce deficits in cognitive and psychomotor performance (Richwine et al, 2005).

β-amyloids which are extracellular deposits containing β-amyloid peptide (Aβ) as the major core deposits, has been shown to induce oxidative stress (Banks & Farr, 2004). The basis for the β-amyloid hypothesis arises from various studies showing that Aβ is toxic to neurons, for example, there is increased Aβ release and apoptotic cell death in cells that over express Aβ precursor protein (APP) (Recuero et al, 2004). Aβ are surrounded by activated microglial cells expressing pro-inflammatory cytokines, chemokines, and neurotoxic mediators. Long-term activation of microglial cells is suspected to contribute to the neuron loss in AD (Grzanna et al, 2004).

The longest isoform of Aβ, consisting of 42 amino acids (Aβ1-42), is produced from APP by sequential cleavage by β- and γ-secretase in the amyloidogenic APP-processing pathway (Andreasson et al, 2007) (Fig 2).
Fig 2: Schematic drawing of APP and generation of Aβ isoform.

The 17-amino acid signal peptide is indicated at the N-terminus. A single membrane-spanning domain is located at amino acids 700-723 in the longest APP isoform (APP770). (A) In the amyloidogenic pathway, β-secretase cleaves after residue 671, generating β-sAPP, which is secreted, and a C-terminal fragment (β-CTF or C99), which is retained in the membrane. The β-CTF can undergo further cleavage by γ-secretase to release Aβ isoforms. (B) In another pathway, APP is first cleaved by β-secretase, but after this, by α-secretase, thus generating the shorter isoforms Aβ1-14, Aβ1-15, and Aβ-16. In another described non-amyloidogenenic pathway, α-secretase cleaves between amino acids 16 and 17 in the Aβ sequence generating α-sAPP, followed by γ-secretase cleavages, generating a fragment called p3 (Aβ17-40/42). This 3-kDa fragment has been isolated from cell-culture medium, and in brains from AD patients. However, the fragment has never been detected in human CSF. AICD, APP intracellular domain, APP, amyloid precursor protein, Aβ, amyloid β, sAPP, soluble amyloid precursor protein (Portelius et al, 2010).