INTRODUCTION
Grape seed extract (GSE)
In Egypt, grapes are considered the second important crop after citrus. GS is one of the by-products of wine production, accounting for 38-52% of pomace on dry weight basis. Its importance is due to its high polyphenol content. These phenolic compounds are mostly known for their antioxidant properties.\(^1,3\). Grape seed oil ranged from 11.8 to 12 % which rich in oleic and linoleic acids and the degree of unsaturation in the oils was over 70%. Alpha-tocopherol was the most abundant tocopherol in the oil.\(^4\) The phenolic compounds in GSE can be divided into two groups: (a) phenolic acids and related compounds and (b) flavonoids. The most common phenolic acids in grape include cinnamic acids (coumaric acid, caffeic acid, ferulic acid, chlorogenic acid, and neochlorogenic acid) and benzoic acids (p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, and gallic acid). Flavonoids include colorless flavan-3-ols (such as catechin, epicatechin, their polymers, and their ester forms with galactic acid or glucose), colored flavanones (the most common flavanone in food is quercetin), and red and blue anthocyanins.\(^5\)

Grape seed proanthocyanidins extract (GSPE) are natural antioxidants composed of various polyphenolic compounds generally believed to protect against reactive oxygen species (ROS)-mediated myocardial ischemia/reperfusion injury and apoptosis of cardiomyocytes.\(^6-9\). While the use of GSPE has become increasingly popular for health promotion and disease prevention, concerns have been raised that high dose GSPE may paradoxically induce toxicity.\(^10-13\) High-dose (500 μg/ml) GSPE may cause cytotoxicity associated with caspase activation and increased apoptotic cell death.\(^14\)

GSE popular with its a broad spectrum of therapeutic effects such as Antioxidant,\(^2,7,15\) anticancer,\(^16-23\) Cardioprotective,\(^8,24-29\) Antimicrobial and antiviral effects,\(^30-36\) anti arthritic activity,\(^37\) hepatoprotective effects,\(^38-40\) and Anti-Alzheimer activity.\(^41-46\)

Grape flavonoids, can prevent AD both by inhibition of neuro-inflammation and by reducing oxidative stress.\(^47\) In a clinical trials, consumption of grape juice was also found to enhance memory functions for older adults with early memory decline.\(^48,49\)

In this review, we present some findings from our laboratory and those of others on the potential benefits of GSE for the prevention and treatment of AD.

Alzheimer’s disease (AD)
In 1907, Alois Alzheimer, a German neuropathologist, initially described the clinical findings of a 51-year-old woman with a 41 year course of progressive dementia.\(^50\) AD is the most common form of adult onset dementia.\(^51\) It has been estimated that approximately 9 million individuals could develop AD by the year 2040, unless preventative strategies are found. Environmental risk factors for AD are associated with lifestyle factors, especially cigarette smoking, fats and alcohol, homocysteine-related vitamins and oxidative stress have a role in AD, as well as The concentration of aluminum or silica in drinking water and elevated levels of strontium, aluminum, iron, barium, mercury, manganese cations combined with deficiencies of magnesium/calcium in the food chains have been suggested for initiation of free radicals mediated progressive pathogenesis of neurodegeneration.\(^55-58\)

AD is characterized by progressive memory loss. Biochemically, AD is characterized by the deposition of soluble Aβ produced the aggregation of the peptide forming Aβ fibrils which exerts a toxic effect and intracellular neurofibrillary tangles consist of phosphotylated tau protein causing destabilization of cell structure and loss of axons, dendrites and synapses, also
neurotoxicity of Aβ occurs in conjugation with free radicals which attack brain cell membrane, increase Ca$^{2+}$ influx, initiate lipid peroxidation, protein oxidation, and DNA oxidation observed in AD brains and damage membrane and cytosolic proteins$^{60-62}$. In the brain, Alzheimer's disease is associated with progressive synaptic and neuronal loss, in particular of basal forebrain cholinergic neurons. In addition, the Alzheimer brain shows accumulation and spreading of two pathological features, i.e. intraneuronal neurofibrillary tangles consisting of phosphorylated Tau protein, and extra cellular senile plaques consisting of amyloid-$\beta$.

Tau is a neuronal protein present in axons and dendrites where it promotes tubulin polymerization and stabilizes microtubules and thus contributes to cell structure and cellular transport$^{64}$. In addition, Tau involved in axonal growth as indicated by the fact that neurons treated with Tau antisense in vitro are unable to grow axons$^{65}$. Hyperphosphorylation of Tau as present in neurofibrillary lesions characteristic in Alzheimer's disease, prevents Tau from binding to microtubules causing destabilization of cell structure thereby likely contributing to loss of axons, dendrites and synapses$^{68}$. Amyloid $\beta$ (Aβ) is generated by sequential proteolytic cleavage of the transmembrane amyloid precursor protein (APP) by membrane bound enzymes, called secretases. The resulting length of the Aβ protein is dependent on initial cleavage of the extracellular domain generating the amyloidogenic end products Aβ 1-42 and Aβ 1-40 when cleaved by $\beta$- and $\alpha$-secretase, or the shorter non-amyloidogenic p3 fragment produced by $\alpha$- and $\gamma$-secretase$^{66}$. The Aβ 1-42 end product in free form is highly neurotoxic, and forms aggregates that appear to be the predominant species in senile plaques$^{67}$. Also, the ratio between soluble Aβ 1-42 and 1-40 in cerebrospinal fluid correlates directly with the age of onset of Alzheimer’s disease$^{68}$ (Fig 1).

Mode of action of GSE as Anti-Alzheimer Inhibition of AChe

In AD, many studies suggest an implication of an abnormal focal accumulation of aluminum in the brain. In this retrograde affection, aluminum may interfere with various biochemical processes including Acetylcholine (Ach) metabolism, and can thus act as a possible etiopathogenic cofactor. Ach is involved in the signal transfer in the synapses. After being delivered in the synapses, Ach in brain is considered to be closely related to short term
memory, and the degree of Ach reduction was positively correlated with dementia severity. The clinical symptoms of AD patients can be improved by increasing the function of Ach system. So it is considered that Ach quantities are a major symbol in judging spatial memory of rats. The determination of key enzyme decompounding and/or compounding Ach is used to reflect indirectly Ach level. Cholinesterases are a large family of enzymatic proteins widely distributed throughout both neuronal and nonneuronal tissues. Principal role of AChE is the termination of nerve impulse transmission at the cholinergic synapses by rapid hydrolysis of Ach. Inhibition of AChE serves as a strategy for the treatment of AD could have a role in the pathogenesis of AD. The deficiency in cholinergic neurotransmission in AD has led to the development of cholinesterase inhibitors as the first-line treatment for symptoms of this disease. Therefore, the drugs approved for the AD therapy act by counteracting the Ach deficiency, that is, they try to enhance the Ach level in the brain.

However, only tacrine, donepezil, rivastigmine, and galanthamine have been approved by the Food and Drug Administration in the United States. These compounds have been reported to have their adverse effects including gastrointestinal disturbances and problems associated with bioavailability, which necessitates the interest in finding better AChE inhibitors from natural resources. There has been a lot of research on the biological effect of plants traditionally used either in infusions or in traditional remedies as AChE inhibitors in vitro and also as memory enhancers in vivo. It has been demonstrated that treatment of Al-intoxicated rats with GSE produced significant decrease in brain AchE activity accompanied with significant increase in brain Ach level in comparison with Al-intoxicated control group. It has been demonstrated that GSE significantly increases Ach release in the hippocampus. Supplementation with GSPE to treated animals significantly (P< 0.05) attenuated the toxicity and oxidative stress in brain evoked by Chlorpyrifos and also restored AChE activity near to control level indicating their ameliorating effect. Pervin et al., investigate the AChE inhibitory activities of grape skin anthocyanin (GSA) extract and demonstrate that GSA administration significantly inhibited AChE in the in vitro assay (IC50 = 363.61 μg/mL). Therefore, GSA could be an excellent source for AD drugs. Several studies recently demonstrated that Anthocyanins including (pelargonidin, delphinidin and cyanidin) also possess antineurodegenerative properties, anticholinesterase activity and also have beneficial effects on memory and cognition, suggesting a clear neuroprotective role.

Inhibition of Oxidative stress
There is growing evidence that oxidative stress is the main risk factor closely related to the development of AD by increasing Aβ production. In view of this fact, natural antioxidants could provide novel and safe therapeutic options for these devastating disorders. The identification of novel antioxidants as potential therapeutics have an important area of neuroscience research. Amongst the most studied categories of natural antioxidants have rapidly gained attention as viable candidates for clinical testing in neurodegeneration and acute neuronal injury such as stroke. A variety of antioxidant compounds derived from nutraceuticals have demonstrated neuroprotective activity in either in vitro or in vivo models of neuronal cell death. The mechanisms of action have been suggested for the neuroprotective effects antioxidant by scavenge free radicals or they indirectly increase endogenous cellular

Figure 2: BDNF Pathway Copyright ProteinLounge.com.
antioxidant defenses, for example, via activation of the nuclear factor erythroid-derived 2-related factor 2 (Nrf2) transcription factor pathway and modulation of signal transduction cascades or effects on gene expression\textsuperscript{93}. The remarkable effects of GSE may be related to the inhibitory effect of monoamine oxidase activity in the brain as described by Mizutani et al.\textsuperscript{94}, which contribute this activity as a mechanism by which resveratrol could reduce oxidative stress, production of H\textsubscript{2}O\textsubscript{2} and lipid peroxidation. It has been reported that GSE show improved viability of neuron cells after H\textsubscript{2}O\textsubscript{2}-induced oxidative stress demonstrated by reduction in lactate dehydrogenase release or propidium iodide staining and also enhances low-level production of intracellular nitric oxide in primary rat astroglial cultures\textsuperscript{41, 46, 95-96}. It has been reported that GSE show improved viability of neuron cells after H\textsubscript{2}O\textsubscript{2}-induced oxidative stress demonstrated by reduction in lactate dehydrogenase release or propidium iodide staining and also enhances low-level production of intracellular nitric oxide in primary rat astroglial cultures\textsuperscript{41, 46, 95-96}. It has been reported that resveratrol (grape flavonoid) suppresses mitochondrial-induced ROS production in the rat brain\textsuperscript{97}, inhibits lipid peroxidation\textsuperscript{98}, and protects against oxidative DNA damage in stroke-prone hypertensive rats\textsuperscript{94}. In addition, Olas et al.\textsuperscript{99, 100} documented that resveratrol was a powerful antioxidant, able to interfere with advanced glycation end products, mediated oxidative DNA damage, and was a useful agent against vascular diseases where ROS were involved in hypertension. **Effect of GSE on BDNF**

BDNF (Brain-derived neurotrophic factor) is critical for the survival and maintenance of sympathetic and sensory neurons vital to learning, memory, and higher thinking. BDNF itself is important for long-term memory\textsuperscript{101}. Without the nerve growth factor, the sympathetic and sensory neurons will undergo apoptosis. Sechi et al.\textsuperscript{102} proposed that diet enriched with antioxidants might be considered a valid alternative and a valuable strategy to counteract aging-related cognitive decline by modulating BDNF levels in plasma and serum. Another study by El Gengaihi et al.\textsuperscript{46} showed that, administration of AlCl\textsubscript{3} in rats led to significant reduction in brain BCl\textsubscript{2} expression (35.0 Pg/mg) as well as BDNF levels in AlCl\textsubscript{3}-intoxicated control (50.5 Pg/mg) compared with those in control rats (52.8 and 99.6 Pg/mg, respectively). After the treatment with GSE there are remarkable increase both in BCl\textsubscript{2} and BDNF (Fig 2).

**Deaggregation of beta amyloid by GSE**

GSE interferes with the aggregation of Aβ peptides and tau into neurotoxic oligomeric Aβ aggregates and tau fibril conformers. Moreover, GSE may also destabilize preformed Aβ and tau protein aggregates. GSPE blocks Aβ fibril formation by interfering with protofibril formation, and initial coil to α-helix/β-sheet secondary structure transitions. Thus, GSE might modulate AD dementia by beneficially modulating both Aβ and tau-mediated neuropathologic mechanisms\textsuperscript{103-105}.

![Grape Seed Extract Diagram](image-url)
Wang et al., 106-108 found that a naturally derived grape seed polyphenolic extract (GSPE) can significantly inhibit amyloid β-protein aggregation into high-molecular-weight oligomers in vitro. When orally administered to Tg2576 mice, this polyphenolic preparation significantly attenuates AD-type cognitive deterioration coincidently with reduced HMW soluble oligomeric Aβ in the brain, suggested that grape seed-derived polyphenolics may be useful agents to prevent or treat AD.

Grape flavonoids can reduce Aβ production either by enhancing α-secretase (ADAM10) activity or by inhibiting β-secretase. They can lead to the production of off-target Aβ oligomers, thereby disrupting fibrillization, and inhibit Aβ aggregation through metal-chelating activity. By acting to improve cerebral vascular blood flow flavonoids may have the potential to reduce brain Aβ levels through a peripheral sink mechanism (Fig. 3)109. Porat et al.,110 suggested that GSPE may inhibit oligomerization of Aβ. This inhibition would be highly significant, because accumulation of soluble extracellular high-molecular-weight oligomeric Aβ species in the brain currently is considered a major risk factor for the onset and progression of cognitive deterioration in AD111-119 Thus, pharmacological strategies for the prevention of Aβ oligomerization in the brain might result in improved cognitive function in AD.

CONCLUSION
Findings presented in this review article support the development of GSE as a preventative and/or therapeutic agent in AD.

REFERENCES


