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Research Paper

Sesame Oil Modulates Scopolamine-Induced Alzheimer-Like Pathological Dysfunction in Rats

Economics

KEYWORDS : Alzheimer's disease; scopolamine; rivastigmine; sesame oil; rats

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ABSTRACT

Aim: This study was carried out to evaluate the possible effectiveness of combination of sesame oil with anti-Alzheimer (AD) medication (rivastigmine) to attenuate scopolamine (Sco)-induced AD-like pathological dysfunction in rats. Methods: Forty male Sprague-Dawely rats (200±15 g) were randomly divided into five groups (n=8 for each group). Group 1, negative control, received saline only. Group 2, positive control, received Sco (1 mg/kg/day, intrapritoneally, ip). Groups from 3 to 5 received rivastigmine (200 mg/kg/day, po), sesame oil (5ml/Kg/day, po) or their combination simultaneously with Sco for 4 weeks. Results: Administration of rivastigmine and/or sesame oil to Sco treated rats significantly increased brain levels of acetylcholine (Ach), brain-derived neurotrophic factor (BDNF), brain fatty acid binding protein (FABP7), both reduced and oxidized glutathione and B-Cell lymphoma (Bcl2) as compared with positive control. On the other hand, the activity of acetylcholinesterase (AchE) and the levels of amyloid beta (Aβ) and the pro-inflammatory cytokines; interleukin-1beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were significantly decreased after administration of rivastigmine and/ or sesame oil as compared with positive control. The group treated with combination of sesame oil and rivastigmine showed more pronounced neuroprotective effects as compared with those treated with sesame oil or rivastigmine alone. Conclusion: Sesame oil exhibited synergistic effect with rivastigmine and can provide an effective option as a coadjuvant for effective improvement of AD.

Introduction

Alzheimer's disease (AD) is the most common age-related devastating neurodegenerative disorder, and is the leading cause of dementia in the elderly, affecting over 27 million people worldwide (Chen et al., 2014). Pathologically, AD is defined by the presence of senile plaques composed of insoluble amyloid beta (Aβ) protein, neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein, and several biochemical factors such as inflammation and oxidative stress (Bihaqi et al., 2012). Further, AD has also been correlated with the loss of cholinergic neurons, decrease in the levels of acetylcholine (Ach) and choline acetyltransferase (ChAT) and down regulation of brain-derived neurotrophic factor (BDNF) expression (Saura & Valero, 2011 and Calabrese et al., 2013).

Scopolamine (Sco), a muscarinic cholinergic antagonist, has been used to develop animal models of AD and can be used to study the effects of antiamnesic drugs (Flood & Cherkin, 1986). Sco increases acetylcholinesterase (AchE) activity in the cortex and hippocampus. AchE inhibitors, such as rivastigmine, donepezil and galantamine, have been used in the treatment of AD (Ballard, 2002). However, these therapies produce modest symptomatic improvements in patients, hence, searching for an alternative or adjuvant neuroprotective therapies is mandatory (Zaki et al., 2013).

Sesame (Sesamum indicum L.) seed is considered as a healthy food and is traditionally used in the Middle East. Sesame oil contains large amounts of polyunsaturated fatty acids, monounsaturated fatty acid, lignin and vitamin E (Hsu et al., 2013). Sesamin, sesamol, sesamolin, sesaminol, and episesamin, abundant lignans found in sesame oil, have been demonstrated to possess several physiological and biochemical properties beneficial for human health, such as hypocholesterolemic, antihypertensive actions (Nakano et al., 2006 and Monteiro et al., 2014), and regulation of lipid and alcohol metabolism in the liver (Kiso, 2004). The neuroprotective effect of sesamin and sesamolin was also observed in vivo using gerbils subjected to a focal cerebral ischemia induced by occlusion of the right common carotid artery and the right middle cerebral artery (Cheng et al., 2006).

The aim of this work was to examine the possible synergistic effect of sesame oil and rivstagmaine in modulating AD syndromes through affecting the cholinergic activity and anti-inflammatory, antioxidative and antiapoptitc effects.

Materials and Methods

Materials:

Chemicals: Scopolamine hydrobromide was purchased from Sigma Chemical CO, USA, daily freshly prepared by dissolving in saline and administered ip at a dose 1 mg/kg body weight in a volume of 1 ml/kg body weight (Chen et al., 2014). Rivastigmine tartrate (sold under the trade name Exelon) was purchased from Novartis, Germany. Sesame oil was purchased from local market and was administered orally at a dose 5ml/ kg body weight according to Saleem et al. (2014). Ach, AchE and BDNF enzyme immunoassay kits were purchased from WKEA MED SUPPLIES CORP, USA, and those for measurements of brain Bcl_2 and Aβ (1-40) peptide were obtained from IBL-AMERICA. Brain FABP7, reduced and oxidized glutathione, TNF-β, IL-6 and IL-1β enzyme immunoassay kits were purchased from IBL Co., Ltd Japan. Kit for measurement of total protein was purchased from Bio diagnostics Cairo, Egypt. All other chemicals were of analytical grade.

Animals: Forty male Sprague-Dawley rats (200 g ± 15) were obtained from Helwan Farm of Serum and Vaccine, Cairo, Egypt. The animals were housed individually in metallic cages and were kept under controlled room temperature (24±2°C) in a 12-h light-dark cycle. All rats were allowed free access to lab chow and water for one week as an adaptation period and through the experimental period. Animals experiment was conducted according to the guidelines of institutional animal ethical committee

Methods

Experimental Design: The animals were randomly assigned to five groups (8rats/group) as follows:

Negative control group: was injected intrapritoneally (ip) with saline (0.9% NaCl) at the same volume as Sco treated rats (1 ml/ Kg body weight).

Positive control group: received Sco (1 mg/kg, ip) dissolved in sa-

line daily

Rivastigmine group: received rivastigmine tartrate at an oral dose of 1 mg/kg according to Bihaqi et al. (2012), followed by Sco (1 mg/kg, ip) after 40 min.

Sesame oil group: received sesame oil at an oral dose of 5 ml/kg body weight, followed by Sco (1 mg/kg, ip) after 40 min.

Rivastigmine + sesame oil group: received rivastigmine tartrate (1mg/kg body weight, po) and sesame oil (5ml/kg body weight, po) followed by Sco (1 mg/kg, ip)

The above mentioned treatments were continued for 4 weeks, after which the animals were sacrificed by decapitation. The brain was dissected out on ice and was stored at -80°C till further use.

Biochemical Estimations:

Determination of brain acetyl choline, BDNF levels and acetyl choline esterase activity: A 10% W/V homogenate of brain samples was prepared by homogenizing with ice-cooled 0.1 M phosphate buffered saline (PBS). The homogenates were then centrifuged at 15000 g. The supernatants were collected and used for evaluation of AchE activity and Ach and BDNF levels using ELIZA kits according the methods of Den Blaauwen et al. (1983), Rios et al. (2001) and Oswald et al. (2008), respectively.

Determination of brain amyloid-β: Five volumes of extraction buffer (1% CHAPS in Tris-buffered saline (TBS) pH 7.6) was added to brain sample and was homogenized. After homogenization, the emulsion was let to stand on ice for at least 3 hours. Then, the emulsion was centrifuged at 70,000 rpm for 20 minutes at 4°C and then the supernatant was diluted with "4, EIA buffer" in the kit and was used for measurement of amyloid-β ELISA kits with monoclonal antibodies specific for rat amyloid-β according to Wang et al. (1996).

Determination of brain cytokines: For the determination of brain cytokines (IL-1ß, IL-6 and TNF-α), 100 mg of brain tissue was homogenized in two volumes of 0.01M PBS containing 0.05% Tween-20. After homogenization and centrifugation at 10,000 g at 4°C for 20 minutes, the resultant supernatant was collected. Then, the levels of IL-1ß, IL-6 and TNF-α were measured using ELISA kits with monoclonal antibodies specific for rat TNF-α, IL-1β and IL-6 according to Beutler et al. (1985), Grassi et al. (1991) and Wong & Clark (1988), respectively.

Determination of brain GSH, GSSG and Bcl-2: Another 100 mg of brain tissue was homogenized in ice-cold tri-hydrochloride buffer (pH 7.2). The homogenate was centrifuged at 800 g for 10 min, followed by centrifugation of the supernatant at 12,000 g for 15 min. The supernatant was removed for determination GSH and GSSG levels according to Pastore et al. (2001) and Bcl-2 level according to Barbareschi et al. (1996) using ELIZA kits.

Rat-brain fatty acid-binding protein (FABP7): 100 mg of brain tissue was rinsed with PBS, homogenized in 1 ml of PBS and stored overnight at -20°C. After two freeze-thaw cycles were performed to break the cell membranes, the homogenates were centrifuged for 5 minutes at 5000 x g, 2 - 8°C. The supernatant was removed immediately and stored at -80°C. The sample was centrifuged again after thawing before the assay. FABP7 was analyzed by ELIZA methods, according to the manufacturer instructions.

Estimation of brain total protein: Total protein was estimated in brain samples by standard spectrophotometric methods according to Henry et al. (1974)

Statistical Analysis: Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Dunncan-test. Values are expressed as mean ± SEM and P<0.05 was considered to be significant (Bailey, 1994).

Results

Table (1): Effects of oral administration of rivastigmine and/ or sesame oil on brain levels of Acetylcholine, Acetylcholine esterase, Brain-derived neurotrophic factor and Amyloid β peptide in Sco treated rats compared with negative and positive controls

Groups	Acetylcholine (µmol/ mg protein)	Acetylcholine esterase (U/mg protein)	Brain-derived neurotrophic factor (pg/ mg protein)	**Amyloid β peptide (pg/mg protein)**
Negative control	94.3±0.53[a]	610.23±6.5[a]	106.79±3.3[a]	12.7±0.75[a]
Positive control	62.19±0.64[b]	890.36±8.9[b]	74.47±0.509[b]	32.2±0.52[b]
Rivastigmine	70.98±0.76[c]	762.8±5.4[c]	84.05±1.22[c]	24.3±0.81[c]
Sesame oil	67.62±0.49[d]	850.46±6.07[d]	81.5±0.722[c]	27.5±0.52[d]
Rivastigmine + Sesame oil	79.29±0.66[e]	709.26±8.9[e]	95.05±0.659[d]	20.2±0.29[e]

The values are expressed as mean ± SEM (n= 8 rats/ group). The same letters means that there is no significant difference between groups. The different letters means that there is a significant difference between groups at p<0.05

Data in Table (1) demonstrate that the level of Ach was significantly reduced by 34.1% while remarkable increment in the activity of AChE was pronounced (45.9%) in the whole brain of Sco treated rats compared with their corresponding negative control. Oral administration of rivastigmine, sesame oil or both of them along with Sco significantly increased the level of Ach by 14.13%, 8.7% and 27.4%, respectively. This increase was accompanied with a significant reduction in the activity of AChE by 14.3%, 4.48% and 20.34%, respectively, as compared with positive control (Table 1).

Statistical analysis revealed that the level of BDNF was significantly decreased by 30.2% in whole brain of Sco treated rats compared with negative control. Rivastigmine, sesame oil or both of them significantly increased BDNF level in brain by 12.86%, 9.4% and 27.6%, respectively, compared with positive control (Table 1).

Sco administration was found to significantly increased Aβ level in brain by 153% compared with control rats. Oral administration of rivastigmine or sesame oil significantly reduced amyloid β level in the brain by 24.5% and 14.59%, respectively, compared with positive control. Administration of both rivastigmine and sesame oil showed the best improvement in Aβ (37.2%) level.

Table (2): Brain levels of TNF-α, IL-6 and IL-1β in rivastigmine and/or sesame oil treated rats compared with negative and positive controls

Groups	TNF-α (pg/mg protein)	IL-6 (pg/mg protein)	IL-1β (pg/mg protein)
Negative control	593.3±7.3[a]	267.2±6.18[a]	10.79±0.196[a]
Positive control	1214.5±24.39[b]	569.43±7.39[b]	106.62±2.53[b]
Rivastigmine	874.3±9.58[c]	462.9±4.88[c]	63.17±1.08[c]
Sesame oil	985.2±9.98[d]	505.93±8.28[d]	85.78±0.916[d]
Rivastigmine + Sesame oil	785.9±12.36[e]	389.1±8.55[e]	44.28±1.72[e]

The values are expressed as mean ± SEM (n= 8 rats/ group). The same letters means that there is no significant difference between groups. The different letters means that there is a significant difference between groups at p<0.05

Repeated injection of Sco elevated the brain levels of pro-inflammatory cytokines; TNF-α, IL-6 and IL-1β by 104.7%, 113.1% and 888%, respectively, as compared with negative control. These levels were significantly lowered in rats orally supplemented with rivastigmine and/ or sesame oil (Table 2).

Data presented in Table (3) show that administration of Sco resulted in significant reductions of GSH and GSSG levels in the brain compared with control. Oral administration of rivastigmine and/or sesame oil during scopolamine treatment was found to increase the levels of both GSH and GSSG compared with positive control group.

Table (3): Brain levels of Bcl-2, GSH, GSSG and FABP7 in different experimental groups

Groups	Bcl-2 (pg/ mg protein)	GSH (µmo/mg protein)	GSSG (µmol/mg protein)	Brain FABP7 (pg/mg protein)
Negative control	93.14±0.14[a]	43.25±0.84[a]	0.646±0.008[a]	247.8±6.58[a]
Positive control	59.63±0.375[b]	24.38±0.45[b]	0.258±0.012[b]	84.83±1.58[b]
Rivastigmine	67.68±0.90[c]	31.09±0.44[c]	0.366±0.012[c]	173.4±2.81[c]
Sesame oil	63.92±0.74[d]	27.18±0.25[d]	0.323±0.008[c]	154.5±3.45[d]
Rivastigmine + Sesame oil	82.73±1.002[e]	33.86±1.01[e]	0.47±0.02[d]	191.63±3.8[e]

The values are expressed as mean ± SEM (n= 8 rats/ group). The same letters means that there is no significant difference between groups. The different letters means that there is a significant difference between groups at p<0.05

Data presented in Table (3) show that administration of Sco resulted in significant reductions of GSH and GSSG levels in the brain compared with control. Oral administration of rivastigmine and/or sesame oil during scopolamine treatment was found to increase the levels of both GSH and GSSG compared with positive control group.

Bcl-2 level was significantly reduced (35.9%) in the brain of Sco treated rats compared to control. Oral treatment with rivastigmine or sesame oil or both of them along with scopolamine was found to increase Bcl-2 level by 13.4%, 7.1% and 38.7%, respectively, compared with positive control (Table 3).

The level of brain FABP7 was significantly reduced by 65.7% in positive control compared to negative control rats. Oral treatment with rivastigmine, sesame oil or both of them along with scopolamine led to remarkable enhancement in the levels of FABP7 by104%, 82% and 125%, respectively, compared with rats treated only with Sco (Table 3).

Discussion

The results of the present study showed that repeated injection of Scoresulted in a decline in cholinergic activity as indicated by reduced level of Ach and the increased activity of AchE in brain. Previous biochemical and behavioral evidence have indicated that central cholinergic transmission declines as a result of Sco administration (Hyde et al., 2013). Sco influences the expression of several genes associated with muscarinic receptor signaling pathways, apoptosis and cell differentiation in rat brain (Hsieh et al., 2003). Hence, it causes profound memory impairment in animals and humans as degeneration and dysfunction of the cortical cholinergic neurons is closely associated with cognitive deficits in AD (Calabrese et al., 2013).

AchE is the enzyme involved in Ach hydrolysis at central cholinergic synapses (Hyde et al., 2013). Thus, cholinesterase inhibitors may compensate for the reduced ACh levels in brains with AD disease. In the current study, rivastigmine, the standard AChE inhibitor, showed decrease in AChE activity. Thereby it may sustain the action of the remaining acetylcholine. Sesame oil, also, significantly lowered AChE activity and increased Ach level in brain. These results may be attributed to the ability of sesame oil to reestablish Ach release, thus it may protect cholinergic neurons. Results of this study agree with those reported by John et al. (2015) who suggest that the protective effect of rivastigmine and sesame oil may be associated with the cholinergic system.

Central cholinergic system is closely associated with neurogenesis and cell proliferation in the hippocampus (Kotani et al., 2006 and Yoo et al., 2011). In this study, the decline in cholinergic activity observed in Sco treated rats was accompanied by a decrease in BDNF level. In the same context, several investigators reported that BDNF expression in the hippocampus was suppressed in the Sco-induced amnesia in mice (Heo et al., 2014 and Weon et al., 2014). BDNF is a neurotrophin involved in neuronal survival and plasticity. BDNF binds to high-affinity receptors and tyrosine kinase B (TrkB) (Givalois et al., 2004 and Kim et al., 2010). BDNF-TrkB interaction promotes the survival and differentiation of neurons and synaptic plasticity of the central nervous systems (Panja and Bramham, 2014). Several studies demonstrated that BDNF is important in long-term memory formation and play roles in neurodegenerative diseases such as AD (Heo et al., 2014 and Weon et al., 2014). In this study, treatment with rivastigmine and/or sesame oil increased the level of BDNF indicating that the neuroprotective activity of sesame oil is exerted via increase in BDNF level.

Studies have found colocalization of AChE with Aβ deposits in brains of AD patients, as well as the capability of AChE to affect amyloid precursor protein (APP) processing and aggregation of Aβ peptides (Moran et al., 1993 and Citron, 2004). Consistent with earlier findings the current results showed that Sco increased the deposition of Aβ in the brain (Safar et al., 2014). It was postulated that AD is caused by changes in Aβ stability and aggregation or altered amyloid APP expression, resulting in a chronic imbalance between Aβ production and clearance. Accumulation of aggregated Aβ initiates a cascade that includes inflammatory changes, formation of NFTs and neurotransmitter loss. Aβ may facilitate Ca^{2+} entry into neurons, causing calcium-activated kinases to excessively phosphorylate tau protein leading to NFTs (Citron, 2004 and Golde et al., 2006). In this study, oral treatment of rivastigmine and/or sesame oil attenuated the Sco induced elevation level of Aβ. This improvement may be explained by the reduction in AChE activity observed in rivastigmine and/or sesame oil treated rats. These results could be partially supported by the results of Bihaqi et al. (2012) who reported that oral administration of Convolvulus pluricaulis extract to Sco treated rats reduced the increased protein and mRNA levels of tau and Aβ levels. They suggested that this protective action may be mediated either by direct interactions of constituents of the extract with the cholinergic nerve terminal or transsynaptically by mechanisms such as modulation of AβPP secretion at one side of the synaptic cleft.

Neuroinflammation is a prominent feature in AD pathology and a potential target for therapy (Morales et al., 2014). In the present study, Sco administration caused an elevation in brain IL-1β, IL-6 and TNF-α levels. This elevation in the inflammatory cytokines may be due to the increased deposition of Aβ in brain. Previous studies have suggested that accumulation of abnormal

protein aggregates like Aβ may trigger neuroinflammation by activation of the brains innate immune system involving microglia and astrocytes. Activation of these cells causes them to produce inflammatory cytokines like IL-1ß and TNF–α resulting in neurodegeneration (Jantzen et al., 2002 and Bombi et al., 2011). IL-1ß further aggravates the immune/inflammatory response by promoting more APP synthesis and by promoting the production of more Aß-binding proteins by astrocytes (Akiyama et al., 2000). Over-expression of IL-1 near amyloid plaques may promote the phosphorylation of tau protein, leading to the formation of NFTs and neuron death (Jantzen et al., 2002 and Lim et al., 2013). Both rivastigmine and sesame oil counteracted the rise in the IL-1β, IL-6 and TNF-α levels in the Sco-treated rats, indicating their role in preventing neuroinflammtion. Similar results were reported by John et al. (2015) who found that sesamol, an active constitute of sesame oil, reduced aluminium chloride induced elevation in TNF–α in rats.

A large body of experimental evidence supports a role for oxidative stress as mediator of nerve cell death in several neurodegenerative disorders, such as AD (Bombi et al., 2011; Lim et al., 2013 and Morales et al., 2014). Loss of the intracellular antioxidant, GSH, is considered to be an early event in the pathogenesis of neurological disorder (Wu et al., 2009). In the current study, Sco significantly reduced the brain levels of GSH and GSSG, indicating that Sco could trigger the oxidative stress in rats. This reduction in GSH and GSSG levels could be attributed to imbalance in the enzymes associated with the synthesis, utilization and degradation of GSH. In this study, both rivastigmine and sesame oil increased GSH and GSSG levels in brain. Sesame oil is a potent antioxidant in various animal model of diseases, including endotoxemia (Hsu et al., 2008), lead intoxication (Hsu et al., 2007), and gentamicin-induced renal injury (Hsu et al., 2011). Also, Zare et al., (2011) reported that sesame oil reduced oxidative stress and led to better behavioral activity in diabetic animals. It is strongly believed that the antioxidant effect of sesame oil is due to the presence of lignans (sesamin, sesamol and sesamolin) and vitamin E in it (Ghafoorunissa et al., 2004).

Apoptosis, another important pathogenesis of AD, has been reported to be associated with the mechanism of central cholinergic system dysfunction and oxidative stress (Hou et al., 2014). In the present study, Sco significantly reduced the level of Bcl-2 in the brain of rats, while sesame oil and/or rivastigmine treatment increased its level. Bcl-2 is an inhibitor of apoptosis which exerts anti-apoptotic effects. Bax, a proapoptotic protein, exerts an opposite effect to Bcl2. It was reported that a high expression of Bax protein promoted cell death. The ratio of Bcl2 to Bax determines the susceptibility of cell apoptosis (Qian et al., 2008). Studies have shown that an increase of Bcl2 and a decrease of Bax prevented the release of cytochrome c in mitochondria, and therefore inhibit the cascade of apoptosis (Hou et al., 2014). In this study, the higher level of Bcl-2 observed in sesame oil and/or rivastigmine treated rats may attributed to their antioxidant and anti-inflammatory effects. It was reported that apoptotic death of dopamine neurons may be initiated by oxidative stress and neuroinflammation. (Marchetti and Abbracchio, 2005). Lahaie-Collins et al. (2008) demonstrated that picomolar doses of sesamin can protect dopamine neuronal cells from 1-methyl-4-phenyl-pyridine-induced cellular death by reducing intracellular reactive oxygen species production.

In this study the level of brain FABP7 was decreased in Sco treated rats. FABP comprise a family of small cytoplasmic proteins which facilitates the solubility of hydrophobic long chain fatty acids. They function primarily in fatty acids (FAs) uptake/transport (Chmurzynska, 2006) and have been widely implicated in cell growth and differentiation (Feng et al., 1994). Brain FABP7 has high affinity for n-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (20:5) and docosahexaenoic acid (22:6), which are present in high concentrations in the plasma membrane of nervous tissue cells (Balendiran et al., 2000). A deficiency of these types of fatty acids affects the behavior of rats, leading to learning disabilities (Innis et al., 1999). Brain-FABP7 also interacts with monounsaturated n-9 FAs, such as palmitoleic acid (16:1) and oleic acid (18:1). Studies also indicate that brain-FABP7 influences the correct migration of neurons to the cerebral cortex (Feng et al., 1994). Schnell et al. (2014) suggested an important role of brain-FABP in adult neurogenesis, which may open new avenues for treatment of neurological diseases such as depression and AD. Rivastigmine and/or sesame oil treatment increased brain-FABP7 in Sco-treated rats. The exact mechanism for the observed increase in brain-FABP7 is unclear and needs further studies. It may be attributed to the fatty acids or lignin contents of sesame oil.

Consequently, the current investigation showed that repeated injection of Sco induced cholinergic dysfunction, inflammatory reactions, oxidative stress, and apoptosis in rat's brain. Oral administration of rivastigmine, sesame oil or their combination corrected these biochemical abnormalities. However, the administration of sesame oil with rivastigmine to Sco treated rats led to maximum corrections in all studied parameters. This improvement may be attributed to the enhancements in the pharma-dynamics or pharma-kinetics properties of rivastigmine in the presence of sesame oil. Furthermore, sesame oil is neuroprotective agent which contains sesamin and sesamolin (Cheng et al., 2006). The later compounds (sesamin and sesamolin) may act in parallel with rivastigmine as agents for AD prevention as well a coadjuvant for AD treatments.

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REFERENCE

Akiyama, H.; Barger, S.; Barnum, S.; Bradt, B.; Bauer, J. and Cole, G.M.(2000): Inflammation and Alzheimer's disease. Neurobiol. Aging 21: 383–421. | Bailey, N.T.J. (1994): Statistical methods in biology.3rd ed. Cambridge University press (Uk). | Balendiran, G.K.; Schnutgen, F.; Scapin, G.; Borchers, T. and Xhong, N. (2000): Crystal structure and thermodynamic analysis of human brain fatty acid-binding protein. J Biol Chem, 275: 27045–27054. | Ballard, C.G. (2002): Advances in the treatment of Alzheimer's disease: benefits of dual cholinesterase inhibition, European Neurology, 47: 64–70. | Barbareschi, M.; Caffo, O.; Veronese, S.; Leek, R.D.; Fina, P.; Fox, S.; Bonzanini, M.; Girlando, S.; Morelli, L.; Eccher, C.; Pezzella, F.; Doglioni, C., Palma, P.D. and Harris, A. (1996): Bcl-2 and P53 expression in node-negative breast carcinoma: a study with long-term follow-up. Human Pathol 27: 1149–1155. | Beutler, B.; Greenwald, D. and Hulmes, J.D. (1985): Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature, 316: 552-554. | Bihaqi, S.W.; Singh, A.P. and Tiwari, M. (2012): Supplementation of Convolvulus pluricaulis attenuates scopolamine-induced tau and amyloid precursor protein (ABPP) expression in rat brain. Indian J Pharmacol, 44: 593-598 | Bombi, L.; Shim, I.; Lee, H. and Hahm, D. (2011): Rehmannia glutinosa ameliorates scopolamine-induced learning and memory impairment in rats. J. Microbiol. Biotechnol. 21: 874–883 | Calabrese, F. Guidotti, G.; Racagni, G. and Riva, M.A. (2013): Reduced neuroplasticity in aged rats: a rolefor the neurotrophin brain- derived neurotrophic factor, Neurobiology of Aging, 34: 2768–2776. | Chen, C.; Li, X.H.; Zhang, S.; Tu, Y.; Wang, Y.M. and Sun H.T. (2014): 7,8-dihydroxyflavone ameliorates scopolamine-induced Alzheimer-like pathologic dysfunction. Rejuvenation Res. 17: 249-54. | Cheng, F.; Jinn, T.; Hou, R.C.W. and Tzen, J.T.C. (2006): Neuroprotective effects of sesamin and sesamolin on gerbil brain in cerebral ischemia, Intr.J Biomedical Sci. 284-288. | Chmurzynska, A. (2006): The multigene family of fatty acid-binding proteins (FABPs): function, structure and polymorphism. J Appl Genet 47: 39–48. | Citron, M. (2004): Beta-secretase inhibition for the treatment of Alzheimer's disease –promise and challenge. Trends Pharmacol. Sci. 25: 92–97. | Den Blaauwen, D.H.; Poppe, W.A. and Tritschler, W. (1983): Acetylcholinesterase with acetylthiocholine iodide as substrate: references depending on age and sex with special reference to hormonal effects and pregnancy. J Clin Chem Clin Biochem 21: 381–386. | Feng, L.; Hatten, M.E. and Heintz, N. (1994): Brain lipid-binding protein (BLBP) – a novel signaling system in the developing mammalian CNS. Neuron 12: 895–908. | Flood, J. F. and Cherkin, A. (1986): Scopolamine effects on memory retention n mice: a model of dementia? Behavioral and Neural Biology, 45: 169–184. | Ghafoorunissa, Hemalatha, S. and Rao M.V. (2004): Sesame lignans enhance antioxidant activity of vitamin E in lipid peroxidation systems. Mol Cell Biochem; 262:195-202 | Givalois, L.; Arancibia, S.; Alonso, G.; Tapia-Arancibia, L. (2004): Expression of brain-derived neurotrophic factor in the rat median eminence cells with sensitivity to stress. Endocrinology, 145: 4737-4747. | Golde, T.E., Dickson, D. and Hutton, M. (2006): Filling the gaps in the A cascade hypothesis of Alzheimers disease. Curr. Alzheimer Res. 3: 421-430. | Grassi, J.; Roberge, C.J. and Frobert, Y. (1991): Determination of IL-1β, IL-1β and IL-2 in biological media using specific enzyme immunometric assay. Immunol. Res., 119: 125-145. | Heo, Y.; Shin, M.; Kim, S.; Kim, T.; Baek, S. and Baek, S. (2014): Treadmill exercise ameliorates disturbance of spatial learning ability in scopolamine-induced amnesia rats. J of Exercise Rehabilitation;10: 155-161. | Henry, R.J.; Cannon, D.C. and Winkelman, J.W. (1974): Clinical chemistry principles and techniques (Harper and Row) 16-40 | Hou, X.; Wu, D.; Zhang, C.; Yan, R.; Yang, C.; Rong, C.; Zhang, L.; Chang, X.; Su, R.; Zhang, S.; He, W.; Qu, Z.; Li, S.; Su, Z.; Chen, Y.; Wang, Q. And Fang, S. (2014): Bushen Yizhi formula ameliorates cognition deficits and attenuates oxidative stress related neuronal apoptosis in scopolamine induced senescence in mice, Inter. J Molecular Medicine 34: 429-439. | Hsieh, M.T.; Hsieh, C.L.; Lin, L.W. ; Wu, C.R. and Huang, G. (2003): Differential gene expression of scopolamine-treated rat hippocampus-application of cDNA microarray technology. Life Sci 73:1007-16. | Hsu, D. Z.; Chen, K. T.; Chu, P. Y.; Li, Y. H. and Liu, M. Y. (2007): Sesame oil protects against lead-plus-lipopolysaccharide-induced acute hepatic injury. Shock 27:334–337 | Hsu, D. Z.; Chien, S.P.; Li, Y.H.; Chuang, Y.C.; Chang, Y.C. and Liu, M.Y. (2008): Sesame oil attenuates hepatic lipid peroxidation by inhibiting nitric oxide and superoxide anion generation in septic rats. JPENJ. Parenter. Enteral Nutr. 32:154–159. | Hsu, D.; Li, Y.; Chu, P.; Periasamy, S. and Liu, M. (2011): Sesame oil prevents acute kidney injury induced by the synergistic action of aminoglycoside and iodinated contrast in rats. Antimicrobial Agents And Chemotherapy, 55: 2532–2536 | Hsu, D.Z.; Chen, S.J.; Chu, P.Y.; Liu, M.Y. (2013): Therapeutic effects of sesame oil on monosodium urate crystal-induced acute inflammatory response in rats. Springerplus. 2: 659. | Hyde, C.; Peters, J. and Bond M. (2013): Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholine esterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model, Age and Ageing, 42: 14–20. | Innis, S.M.; Sprecher, H.; Hachey, D.; Edmond, J. and Anderson, R.E. (1999): Neonatal polyunsaturated fatty acid metabolism. Lipids 34: 139–149. | Jantzen, P.T.; Connor, K.E.; DiCarlo, G.; Wenk, G.L.; Wallace, J.L. and Rojiani, A.M. (2002): Microglial activation and beta-amyloid deposit reduction caused by a nitric oxide-releasing non steroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. J. Neurosci. 15: 2246–2254. | John, J.; Nampoothir, M.; Kumar, N.; Mudgal, J.; Nampurath, G.K. and Chamallaudi, M.R. (2015): Sesamol, a lipid lowering agent, ameliorates aluminium chloride induced behavioral alterations in rats. Phcog Mag, 11:327-336. | Kim, S.E.; Ko, I.G.; Kim, B.K.; Shin, M.S.; Cho, S.; Kim, C.J.; Kim, S.H.; Baek, S.S.; Lee, E.K. and Jee, Y.S. (2010): Treadmill exercise prevents aging-induced failure of mem¬ory through an increase in neurogenesis and suppression of apoptosis in rat hippocampus. Exp Gerontol, 45:357-365. | Kiso, Y. (2004): Antioxidative roles of sesamin, a functional lignan in sesame seed, and it's effect on lipid- and alcohol-metabolism in the liver: a DNA microarray study. Bio Factors, 21:191-6. | Kotani, S.; Yamauchi, T.; Teramoto, T. and Ogura, H. (2006): Pharmacological evidence of cholinergic involvement in adult hippocampal neurogenesis in rats. Neuroscience, 142:505-514. | Lahaie-Collins, K.; Bournival, J.; Plouffe, M.; Carange, J. and Martinoli, M. (2008): Sesamin modulates tyrosine hydroxylase, superoxide dismutase,catalase, inducible NO synthase and interleukin-6 expression in dopaminergic cells under MPP+-induced oxidative stress, Oxidative medicine and cellular longevity 1: 54-62 | Lim, D.; Iyer, A.; Ronco, V.; Grolla, A.A.; Canonico, P.L. and Aronica, E. (2013): Amyloid beta deregulates astroglial mGluR5-mediated calcium signaling via calcineurin and Nf-kB. Glia 61: 1134–1145. | Marchetti, B. and Abbracchio, M.P. (2005): To be or not to be (inflamed)—Is that the question in anti-inflammatory drug therapy of neurodegenerative disorders? Trends Pharmacol Sci, 26 :517-25. | | Monteiro, E.M.; Chibli, L.A.; Yamamoto, C.H.; Pereira, M.C.; Vilela, F.M.; Ro¬darte, M.P. (2014): Antinociceptive and anti-inflammatory activities of the sesame oil and sesamin. Nutrients.6:1931–44. | Morales, I.; Guzmán-Martínez, L.; Cerda-Troncoso, C.;. Farías, G.A. and Maccioni R.B. (2014): Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches, Cellular Neuroscience 8: 1-9. | Nakano, D.; Kwak, C.J.; Fujii, K.; Ikemura, K.; Satake, A.; Ohkita, M.; Takaoka, M.; Ono, Y.; Nakai, M.; Tomimori, N.; Kiso, Y. and Matsumura Y. (2006): Sesamin metabolites induce an endothelial nitric oxide-dependent vasorelaxation through their antioxidative property-independent mecha- nisms: possible involvement of the metabolites in the antihypertensive effect of sesamin. J Pharmacol Exp Ther; 318:328-35. | Oswald, C.; Smits, S.H.; Hoing, M.; Sohn-Bosser, L.; Dupont, L.; Le Rudulier, D.; Schmitt, L. and Bremer, E. (2008): Crystal structures of choline/acetylcholine substrate-binding protein chox from sinorhizobium meliloti in the liganded and unliganded–closed states. J Biol Chem. 283: 32848–32859. | Panja, D. and Bramham, C.R. (2014): BDNF mechanisms in late LTP formation: a synthesis and breakdown. Neuropharmacology, 76: 664–676. | Pastore, A.; Piemonte, F.; Locatelli, M.; Gaeta, L.; Tozzi, G. and Federici, G. (2001): Determination of blood total, reduced and oxidized glutathione in pediatric subjects. Clin. Chem. 47: 1467-1469. | Qian, Y.F.; Wang, H.; Yao, W.B. and Gao, X.D. (2008): Aqueous extract of the Chinese medicine, Danggui Shaoyao San, inhibits apoptosis in hydrogen peroxide induced PC12 cells by preventing cytochrome c release and inactivating of caspase cascade. Cell Biol Int., 32: 304 311,. | Rios, M.; Fan, G.; Fekete, C.; Kelly, J.; Bates, B.; Kuehn, R.; Lechan, R. M.; Jaenisch, R. (2001): Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. Molec. Endocr. 15: 1748-1757. | Safar M.M.; Arab, H.H.; Rizk, S.M. and El-Maraghy (2014): Bone marrow-derived endothelial progenitor cells protect against scopolamine induced Alzheimer-like pathological aberrations. Mol Neurobiol, (Epub ahead of print) | Saleem, M.T.; Chetty, M.C. and Kavimani, S. (2014): Antioxidants and tumor necrosis factor alpha-inhibiting activity of sesame oil against doxorubicin-induced cardiotoxicity. Ther Adv Cardiovasc Dis. 8:4-11. | Saura C. A. and Valero, J. (2011): The role of CREB signaling in Alzheimer's disease and other cognitive disorders, Reviews in the Neurosciences, 22: 153–169. | Schnell, A.; Chappuis, S.; Schmutz, I.; Brai, E. and Ripperger, J.A. (2014) The Nuclear Receptor REV-ERBa Regulates Fabp7 and Modulates Adult Hippocampal Neurogenesis. PLoS ONE, 9: | Wang, R.; Sweeney, D.; Gandy, S.E. and Sisodia, S.S. (1996): The profile of soluble amyloid beta protein in cultured cell media. Detection and quantification of amyloid beta protein and variants by immunoprecipitation-mass spectrometry. J Biol Chem. 271:31894-902. | Weon, J.B.; Yun, B.R.; Lee, J.; Eom, M.R.; Ko, H.; Lee, H.Y.; Park, D.; Chung, H.; Chung, J.Y. and JeMa C. (2014): Cognitive-Enhancing Effect of Steamed and Fermented Codonopsis lanceolata: A Behavioral and Biochemical Study. Evidence-Based Complementary and Alternative Medicine, 9 pages | Wong, G.G. and Clark, S.C. (1988): Multiple actions of interleukin 6 within a cytokine network. Immunology Today, 9: 137-139. | Wu, J.; Ji, H.; Wang, Y.Y.; Wang, Y.; Li, Y.Q.; Li, W.G.; Long, Y.; Xia, Y.Z. and Hong, H. (2009): Glutathione depletion upregulates P-glycoprotein expression at blood-brain barrier in rats. J Pharm Pharmacol, 61: 19-24. | Yoo, D.Y.; Kim, W.; Yoo, K.Y.; Lee, C.H.; Choi, J.H.; Kang, I.J.; Yoon, Y.S.; Kim, D.W.; Won, M.H. and Hwang, I.K. (2011): Effects of Nelumbonucifera rhizome extract on cell proliferation and neuroblast differentiation in the hippocampal dentate gyrus in a scopolamine-induced amnesia animal model. Phy¬tother Res. 25:809-815. | Zaki, H.F.; Abd-El-Fattah, M.A. and Attia, A.S. (2013): Naringenin protects against scopolamine induced dementia in rats. Bulletin of faculty of pharmacy, Cairo University | Zare, K.; Tabatabaei, S.R.F.; Shahriari, A. and Jafari, R. (2011): Effect of butter and sesame oils on avoidance memory of diabetic rats. Iranian J of diabetes and obesity, 3: 65-70. |