The Neurotherapeutic Properties of Black Raisins and Ginkgo Against Oxidative Stress and Memory Impairment in Alzheimer's Disease Induced by Aluminum Chloride

Amal Z. Nasef & Samah M. El-banna

Department of Nutrition and Food Science, Faculty of Home Economics, Menoufia University, Shebin El-kom, Egypt.

مجلة البحوث في مجالات التربية النوعية

معرف البحث الرقمي DOI: 10.21608/JEDU.2024.270948.2024

المجلد العاشر العدد 51 . مارس 2024

الترقيم الدولي

P-ISSN: 1687-3424 E- ISSN: 2735-3346

موقع المجلة عبر بنك المعرفة المصري https://jedu.journals.ekb.eg/

موقع المجلة http://jrfse.minia.edu.eg/Hom

العنوان: كلية التربية النوعية . جامعة المنيا . جمهورية مصر العربية

The Neurotherapeutic Properties of Black Raisins and Ginkgo Against Oxidative Stress and Memory Impairment in Alzheimer's Disease Induced by Aluminum Chloride

Alzheimer's disease (AD) is a type of neurodegenerative disease that worsens with time and significantly reduces cognitive function. The pathophysiology of several neurodegenerative disorders has been found to involve processes that are influenced by oxidative stress. Aluminum is a strong neurotoxin that can cause oxidative stress, which is linked to neurological conditions including AD. The purpose of the study was to look at the neurotherapeutic properties of dried black raisins(DBR) and ginkgo(Gb) against oxidative stress and spatial memory impairment in AD. 35 mature males Sprague Dawley rats weighing 150 ± 10g were randomly assigned to two primary groups of rats. The first main group, (n=5 rats) , served as a negative control group that only had a standard diet. The second main group (Alzheimer-rats)(n=30) were given oral administration of AlCl3 (100 mg/Kg body weight/day) for 30 days. Then it was divided into six subgroups. Subgroup (1), serving as the positive control , was provided with a basal diet for 28 days. Subgroup (2) the rats in this group were orally administered rivastigmine at a daily dosage of 0.25 mg while being fed a basal diet. Subgroup (3) is given a basal diet with 10% DBR from the diet. Subgroup (4) is given a basal diet with 20% DBR from the diet. Subgroup (5) is given a basal diet with 10% *Gb* from the diet. Subgroup (6) is given a basal diet with 20% *Gb* from the diet. After 28days, biological, biochemical and histological parameters were assessment. The results showed suppression and inhibition of some neurotransmitter levels, such as lactate dehydrogenase (LDH), xanthine oxidase (XO), interleukin-6 (IL-6), acetylcholinesterase (AChE) , tumor necrosis factor alpha (TNF-α), amyloid beta protein (AβP), acetylcholine (ACH) and acetylcholinesterase (AchE) activity. Through regulation and improving at oxidative stress (glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) ,serotonin (5- HT), dopamine

(DA) and Phosphatidylcholine transfer protein (PCTP) as evidenced in histopathological results. The best results were for groups fed with 20% of DBR and Gb. **Conclusion**: It could be concluded that administration of Gb and DBR reduces memory impairment, oxidative stress , improved cholinergic agent, dopaminergic dysfunction , memory loss and neurotoxicity and may be a useful therapy for AD related cognitive decline.

Keywords: Aluminum chloride ,Alzheimer disease, acetylcholinesterase, neurotransmitter levels, inflammatory cytokines , oxidative stress.

1. Introduction

The pathological classification of Alzheimer disease (AD) is based on the progressive loss of synaptic and neuronal functions, which leads to a decline in cognitive function and memory. The primary histopathological features of AD are thought to be the build-up of amyloid beta peptides (Aβ) in neuronal cells and the formation of intracellular neurofibrillary knots **(Armstrong, 2013** & **Murdock and Tsai 2023).**Numerous factors, including age, sex, heredity, head trauma, exposure to the environment, infectious agents, oxidative stress, and cerebrovascular risk factors are probably some of the causes of AD. (**Tramutola *et al* .,2017)** .

Several pathogenic pathways of vascular involvement in AD have been identified. These include disruption of the blood-brain barrier, dysregulation of neurovascular coupling, and poor clearance of metabolic waste such as beta-amyloid, a toxic peptide considered to be the hallmark of AD **(Eisenmenger *et al*., 2023).** Neurotransmitter malfunction in the brain, particularly in the regions of serotonin (5-HT), acetylcholine (Ach), dopamine (DA), norepinephrine (NE), glutamate (Glu), and gamma-aminobutyric acid (GABA), is linked to the degenerative characteristics of AD **(Chalermpalanupap *et al*., 2013)** .

Aluminum (Al) is the most frequent metal in the coating of the earth, the third most abundant element. Al is present in food, cooking utensils, antacids, deodorants, and baby formulas that humans consume. Al has been shown to be harmful to the brain

because it promotes neurodegeneration and impairs cognition and memory (**Abu-Taweel and Al-Mutary, 2021).** According to reports, there has been a demonstrated a connection between the pathogenesis of neurodegenerative diseases such as AD, Guam-Parkinson's dementia, amyotrophic lateral sclerosis, etc. and the buildup of Al in the brain **(Kaur *et al.*, 2022).**

Rivastigmine (or Exelon) is a cholinesterase inhibitor, currently being used to treat mild-to-moderate AD symptoms. Beyond AD, rivastigmine may prove to be a useful therapeutic drug in the treatment a number of other neurodegenerative illnesses. Rivastigmine-treated AD patients showed increased oxidative and enzymatic activity, such as pyruvate-malate and glycerol-3-phosphate oxidation, when compared to control or untreated individuals with dementia **(Ray *et al.*, 2020) & (Müller, 2007)**.At the maximum dosage, rivastigmine exhibits more cholinesterase inhibition, but it may also cause more adverse effectsthe profile of side effects is comparable to that of donepezil, with a greater frequency of symptoms associated with gastrointestinal disorders **(Kumar and Kumar 2009).**

Aromatic acid and a variety of phenolic compounds are present in several areas of the *Vitis vinifera* L. plant, which produces black raisins(BR). The primary components of grapes include proanthocyanidins, flavonoids, hydroxybenzoic acid, hydroxycinnamic acid, kaempferol, quercetin, catechins, and proanthocyanins, among others **(Radulescu *et al*, 2020**, **Goufo *et al.*, 2020** and **Filocamo *et al.*, 2015).** The fruit of the grape is high in protein, lipids, phenolic acids, anthocyanins, flavonols, resveratrol, stilbenes, and vitamins C (**Arora *et al.*, 2016)**.

When compared to other fruits, raisins have some of the greatest amounts of antioxidant oxygen radical absorbance capacity (ORAC) and polyphenolic content. Additionally, raisins are a good source of boron, a trace element required for proper brain function including attention, memory, and hand-eye coordination **(Jeszka *et al.*, 2017).** One polyphenolic component that is particularly effective is resveratrol, which is mostly found

in grapes. It possesses the antioxidant and neuroprotective qualities of grapes as well as the polyphenolic derivative of grape, which may have neuroprotective properties **(Foroughi *et al*., 2023 and Sahu *et al*., 2023)**.

Ginkgo biloba (Gb), a centuries-old herbal extract, is currently being embraced by the new age of nutraceuticals . Quercetin, kaempferol, isorhamnetin, ginkgolides, and bilobalide are the main flavonoids and terpenoids found in Gb. These active ingredients work against cancer by influencing important biological processes like autophagy, cell cycle arrest, apoptosis, and the suppression of invasion and metastasis through a variety of signaling channels. The extract from it exhibits advantageous characteristics in the management of various illnesses, including diabetic cardiomyopathy, neurodegenerative diseases, cataracts, hearing impairment, myocardial lesion, hippocampus neuronal lesions, changes in testicular morphology, and liver damage **(Souza *et al*., 2020 &Hu *et al*., 2024)**. Gb extracts have the ability to improve rats' neurological disease by inhibiting lipid peroxidation, increasing the body's natural antioxidant enzymes, and lowering the activity of the enzyme acetylcholinesterase in the brain **(Elhallouty *et al*., 2022)**. Several human clinical trials using Ginkgo leaf showed similar advantages in improved cognition, memory loss, or enhanced blood flow, which may be effective for Alzheimer's disease, vertigo, dyslexia, and other neuropsychiatric disorders **(Zifko *et al*., 2022 & Arunima *et al*., 2021)**. Hence, this experiment was carried out to investigate the neuroprotective properties of black raisins and ginkgo against oxidative stress and spatial memory impairment in AD induced by (AlCl3).

2. MATERIALS AND METHODES:

2.1. Materials:

2.1.1.Plants: Black raisins (*Vitis vinifera L.*) was brought from a local herblist in Matrouh Governorate, Egypt.

Ginkgo (*Ginkgo biloba L.*) was brought from a local herblist in Shebin El-Kom, Menoufia, Egypt.

2.1.2.Chemicals : In Shebin El-kom, Menoufia, Egypt, the local bazaar was where corn oil and starch were bought. Dextrin, L-cysteine, casein, minerals, vitamins, and cellulose were obtained from the Cairo Corporation for Chemical Trade. Almiuim chlorid (AL) was given by Sigma Chemical Company.

2.1.3. Rivastigmine (Exelon), Novartis pharmaceuticals (Cairo, Egypt), in the form of 1.5 mg capsules. The required dose of the capsule content was weighed using a digital scale .

2.1.4. Animals: The 35 albino rats (adult male), Sprague Dawley, weighing 150 ± 10 g were obtained from the National research institute, Animal House (Cairo, Egypt). Rats were kept in groups in well-ventilated cages under sanitary conditions in the Biological Laboratory, Home Economics Faculty, Nutrition and Food Sci. Department, Shibin El-kom (Menoufia), Egypt and consumed the standard diet AIN-93 as reported by **Reeves *et al.*, (1993)** for a seven-day adaptation period. This investigate was ethically accepted by the Institutional Animal Ethics committee of Menoufia University (Reg. No, MUFHE /F/NFS/3/24).

2.2. Methods:

2.2.1. Preparation of dried black raisins (DBR).

It was dried by shade methods; grapes are placed in mesh trays, placed in a contained space, and allowed to dry in the shade. This method's temperature range was 20 to 35 °C **(Pangavhane and Sawhney, 2002)**. After that they were purchased in closed packages.

2.2.2. Alzheimer's disease induction.

After dissolving in 0.9 sodium chloride at pH 7.4 for thirty days, rats were given AlCl3 (100 mg/Kg body weight/day) orally **(Chen *et al.*, 2021).**

2.2.3. Experimental protocol.

The 35 albino rats (adult male), Sprague Dawley , weighing roughly 150 ± 10g were acquired from the Laboratory of Animal Colony, Helwan, Egypt. They were given a standard diet, kept in clean, well-ventilated cages, and allowed unrestricted access to water**.** Following this period, the rats were divided into two main groups. The first main group, (n=5 rats) was a negative control group and was fed a standard diet only . The thirty rats in the positive control group were given AlCl3 (100 mg/Kg body weight/day) orally after it had been dissolved in 0.9 sodium chloride at pH 7.4 for thirty days. **(Chen *et al.*, 2021)** as a model of alzhimer disease in rats. The second main group (Alzheimer-induced) was divided into six subgroups. Subgroup (1), serving as the positive control, was provided with a basal diet for 28 days. Subgroup (2), Rivastigmine was given orally to the rats at a dose of 0.25 mg per day **(Carageorgiou *et al.*, 2008)** and fed on a basal diet. Subgroup (3) is given a basal diet with 10% DBR from the diet .Subgroup (4) is given a basal diet with 20% DBR from the diet. Subgroup (5) is given a basal diet with 10% *Gb* from the diet. Subgroup (6) is given a basal diet with 20% *Gb* from the diet .

2.2.4. Blood and tissue samples collection.

Rats were weighed after 28 days and fasted for one night prior to exsanguination. Blood was taken from the hepatic portal vein of each rat and placed in sterile, dry centrifuge tubes. The serum was placed in the plastic vial and maintained frozen at -20˚C **(Schermer, 1967)**. And, brain tissues were dissected quickly on ice for histopathological assay. The relative organ weight was calculated as follows:

$$\text{Relative organs weight } \% = \frac{\text{Organ weight (g)}}{\text{Total body weight (g)}} \times 100$$

2.2.5. Biological assessment.

According to **Chapman *et al.*, (1959)**, feed efficiency ratio (FER), body weight gain (BWG) and feed intake (FI) were calculated during the experiment. Using the following formulas:

$$BWG = \text{Final weight} - \text{initial weight}$$

$$FER = \frac{\text{Gain in body weight (g)}}{\text{Feed intake (g)}}$$

2.2.6. Biochemical analysis.

Interleukin -6 levels in the serum was determined according to **Henry, (1964)**. Antioxidant indications were assessed, such as superoxide dismutase (SOD), according to **Nandi and Chatterjee ,(1988)**. Catalas (CAT) according to **Soto *et al.*,(2011)**. Malondialdehyde (MDA), according to **Giera *et al.*,(2012)**, and tumor necrosis factor -α (TNF),according to **Acharya *et al.*, (1996)**. Acetylcholine esterase (AChE) was estimated according to **Carageorgiou *et al.*, (2005)**.Dopamine (DA) and serotonin (S.T.) were determined according to **Sasa and Blank (1977)**. According to **Gaballah *et al.* (2016),** serum levels of dopamine, serotonin, and norepinephrine were measured by enzyme linked immunoassay using a BioTech ELISA reader USA. Estimating acetylcholine esterase As per **Khan *et al.* (2018),** AChE activity was measured in the entire brain homogenate. LDH (lactate dehydrogenase) was estimated according to **Bergmeyer *et al.*, (1965).** Glutathione (GSH) was estimated according to **Beutler *et al.*, (1960)**. Amyloid beta protein (ABP) was assessed according to **Funato *et al.*, (1998).**Hydroxy tryptamine (5- HT) was appreciated according to **Su *et al.*, (2008)**. Xanthin oxidase (XO) was appreciated according to **Martí *et al.*, (2001)**. Phosphatidylcholine transfer protein (PCTP) appreciated according to **Runne *et al.*, (2007).**

2.2.7. Tissue preparation and histological examinations

Rats were dissected, and their brains were taken out, cleaned in saline, and split in half in the sagittal plane. 10% formalin was used to fix one half for histological analysis**.** After the other half's hippocampal and cortex were removed, they were promptly frozen at -80 °C to prepare the tissues for homogenization. The homogenate was centrifuged at 3000 rpm

and 4 °C for 15 minutes. Subsequently, the supernatant was isolated, divided into equal parts, and kept cold in an eppendorf tube for the biochemical test. Following a 24-hour fixation in 10% formalin saline, the brain tissues were serially diluted with alcohol to induce dehydration. To be viewed under a light microscope, hematoxylin and eosin (H and E) staining was performed on brain tissues that had been paraffin fixed and sectioned into sections that were 3 µm thick **Grafström *et al.* (2008)**.

2.2.8 Statistical analysis

The results were assessed using the statistical software SPSS for Windows Version 10, and they were displayed as Means ± standard deviation. The variances between the groups were analyzed using the one-way ANOVA testing function of the statistics package program, and the levels of significance were assessed at a significance level of $P \leq 0.05$ using Duncan's multiple comparison tests as a post hoc test **(Artimage and Berry, 1987)**.

3. RESULTS AND DISCUSSION

The results of the current study were presented as follows:

3.1. Biological results:

The effect of rivastigmine, dried black raisins and ginkgo on nutritional evaluation in rats with Alzheimer's disease.

Table (1) shows the effect of rivastigmine, DBR and Gb on FI, BWG, FER and RBW in rats with AD . It was found that the Alzheimer's rats had a significant decrease in the BWG, FI and FER as compared to the normal rats. This decrease in biological levels is due to chronic exposure to AlCl3 in rats which induces disturbance in appetite and feeding. These results supported those of **Ismail *et al.* (2023)** who discovered that AlCl3 considerably lowered the experimental subgroups' BWG relative to the control. When compared to the recovery subgroup that received only AlCl3 treatment, the rivastigmine-treated subgroups had considerably improved and restored their BWG. This may be explained by the recorded progressive return of appetite and

elevated feed intake. Likewise, **Han *et al.* (2023)** and **Abbas *et al.* (2022)** showed that the rats exposed to AlCl3 for an extended period of time experienced a significant reduction in body weight and brain weight when compared to the normal control group. This is in line with earlier studies that showed aluminum to be detrimental to normal metabolism. The weight loss was mediated through protein and lipid oxidation, inhibiting glycolysis and the Krebs cycle.(**Upadhyaya *et al.*, 2019 and Olanrewaju *et al.*, 2018)** reported that rivastigmine treatment resulted in regain of BW in AlCl3 -treated rats.

Supplementation of the AD diet with different concentrations of rivastigmine, DBR and Gb significantly ($P \leq 0.05$) showed a significant increase in body weight gain , feed intake and efficiency ratio compared to the positive control group ($P \leq 0.05$). The highest mean value was recorded for the group fed on 20% of the meals of DBR and Gb . In the same table described no significant differences were observed in the body weight gain , feed intake and feed efficiency ratio between Alzheimer's rats supplemented with 0.25mg rivastigmine and those supplemented with 10% DBR . Numerous studies have demonstrated that rivastigmine transdermal patches may help people with AD who are malnourished or have lost their appetite. **Tsuno *et al.*, (2019).** Furthermore, according to **Patel *et al.* (2011),** raisins increase fullness and reduce hunger. **Anderson *et al.* (2009)** suggest that soluble fibers' ability to delay stomach emptying could potentially be a factor in satiation.

Table (1) The effect of rivastigmine, dried black raisins, and ginkgo biloba on nutritional evaluation in rats with Alzheimer's disease

Parameter / Groups	BWG(g)	FI(g/day)	FER(rat/day)	RBW (g)
Control(-)	14.35^{a}± 0.538	14.600^{a}±0.436	0.983^{a} ±0.034	2.598a ± 0.077
Alzheimer's rats	8.405^{e}± 0.437	10.312^{d}±0.285	0.816^{d} ±0. 060	1.790d ± 0.085
0.25 mg rivastigmine	11.115^{d}± 0.168	12.150^{c}±0.676	0.914^{bc} ±0.017	2.184bc ± 0.101

DBR (10%)	12.033^{c}± 0.361	12.423^{c}±0.304	0.968^{ab} ±0.017	2.23bc ± 0.059
DBR (20%)	13.14^{b} ±0.170	13.606^{b}±0.349	0.966^{ab} ±0.021	2.30b ± 0.228
Gb (10%)	10.367^{d}± 0.236	11.713^{c}±0.180	0.885^{c} ±0.026	2.09c ± 0.082
Gb (20%)	13.03^{b} ±0.846	13.455^{b}±0.419	0.967^{ab} ±0.035	2.334b ± 0.062

The values are shown as means + standard deviation (SD); means with different letters in the same column indicate a significant difference ($p \leq 0.05$) . DBR: draied black raisins. Gb: *Ginkgo biloba*, FI: feed intake. FER:feed efficiency ratio BWG: body weight gain.. RBW: relative brain weight. .

3.2. Biochemical results:

The effect of rivastigmine, dried black raisins and ginkgo biloba on CAT, SOD, GSH and LDH in rats with Alzheimer's disease .

Table (2) presents the effects of rivastigmine, DBR and Gb on catalase (CAT), super oxide dismutase (SOD), glutathione (GSH) and lactate dehydrogenase (LDH) in AD rats. It was found that the AD rats had a significant decrease in CAT, SOD and GSH as compared to the normal rats. This decrease is due to chronic exposure to AlCl3 in rats which induce a reduction in antioxidant parameter levels. Experiments have demonstrated that the brain is an extremely susceptible organ because of its rapid rate of O2 consumption, high concentration of polyunsaturated fatty acids, and iron, which all contribute to lipid peroxidation. Additionally, the double bonds in unsaturated fatty acids tend to draw in free radicals. Furthermore, the antioxidant content of brain tissues is lower than that of other organs, together these elements increase the nervous system's vulnerability to oxidative injury. These results were in line with those of **Newairy *et al.*, (2009)** who discovered that by reducing the levels of the total antioxidant parameter, Al exacerbated the imbalance between pro-oxidant and antioxidant potentials. Increased tissue MDA levels and decreased tissue glutathione peroxidase activity in the AlCl3-treated group relative to the control group demonstrate how AlCl3 affects oxidative stress. **Nedzvetsky *et al.* (2006)** observed that rats' frontal cortex MDA levels increased considerably when exposed to Al, which is consistent with our observations. Brain alterations in biochemistry, neurochemistry, and behavior are brought on by

exposure to AlCl3. Additionally, zebrafish treated with AlCl3 showed considerably lower levels of reduced glutathione (GSH) and superoxide dismutase (SOD), whereas higher amounts of malondialdehyde (MDA) were observed, suggesting a high level of oxidative stress **(Kaur *et al.*, 2022).**

When compared to the positive control group, the supplemental AD diet with varying concentrations of rivastigmine, DBR, and Gb significantly ($P \leq 0.05$) increased CAT, SOD, and GSH. The highest mean value was recorded for the group fed on 20% of the DBR and GB meals. In the same table described no significant differences were observed in CAT, SOD and GSH between Alzheimer's rats supplemented with 0.25mg rivastigmine and those supplemented with 10% DBR. These improvements in results may be due to the amount of polyphenol and phenolic acid components, which have antioxidant qualities, found in ginkgo and raisins . By removing free radicals, activating antioxidant enzymes, chelating metal catalysts, lowering α-tocopherol radicals, and blocking oxidases, natural polyphenols are essential to the body.

The same table represented the effect of rivastigmine, DBR and Gb on LDH in rats with AD. It was found that the AD rats had a significant increase in the LDH level as compared to the normal rats. These increase due to chronic exposure to AlCl3 in rats which induces a reduction in antioxidant parameter levels. The addition of an AD diet with different concentrations of rivastigmine, DBR and Gb significantly ($P \leq 0.05$) showed a statistically significant decrease in LDH levels when compared to the positive control group ($P \leq 0.05$). The lowest mean value was for the group fed on 20% of the meal of DBR and Gb. In the same table described no significant differences were observed in LDH between Alzheimer's rats supplemented with 0.25mg rivastigmine and those supplemented with 10% DBR . These outcomes concurred with According to these findings, rivastigmine reduced neurotoxicity brought on by mitochondrial enzyme activity, and enhanced antioxidant enzyme levels in the brain, and alleviated behavioral impairment **(Kumar and Kumar 2009).** Moreover, *Vitis vinifera* extract was found to be comparable to normal

controls in its ability to regulate the brain's levels of antioxidant parameters when mixed with Al **(Lakshmi *et al.*, 2013).** In AD rats, the black raisin had neuroprotective properties. It raised brain levels of GSH, GSSG, and SOD and stopped LPO from developing **(Aljarari and Bawazir 2019).** *Ginkgo biloba* extract (EGb) treatment of rats infected with reproductive toxicity increased SOD and CAT levels while decreasing MDA levels **(Sakr *et al.*, 2015)**. Rats protected by GB extract administration showed large increases in liver and brain GSH and CAT and significant decreases in serum ALT, AST, ALP, and GGT as well as liver and brain MDA. **(Abou Zaid *et al.*, (2017)**. Additionally, *ginkgo biloba* extracts may be able to prevent AD by reducing oxidative stress, raising antioxidant enzyme levels, and enhancing changes in brain enzyme activity. Consequently, receiving these herbs may motivate elderly individuals to enhance their overall health. **(Osman *et al.*, 2018)**.

Table (2) The effect of rivastigmine, dried black raisins and ginkgo on CAT, SOD, GSH and LDH in rats with Alzheimer's disease .

Parameters / Groups	CAT (ng-ml)	SOD (U-ml)	GSH (ng-ml)	LDH (U-L)
Control(-)	$46.39^{a} \pm 3.10$	$83.77^{a} \pm 2.48$	$222.83^{a} \pm 3.69$	$183.33^{e} \pm 7.02$
Alzheimer's rats	$22.67^{e} \pm 2.52$	$23.91^{e} \pm 1.25$	$32.33^{e} \pm 1.92$	$336.00^{a} \pm 4.58$
0.25 mg rivastigmine	$38.72_{d} \pm 1.38$	$42.34^{d} \pm 2.06$	$142.13^{d} \pm 5.47$	$227.00^{b} \pm 2.00$
DBR (10%)	$38.58^{d} \pm 0.77$	$44.96^{cd} \pm 3.61$	$142.13^{d} \pm 5.55$	$225.00^{bc} \pm 2.65$
DBR (20%)	$42.61^{bc} \pm 1.32$	$48.35^{bc} \pm 2.88$	$175.33^{b} \pm 4.13$	$214.00^{d} \pm 5.57$
Gb (10%)	$39.26^{cd} \pm 1.94$	$48.23^{bc} \pm 2.1$	$168.15^{c} \pm 2.57$	$218.00^{cd} \pm 2.65$
Gb (20%)	$43.12^{ab} \pm 1.34$	$51.00^{b} \pm 1.00$	$178.25^{b} \pm 2.99$	$214.00^{d} \pm 2.00$

The values are shown as means + standard deviation (SD); means with different letters in the same column indicate a significant difference ($p \leq 0.05$) . DBR: draied black raisins. Gb: *Ginkgo biloba*. CAT: Catalase, SOD: Super oxide dismutase, GSH: Glutathione , LDH:Lactate dehydrogenase .

The effect of rivastigmine, black raisins and ginkgo on XO, TNF-α and IL-6 in rats with Alzheimer's disease .

Table (3) presentes the effects of rivastigmine, DBR and Gb on xanthine oxidase (XO), tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in AD rats. It was found that the AD rats had a significant increase in XO, TNF-α and IL-6 as compared to the normal rats. This increase is due to chronic exposure to AlCl3 in rats. These findings corroborated those of **Cao *et al.* (2016),** who demonstrated that in developing rats exposed to AlCl3, mRNA levels of IL-1β, IL-6, TNF-α, and MCH II increased, whereas mRNA levels of these compounds dropped and hampered learning and memory. Our results suggest AlCl3 can induce neuroinflammation that leads to learning and memory deficits. Additionally, **Rajendran *et al.*, (2023)** found that daily AlCl3 therapy increased MDA buildup, decreased TAC and CAT activity, and elevated TNF-α and IL-1β levels. In addition, aluminum reduced the amounts of ACh, serotonin, and dopamine in the brain. On the other hand, IMP considerably lessens the impact of AlCl3 by controlling the inflammatory response and altering the antioxidant system by focusing on Nrf2 (NF-E2-related factor 2) and mitogen-activated protein kinase (MAPK). According to **Abdel Maksoud *et al.* (2020)** when AlCl3 was administered to normal rats, the concentrations of IL-2, IL-6, and TNF were significantly higher than in the control group.

Supplementation of the AD diet with different concentrations of rivastigmine, DBR and Gb significantly ($P \leq 0.05$) showed a significant decrease in XO, TNF-α and IL-6 compared to the positive control group ($P \leq 0.05$). The best treatment was recorded for the group fed on 20% of the meal of DBR and Gb. In the same table was described no significant differences were observed in XO, TNF-α and IL-6 between Alzheimer's rats supplemented with 0.25mg rivastigmine, supplemented with 10% DBR and 10% Gb. These findings corroborated those indicating that vitamin D3 and rivastigmine in STZ promoted Alzheimer's in rats by reducing inflammation. In Alzheimer's disease-affected mice, rivastigmine and vitamin D3 had a neuroprotective impact by lowering inflammatory mediators (TNF-α and IL-1β), amyloid β peptide, and raising brain

acetylcholine levels **(Ibrahim *et al.*, 2018).** The cytokine TNF-α pathway, which releases IL-8 to initiate the inflammatory process, can be inhibited by *vitis vinifera* leaf extract **(Jang *et al.*, 2021).** Moreover, Gb has anti-inflammatory qualities by preventing the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. Gb has been shown to have beneficial effects on cardiac injury, brain damage, neurodegenerative disorders, and renal and liver damage in animal models **(Souza *et al.*, 2020)**.

Table (3):- The effect of rivastigmine, black raisins and ginkgo on XO and TNF-α in rats with Alzheimer's disease :-

Parameters / Groups	XO (ng-ml)	TNF-α (pg-ml)	IL.6 (pg-ml)
Control(-)	0.604^{e} ±0.103	27.51^{e} ± 0.86	36.48^{d} ± 2.18
Alzheimer's rats	16.48^{a} ± 1.641	174.33^{a} ± 4.04	96.8^{a} ± 1.31
0.25 mg rivastigmine	4.626^{b} ± 0.363	54.60^{b} ± 0.53	48.00^{b} ± 1.00
DBR (10%)	3.640^{b} ±0.106	44.66^{c} ± 1.53	46.73^{b} ± 1.64
DBR (20%)	1.683^{c} ± 0.284	33.00^{d} ± 2.00	37.67^{d} ± 1.527
Gb (10%)	3.723^{b} ± 0.240	45.33^{c} ± 0.58	41.53^{c} ± 1.29
Gb (20%)	1.376^{c} ± 0.446	33.00^{d} ± 1.00	38.00^{d} ± 1.00

The values are shown as means + standard deviation (SD); means with different letters in the same column indicate a significant difference ($p \leq 0.05$) . DBR: draied black raisins. Gb: Ginkgo biloba. XO: Xanthine oxidase. TNF-α: Tumor Necrosis Factor Alpha , IL-6:Interleukin-6

The effect of rivastigmine, black raisins and ginkgo on ABP and ACHE in rats with Alzheimer's disease :-

Table (4) shows the effect of rivastigmine, DBR and Gb on amyloid beta protein (AβP) and acetylcholinesterase (ACHE) in rats with Alzheimer's disease (AD) . It was found that the Alzheimer's rats had a significant increase in ABP and ACHE as compared to the normal rats. This increase is due to chronic exposure to AlCl3 in rats. These findings were consistent with those of **Lakshmi *et al.*, (2014)** who demonstrate that exposure to Al significantly reduced the brain's acetylcholinesterase activity. Rats treated with AlCl3 had a large rise in homogenate levels of AchE and LPO in the brain and hippocampus regions but a

significant decrease in DA, NE, GABA, GSH, GSSG, and SOD**(Aljarari and Bawazir, 2019).** The pathophysiology of AD appears years before cognitive symptoms do. The disease is characterized by two degenerative processes: the microtubule protein tau forming neurofibrillary tangles (NFTs) and the amyloid-β (Aβ) peptide aggregating into plaques. Nonetheless, it is believed that additional degenerative brain processes are important disease mediators of NFT pathology and Aβ plaque **(Erik *et al.*, 2023)**. AlCl3 considerably raised the levels of phosphorylated tau and Aβ-amyloid in the brain in comparison to the control group **(Nafea *et al.*, 2023)** and **(Elhallouty *et al.*, 2022).**

Supplementation of the AD diet with different concentrations of rivastigmine, DBR and Gb significantly ($P \leq 0.05$) showed a significant decrease in AβP and ACHE compared to the positive control group ($P \leq 0.05$). The lowest mean value was recorded for the group fed on 20% of the meal of DBR and Gb**.** In the same table described no significant differences were observed in AβP and ACHE between Alzheimer's rats supplemented with 0.25mg rivastigmine and supplemented with 10% DBR and 10% Gb. These outcomes corroborated the findings of **Nafea *et al.* (2023)** who found that rivastigmine in the treatment groups considerably ($p < 0.05$) reduced the levels of tau and Aβ-amyloid in the brain when compared to the AlCl3 group. Rivastigmine therapy markedly raised DA, NE, and GABA levels while lowering homogenate AchE activity levels in the cortical and hippocampal regions of AD-rats **(Aljarari and Bawazir 2019).** The hydroacetonic extract of *V. vinifera L.* demonstrated a decrease in serum amyloid beta (Aβ) in agreement with findings from **Cirmi *et al.*, (2016)** and **Stefani and Rigacci (2013)**. AChE activity was markedly decreased and returned to normal following the administration of G biloba alone, vitamin C, and their combination (**Elhallouty *et al.*, 2022).** Comparing the administered Ginkgo biloba extract (GBE) to the sick group, a synergistic inhibitory effect was seen on AChE hippocampus activity **(Assi *et al.*, 2023).**

Table (4): The effect of rivastigmine, black raisins and ginkgo on AβP and ACHE in rats with Alzheimer's disease

Parameters / Groups	AβP(ng-ml)	ACHE(pg-ml)
Control(-)	806.30^{d} ±5.48	105.53^{e} ±2.64
Alzheimer's rats	1308.33^{a} ±7.46	637.00^{a} ±1.00
0.25 mg rivastigmine	1007.76^{b} ±2.42	231.66^{b} ±4.73
DBR (10%)	1006.67^{b} ±3.51	224.67^{c} ±1.53
DBR (20%)	835.83^{c} ±1.76	184.67^{d} ±4.51
Gb (10%)	1006.67^{b} ±3.51	223.66^{c} ±3.51
Gb (20%)	835.33^{c} ±4.73	185^{d} ±5.00

The values are shown as means + standard deviation (SD); means with different letters in the same column indicate a significant difference ($p \leq 0.05$) . DBR: draied black raisins. Gb: *Ginkgo biloba*. AβP: amyloid beta protein , ACHE: acetylcholinesterase .

The effect of rivastigmine, black raisins and ginkgo on ACH, DA, 5-HT and PCTP in the brain of rats with Alzheimer's disease:

Table (5) shows the effect of rivastigmine, DBR and Gb on acetylcholine (ACH), dopamine (DA), serotonin (5- HT) and phosphatidylcholine transfer protein (PCTP) in rats with Alzheimer's disease (AD) . It was found that the Alzheimer's rats had a significant increase in ACH but the levels of DA, HT and PCTP decreased significantly as compared to the normal rats. These alterations in biochemical levels were brought on by rats' prolonged exposure to AlCl3. According to **Fayed *et al.*, (2021)** these alterations are related to the inhibitory effect of aluminum on serotonin through cholinergic input loss. These results were consistent with the administration of AlCl3 to rats, which resulted in lower levels of serotonin and its metabolite 5-hydroxyindoleacetic acid in the cortex **(Kumar, 2002).** Al reduced dopamine D1-like and D2-like receptor expression predominantly in the brain cortex and rostral striatum **(Kim *et al.*, 2007)**. Brain alterations brought on by exposure to AlCl3 include behavioral, metabolic, and neurochemical ones. Furthermore, in AlCl3-treated zebrafish, reduced glutathione (GSH) and

superoxide dismutase (SOD) levels were significantly lower while malondialdehyde (MDA) levels were found to be higher, indicating considerable oxidative stress. The brain's levels of glutamate were elevated and GABA, dopamine, noradrenaline, and serotonin were markedly reduced, suggesting a disruption in the neurotransmitter system. According to these results, AlCl3 profoundly alters morphology, neurotransmitters, biochemistry, behavior, and molecules, which eventually results in AD **(Kaur *et al.*, 2022).**

Considering the results of this study, The administration of rivastigmine, black raisins, and ginkgo to AD-rats has been shown to significantly ($P \leq 0.05$) reduce ACH, while increasing DA, 5-HT, and PCTP in comparison to the positive control group ($P \leq 0.05$). The beast mean value was recorded for the group fed on 20% of the meals of DBR and Gb **.** In the same table described no significant differences were observed in the ACH, DA, 5-HT and PCTP between Alzheimer's rats supplemented with 10% DBR and supplemented with 10% Gb. The black raisin and ginkgo contain

phytochemical compounds , proanthocyanidins, and stilbenoids may act as an AChE inhibitor. AChE inhibitors have the advantageous effect of improving cholinergic transmission in the brain, which decreases β-amyloid aggregation and the development of neurotoxic fibrils in AD

These findings corroborated those of **Mehri *et al.*, (2023)** who discovered that rivastigmine therapy enhanced spatial memory , raised levels of Ach and decreased levels of acetylcholinesterase. In AD rats, the black raisin exhibited neuroprotective effects by increasing the production of DA, NE, and GABA in the brain and reducing the activity of the AchE enzyme, which breaks down Ach, an excitatory neurotransmitter. It might lessen AD's neurological features **(Aljarari and Bawazir 2019).** According to **Xie *et al.*, (2014)** the hydroacetonic extract of *Vitis vinifera* demonstrated a large increase in brain/serum (ACh) and a significant decrease in brain/serum (AChE). Rats treated with *G.biloba* extract showed a substantial reduction in AChE activity in their brains when compared to those treated with AlCl3. It demonstrates that *G. biloba* and vitamin C, when combined,

inhibited AChE activity, which prevented acetylcholine breakdown and enhanced cholinergic neurotransmission. It shows that *G. biloba* and vitamin C together decreased AChE activity, hence enhancing cholinergic neurotransmission and preventing the breakdown of acetylcholine. Inhibiting acetylcholinesterase (AChE) is now the most effective treatment for AD, senile dementia, ataxia, and Parkinson's disease **(Hussein *et al.*, 2020).** Treatment with GbE (150 mg/kg b.w./day) restored the lowered antioxidant enzyme activities, DA level, and TH expression while also dramatically lowering the raised oxidative stress indicators and proinflammatory cytokines. Histological findings that amply demonstrated GbE's neuroprotective action against ROT-induced Parkinson's disease (PD) validated these findings **(Mohammed *et al.*, 2020).**

Table (5). The effect of rivastigmine, black raisins and ginkgo on ACH, DA, 5-HT and PCTP in rats with Alzheimer's disease In brain tissue.

Parameters / Groups	ACH(pg-mg)	DA(ng-mg)	5-HT(ng-mg)	PCTP(ng-mg)
Control(-)	216.13^{e} ±1.03	7.59^{a} ±0.18	125.13^{a}±1.33	7.74^{a} ±0.31
Alzheimer's rats	420.67^{a} ±1.60	0.43^{e} ±0.08	21.52^{e} ±0.58	0.47^{e} ±0.31
0.25mg rivastigmine	286.93^{b} ±1.20	4.11^{d} ±0.9	85.72^{d}±1.70	5.83^{d} ±0.21
DBR (10%)	281.18^{c} ±3.16	3.73^{d} ±0.21	93.19^{c} ±2.11	6.59^{c} ±0.36
DBR (20%)	223.00^{d} ±1.73	6.5^{b} ±0.78	112.40^{b}±2.42	7.18^{b} ±0.28
Gb (10%)	283.87^{bc} ±1.63	5.500^{c}±0.46	92.33^{c} ±2.30	6.55^{c} ±0.15
Gb (20%)	220.77^{d} ±1.91	6.500^{b}±0.26	112.73^{b} ±1.72	7.33^{ab} ±0.42

The values are shown as means + standard deviation (SD); means with different letters in the same column indicate a significant difference ($p \leq 0.05$) . DBR: draied black raisins. Gb: Ginkgo biloba. ACH: acetylcholine. DA: dopamin. 5- HT: serotonin . PCTP:Phosphatidylcholine transfer protein

After reviewing all the results and tables mentioned above we revealed that the AlCl3 treated group with black raisins and ginko had a significant decrease in biological assessment including, BWG, FI, FER and RPW. Also, there were significant decreases in some neurotransmitter levels in serum as AβP and AchE and there were a significant decreases in some neurotransmitter levels

in brain as ACH, DA, 5- HT and PCTP, Moreover, there was a significant increase in antioxidants parameters such as GSH, SOD, CAT, LDH and XO. But a significant decreases in inflammatory cytokines include, IL-6 and TNF-α. We may conclude that ginko and black raisins maintain AD-affected rats' brains structural integrity.

3.3. Histopathological examination of the brain.

The brain (Cerebral cortex) of rats from Group 1 showed no histopathological alterations and intact neurons (photo 1). Meanwhile, sections from Group 2 revealed marked necrosis, shrunken and pyknosis of neurons and congestion of cerebral blood vessels and neuronophagia (photo2 &3). Otherwise, sections from Group 3 described necrosis of some neurons (photo 4). Furthermore, sparse necrosis of neurons was the only histopathological finding observed in cerebral cortex of rats from Group 4 (photo 5). Also, examined sections from Group 5 showed no histopathological alterations (photo 6). Meanwhile, the cerebral cortex of rats from Group 6 manifested only necrosis of some neurons (photo 7). On the other hand, sections from Group 7 exhibited no histopathological alterations (photo 8). The fewer alterations in the cerebral cortex's shape, the fewer aberrant variations and irregularities in the arrangement of neurons, and the higher quantity of pyramidal and granular neurons in BDR and Gb rats demonstrate the neuroprotective role of foods high in antioxidants in the structure and function of the brain. These outcomes concurred with **Ghorbanian *et al.*, (2018)** who found that In comparison to the control group, the older rats in the raisin group had a reduced lateral ventricle diameter and a lower death and degeneration rate.

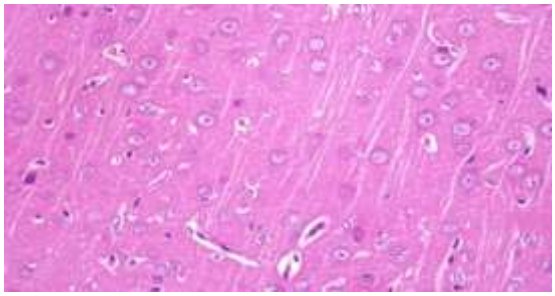

photo (1): Cerebral cortex of rat from group 1(control negative) showing no histopathological alterations and intact neurons (H & E X 400).

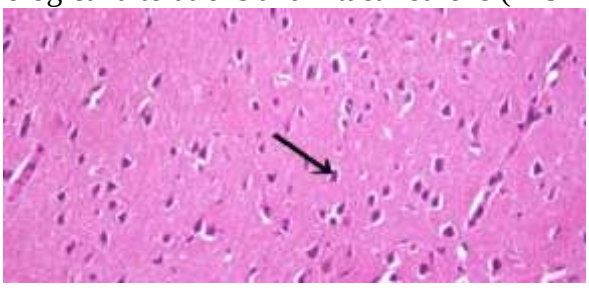

photo (2): Cerebral cortex of rat from group 2 (control positive) showing marked necrosis, shrunken and pyknosis of neurons (arrow) (H & E X 400).

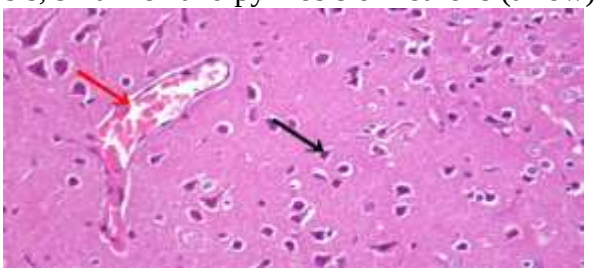

photo (3): Cerebral cortex of rat from group 2(control positive group) showing marked necrosis, shrunken and pyknosis of neurons (black arrow) and congestion of cerebral blood vessel (red arrow) (H & E X 400).

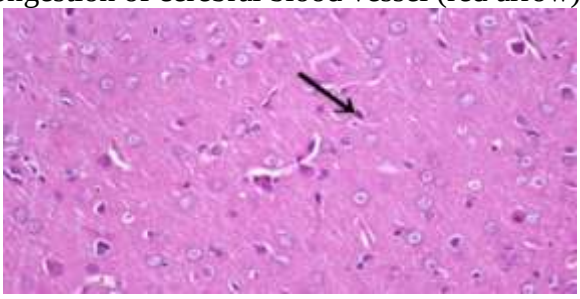

photo (4): Cerebral cortex of rat from group 3(0.25 mg revastigmine) showing necrosis of some neurons (black arrow) (H & E X 400).

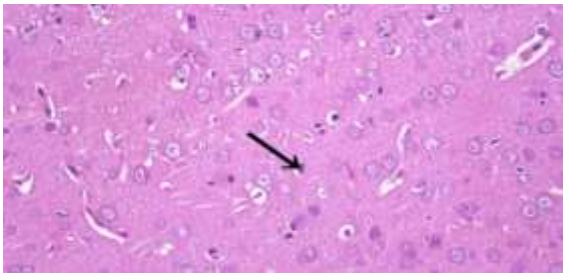

photo (5): Cerebral cortex of rat from group 4 (10% black raisins) showing sparsely necrosis of neurons (black arrow) (H & E X 400).

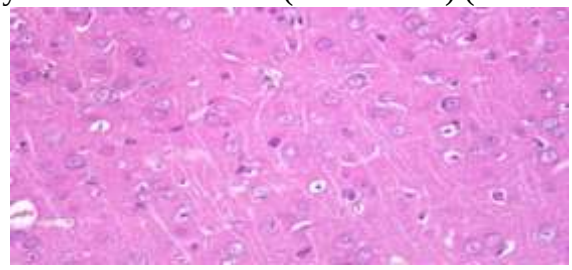

photo (6): Cerebral cortex of rat from group 5(20% black raisins) showing no histopathological alterations (H & E X 400).

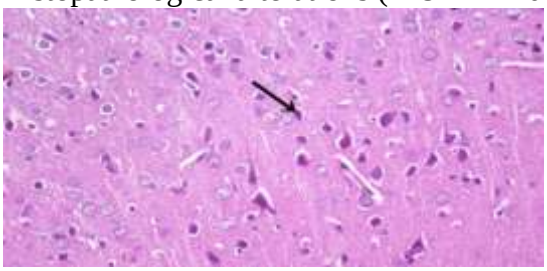

photo (7): Cerebral cortex of rat from group 6 (10% Gb)showing necrosis of some neurons (black arrow) (H & E X 400).

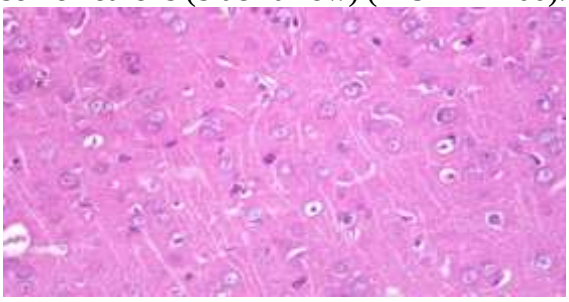

photo (8): Cerebral cortex of rat from group 7 (20% Gb) showing no histopathological alterations (H & E X 400).

4. Conclusion:

Excessive use of minerals, especially aluminum, is harmful to health in general and to brain cells in particular, which

has a direct effect as a cause of Alzheimer's disease. There are many things that lead to an increase in the rate of aluminum pollution in Egyptian society, such as pesticides and the incorrect use of food equipment. Therefore, our regular use of foods rich in their content of phenolic compounds and antioxidants, especially black raisins and Ginkgo, is one of the important things that reduces these risks significantly compared to ours using medications for Alzheimer's disease. There is still a need for more studies to prove the dosage and duration of these aspects, whether through experiments on laboratory animals or humans.

5. References

Abbas, F.; Eladl, M. A.; El-Sherbiny, M.; Abozied, N.; Nabil, A.; Mahmoud, S. M. and Ibrahim, D. (2022): Celastrol and thymoquinone alleviate aluminum chlorideinduced neurotoxicity: Behavioral psychomotor performance, neurotransmitter level, oxidative-inflammatory markers, and BDNF expression in rat brain. Biomedicine & Pharmacotherapy, 151, 113072.

Abdel Maksoud, H. A.; Said, A. M.; Abdeldaiem, M. A. and Hassan, M. H. (2020): Aluminum Chloride Induced Inflammatory process in Rat's Brain. Sch. Int .J. Biochem.; 3(10): X.

Abou Zaid, O. A. R.; Mansour, S. M. and El-gendy, A. E. (2017): Ameliorative effect of Ginkgo biloba on brain and liver oxidative stress, antioxidant status and liver markers enzymes on Hepatic encephalopathy. International Journal of Chemical and Natural Science. ;5 (2): 526-531.

Abu-Taweel, G. M. and Al-Mutary, M. G. (2021). Pomegranate juice reverses AlCl3-Induced neurotoxicity and improves learning and memory in female mice. Environmental research, 199, 111270.

Acharya, A.; Sayani, F.; Teague, K. and Weber, B. (1996): An Essential Role for NF-kappa B in Preventing TNF-alphaInduced Cell Death Amer A. Beg and David Baltimore Science 274: 784-786 .

Aljarari, R.M. and Bawazir, A. E. (2019): Effect of Black Raisins (*Vitis vinifera*) on Aluminum Chloride Induced Alzheimer's Disease in Male Albino Rat. International Journal of Pharmaceutical Research & Phytopharmacological Research. Allied Sciences, 8(3):193-203.

Anderson, J.W.;Baird. P.; Davis ,R.H.; Ferreri, S.; Knudson, M.; Koraym, A.; Waters, V. and Williams ,C.L. (2009). Health benefits of dietary fiber. Nutr Rev 67: 188–205.

Armstrong R.A. (2013): What causes alzheimer's disease? *Folia Neuropathol.* ;51:169–188.

Arora, P.; Ansari, S.H.; Najmi, A.K.; Anjum, V. and Ahmad, S. (2016): Investigation of anti-asthmatic potential of dried fruits of *Vitis vinifera L.* in animal model of bronchial asthma. Allergy, Asthma & Clinical Immunology; 12(1): 12-42.

Artimage, G.Y. and Berry, W.G. (1987): Statistical Methods 7th Ed. Ames, Iowa State University Press, 39-63.

Arunima, C.; Julia J. J. and Prasobh, G. R. (2021): a review on role of ginkgo biloba in treating alzheimer's disease. World Journal of Pharmaceutical Research; 10 (10):. 483-489.

Assi, A. A.; Farrag, M. M.; Dalia M. Badary, D.M. Allam, E.A. H. and Nicola, M.A. (2023): Protective effects of curcumin and *Ginkgo biloba* extract combination on a new model of Alzheimer's disease. Inflammopharmacology; 31, 1449–1464.

Bergmeyer, U.; Bernt, E. and Hess, B. (1965): Methods of Enzymatic Analysis (Second Printing, Revised): LDH (Lactate dehydrogenase), 736-743.

Beutler E, Duron O, Kelly B. (1960): Improved method for determination of blood glutathione. J. Lab. Clin. Med.; 61: 882-888.

Cao, Z.; Yang, X.; Zhang, H.; Haoran Wang, H.; Wanyue Huang, W.; Xu F., Zhuang, C. ; Wang, X. and Li, Y. (2016): Aluminum chloride induces neuroinflammation, loss of neuronal

dendritic spine and cognition impairment in developing rat. Chemosphere; 151:289-295.

Carageorgiou H, Sideris AC, Messari I, Liakou CI, Tsakiris S. (2008): The effects of rivastigmine plus selegiline on brain acetylcholinesterase,(Na+, K+)-, Mg2+-ATPase activities, antioxidant status, and learning performance of aged rats. Neuropsychiatric disease and treatment.4(4):687.

Carageorgiou, H.; Tzotzes, V.;Sideris, A.; Zarros, A. and Tsakiris, S. (2005): Cadmium effects on brain acetylcholinesterase activity and antioxidant status of adult rats: modulation by zinc, calcium and L-cysteine co-administration. Basic & Clinical Pharmacology & Toxicology, 97(5), 320–324.

Chalermpalanupap, T.; Kinkead, B.; Hu, W.T.; Kummer, M.P.; Hammerschmidt, T.; Heneka, M.T.; Weinshenker, D. and Levey, A.I.(2013): Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. Alzheimer's research & therapy. 1;5(2):21.

Chapman, D., Castilla, R. and Cambell, J. (1959). Evaluation of Protein in Foods: A Method for the Determination of Protein Efficiency Ratio. Canadian Journal of Biochemistry and Physiology, 37, 697-686.

Chen, X.; Zhang, M.; Ahmed, M.; Surapaneni, K. M.; Veeraraghavan, V. P. and Arulselvan, P. (2021). Neuroprotective effects of ononin against the aluminium chloride-induced Alzheimer's disease in rats. Saudi journal of biological sciences, 28(8), 4232–4239.

Cirmi, S.; Ferlazzo, N.; Lomnardo, G.E.; Ventura-Spagnolo, E.; Gangemi, S.; Calapai, G.; and Navarra, M. (2016): Neurodegenerative diseases: Might Citrus flavonoids play a protective role? Molecules 2016; 21(10): 1312.

Eisenmenger, L. B.; Peret, A.; Bolanle Famakin, B. M.; Spahic, A.; Roberts, G.S.; Bockholt , J.H.; Kevin M. J.;

Mohnson , K.M and Paulsen, J.S. (2023): Vascular contributions to Alzheimer's disease. (254) : 41-53.

Elhallouty, S.A.; Rashad, A. M.; Abd elrhman, E. A.; Haidy Elkaramany, H. A. K.; Ibrahim, M. G Salem, N. T. ; Adeeb, R. A.; Aniss Y. W. and Elshahid, Z. A.(2022) Effect of *Ginkgo biloba* leaf extract in combination with vitamin C, E and D on Aluminum Chloride induced Alzheimer in rats. Egypt. J. Chem.; 65, (131) 827-841.

Erik C. B. Johnson, E.C.; Bian, S.; Rafi U. Haque, R. U.; E. Kathleen Carter , E. K.; Caroline M. Watson, C. M. *et al*., (2023):Cerebrospinal fluid proteomics define the natural history of autosomal dominant Alzheimer's disease. *Nature Medicine*; (29):1979–1988.

Fayed, F. Elsawy, S. Shebl, M. Khattab, H. (2021): Study the Role of Vitamin D on Some Brain Degenerative Disorders in Male Albino Rats. Bull. Egypt. Soc. Physiol. Sci.; 42(1):39-51.

Filocamo, A.; Bisignano, C.; Mandalari, G.; Navarra, M. (2015): In Vitro Antimicrobial Activity and Effect on Biofilm Production of a White Grape Juice (*Vitis vinifera*) Extract. Evid. Based Complement. Alternat. Med.;, ID 856243.

Foroughi, s.; shahanipour, K.; Monajemi, R.; Ahadi, A. M. (2023): Investigating the effect of resveratrol and black grape extract on morphological changes and expression profiles of genes related to Alzheimer's disease in PC12 model cells. Molecular Biology Reports.

Funato, H.; Yoshimura, M.; K. Kusui,K.; Tamaoka, A.; Ishikawa,K.; Ohkoshi, N.; Namekata, K. and R. Okeda, R. and Ihara, Y. (1998): Quantitation of amyloid beta-protein (A beta) in the cortex during aging and in Alzheimer's disease. Am. J. Pathol.; 152(6):1633-1640.

Gaballah, H.H.; Zakaria, S.S.; Elbatsh, M.M. and Tahoon, N.M. (2016): Modulatory effects of resveratrol on endoplasmic reticulum stress-associated apoptosis and oxido inflammatory

markers in a rat model of rotenone-induced Parkinson's disease. Chem. Biol. Interact.; (251): 10–16.

Ghorbanian, D.; Gol, M.; Pourghasem ,M.; Faraji, J.; Pourghasem, K. and Soltanpour, N.(2018) Spatial Memory and Antioxidant Protective Effects of Raisin (Currant) in Aged Rats. Preventive Nutrition and Food Science ;23(3):196.

Giera, M.; Lingeman, H.; and Niessen, W. (2012): Recent advancements in the LC-and GC-based analysis of malondialdehyde (MDA): a brief overview. Chromatographia; 75(9), 433-440.

Goufo, P.; Singh, R.K. and Cortez, I. A. (2020): Reference List of Phenolic Compounds (Including Stilbenes) in Grapevine (*Vitis vinifera L.*) Roots, Woods, Canes, Stems, and Leaves. Antioxidants. Antioxidants (Basel)journal 9(5), 398.

Grafström, G.; Nittby, H.; Brun, A.; Malmgren, L.; Persson, B. R.; Salford, L. G. and Eberhardt, J. (2008): Histopathological examinations=of rat brains after long-term exposure to GSM-900 mobile phone radiation. Brain research bulletin, 77(5), 257-263.

Han, S.; Lemire, J.; Appanna, V. P.; Auger, C.; Castonguay, Z.Hawash, Z.A.; Yassien,E. M.; Badriyah S. Alotaibi, B. S.; El-Moslemany, A. M. and Shukry, M. (2023): Assessment of Anti-Alzheimer Pursuit of Jambolan Fruit Extract and/or Choline against $AlCl_3$ Toxicity in Rats. Toxics; 11(6): 509.

Henry, R.J. (1964): Clinical Chemistry: Principles and Technics. New-York: Hoeber Medical Division Harper and Row. 190.

Hu, D.; Wang, H. J.; Yu, L. H. Guan, Z. R.; Jiang, Y. P.; , Jun-Hu Hu, J. H. *et al*., (2024):The role of Ginkgo Folium on antitumor: Bioactive constituents and the potential mechanism. Journal of Ethnopharmacology**;** 321: 117-202.

Hussein, R.A.; Afifi, A.H.; Soliman , A.A.F.; El Shahid , Z.A.; Zoheir, K.M.A. and Mahmoud, K.M. (2020): Neuroprotective

activity of Ulmus pumila L. in Alzheimer's disease in rats; role of neurotrophic factors, Heliyon ; 12 (6): e05678.

Ibrahim, A. N.; Attallah, M. I. and Elnaggar, R. A. (2018): Combination of Cholecalciferol and Rivastigmine Improves Cognitive Dysfunction and Reduces Inflammation in STZ Induced Alzheimer's Model Experimentally in Rats. Egyptian Journal of Basic and Clinical Pharmacology; 8:16.

Ismail, Z.M.; Morcos, M. A.; Ragai, M.M. and Sarah, S. M. (2023): Histological Study on the Effect of Rivastigmine and Coconut Oil on the Hippocampus of Experimentally Induced Alzheimer's Disease in Adult Male Albino Rats. The Egyption J. of Histology; 46 (2):723-742.

Jang, D. I.; Lee, A. H.; Shin, H. Y.; Song, H. R.; Park, J. H.; Kang, T. B.; *et al*. (2021): The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. Int. J. Mol. Sci.; 8; 22 (5) : 2719.

Jeszka-Skowron M, Zgoła-Grześkowiak A, Stanisz E, Waśkiewicz A.(2017) : Potential health benefits and quality of dried fruits: Goji fruits, cranberries and raisins. Food chemistry. 15;221:228-36.

Kaur, K. Narang , R.K. and Singh, S. (2022): $AlCl_3$ induced learning and memory deficit in zebrafish. NeuroToxicology**;** 92, 67-76.

Khan, R.A.; Khan, M.R. and Sahreen, S., (2018): Brain antioxidant markers, cognitive performance and acetylcholinesterase activity of rats: efficiency of Sonchus asper. Behav. Brain Funct.; 2012(8): 21.

Kim, S.; Nam, J.; Kim, K. (2007): Aluminum exposure decreases dopamine D1 and D2 receptor expression in mouse brain. Hum Exp Toxicol 26(9):741-746, 2007.

Kumar, P. and Kumar, A. (2009): Protective effect of rivastigmine against 3-nitropropionic acid-induced Huntington's disease like symptoms: possible behavioural, biochemical and

cellular alterations. European journal of pharmacology. 1;615(1-3):91-101.

Kumar, S.(2002): Aluminium-induced changes in the rat brain serotonin system. Food Chem. Toxicol.; 40(12):1875-1880.

Lakshmi, B.V.S.; Sudhakar, M.and Aparna, M. (2013): Protective potential of Black grapes against lead induced oxidative stress in rats. Environmental Toxicology and Pharmacology; 35 (3): 361-368.

Lakshmi,V.S ; Sudhakar, M. and Anisha, M. (2014): Neuroprotective role of hydroalcoholic extract of *Vitis vinifera* against Aluminium- Induced Oxidative Stress in Rat brain NeuroToxicology. 41: 73-79.

Martí, R.; Varela, E.; Pascual, C. and Segura, R.M. (2001): Determination of xanthine oxidoreductase forms: influence of reaction conditions. Clinica. Chimica. Acta.; 303 (1): 2117-2125.

Mehri, K.; Oskuye, Z.Z.; Nassireslami, E.; Karami, E.; Parvizi, M. R. (2023): Rivastigmine ameliorates botulinum-induced hippocampal damage and spatial memory impairment in male rats. NeuroToxicology; 98: 29-38.

Mohammed, N. A.; Abdou, H. M.; Tass, M. A.; Alfwuaires, M; Abdel-Moneim, A. M.; Essawy, A. E. (2020): Oral Supplements of *Ginkgo biloba* Extract Alleviate Neuroinflammation, Oxidative Impairments and Neurotoxicity in Rotenone-Induced Parkinsonian Rats. Current Pharmaceutical Biotechnology; 21 (12):1259-1268.

Müller, T. (2007): Rivastigmine in the treatment of patients with Alzheimer's disease. Neuropsychiatr Dis. Treat.; 3(2): 211–218.

Murdock, M.H. and Tsai, L.H. (2023): Insights into Alzheimer's disease from single-cell genomic approaches. *Nature Neuroscience*; (26):181–195.

Nafea, M.; Elharoun, M.; Abd-Alhaseeb M.M. and Helmy M.W. (2023): Leflunomide abrogates neuroinflammatory

changes in a rat model of Alzheimer's disease: the role of TNF-α/NF-κB/IL-1β axis inhibition. Pharmacology; 396: 485–498.

Nandi, A., and Chatterjee, I. B. (1988): Assay of superoxide dismutase activity in animal tissues. Journal of Biosciences; 13(3), 305-315.

Nedzvetsky, V.S.; Tuzcu, M.; Yasar, A.; Tikhomirov, A.A. and Baydas , G.(2006) : Effects of vitamin E against aluminum neurotoxicity in rats. Biochemistry (Mosc) 71(3):239-244.

Newairy, A.S.; Salama, A.F.; Hussien, H.M. and Yousef, M.I. (2009): Propolis alleviates aluminium - induced lipid peroxidation and biochemical parameters in male rats. Food Chem Toxicol 47(6):1093 -8.

Olanrewaju, J.A.; Akinola, O.B.; Olatunji ,S.Y.; Owolabi, J.O.; Fabiyi, O.S.; Ukonne, U.E. and Desalu, A.B.O. (2018) : Effects of Virgin Coconut Oil on Aluminium Chloride-Induced Alzheimer-Like Dementia in the Prefrontal Cortex. JAMPS; 18(1): 1-12.

Osman, N.N.; Alanbari, K.H. and. Al-Shreef, H. A. (2018):evaluation of the possible antioxidant effects of peganum harmala and ginkgo biloba in ameliorating alzheimer's disease in rat model. ijpsr; 9(8): 3189-3198 .

Pangavhane, D. R. and Sawhney, R. L. (2002). Review of research and development work on solar dryersfor grape drying. Energ. Convers. Manage., 43: 45-61.

Patel, B.P.; Bellissimo, N.; Luhovvyy, B.; Bennett, L.J.; Hurton, E.; Painter, J.E. and Anderson, G.H. (2011). A pre-meal raisin snack increases satiety and lowers cumulative food intake in normal weight children. Appl Physiol Nutr Metab 36: 475.

Radulescu, C.; Buruleanu, L.C.; Nicolescu, C.M.; Olteanu, R.L.; Bumbac, M.; Holban, G.C.; Simal-Gandara, J. (2020): Phytochemical Profiles, Antioxidant and Antibacterial Activities of Grape (*Vitis vinifera L.*) Seeds and Skin from Organic and Conventional Vineyards. Plants (Basel) journal. 9(11): 1470.

Rajendran, P.; Althumairy, D.; Bekhet, G. and Ahmed, E. (2023): Isoimperatorin therapeutic effect against aluminum induced neurotoxicity in albino mice. Journal Frontiers in Pharmacology; 14: 13.

Ray, B.; Maloney, B.; Sambamurti, K.; Karnati, H. K.; Nelson, P.T.; Greig, N. G. and Lahiri, D. K. (2020): Rivastigmine modifies the α-secretase pathway and potentially early Alzheimer's disease. Translational Psychiatry; 10:47.

Reeves, P. G., Nielsen, F. H., & Fahey, G. C., Jr (1993). AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition ad hoc writing committee on the reformulation of the AIN-76A rodent diet. The Journal of nutrition, 123(11), 1939–1951.

Runne, H.;Kuhn, A.; Wild, E. J.,; Pratyaksha, W.;Kristiansen, M.; Isaacs, J. D.; Régulier, E.;Delorenzi, M.; Tabrizi, S. J., and Luthi-Carter, R. (2007). Analysis of potential transcriptomic biomarkers for Huntington's disease in peripheral blood. Proceedings of the National Academy of Sciences of the United States of America, 104(36), 14424–14429.

Sahu, A.; Singh, D. and Shukla, R. (2023): bioactive compounds and reported pharmacological activities of *vitis vinifera l.* an overview. World Journal of Pharmaceutical Research; 12 (14): 27-38.

Sakr, S.; Hoda, A. ;Mahran, N.; Basily, S. and Saif M. E. (2015): Effect of *Ginkgo biloba* extract on cyclophosphamide-induced reproductive toxicity and oxidative stress in male albino mice. World J. Pharm. Sci.; 3(1): 16-25.

Sasa, S. and Blank, C. L. (1977): Determination of serotonin and dopamine in mouse brain tissue by high performance liquid chromatography with electrochemical detection. Analytical Chemistry; 49(3): 354 359.

Schermer, S. (1967): The Blood Morphology of Laboratory Animal. Longmans, Printed in Great Britain, Green and Co. LTd, P. 350.

Soto, P.; Gaete, H. and Hidalgo, M. E. (2011): Evaluación de la actividad de la catalasa, peroxidaciónlipídica, clorofila-a y tasa de crecimientoenlaalgaverdedeaguadulcePseudokirchneriellasubcapitataexpuesta a cobre y zinc. Latin american journal of aquatic research; 39(2), 280-285.

Stefani, M. and Rigacci, S. (2013): Protein folding and aggregation into amyloid: The interference by natural phenolic compounds. Int. J. Mol. Sci.; 14(6): 12411–57.

Su, F.; Wang, F.; Zhu, R. and Li, H. (2008): Determination of 5-Hydroxytryptamine, Norepinephrine, Dopamine and Their Metabolites in Rat Brain Tissue by LC–ESI–MS–MS. Chromatographia; 69: 207–213.

Tramutola, A.; Lanzillotta, C.; Perluigi, M. and Butterfield, D.A(2017): Oxidative stress, protein modification and Alzheimer disease. Brain research bulletin. 1;(133) :88-96.

Tsuno, N., Mori, T., Ishikawa, I., Bando, N., Park, H., Matsumoto, Y., Mori, I., Tanaka, M., Hirano, T., & Nakamura, Y. (2019). Efficacy of rivastigmine transdermal therapy on low food intake in patients with Alzheimer's disease: The Attitude Towards Food Consumption in Alzheimer's Disease Patients Revive with Rivastigmine Effects study. Geriatrics & gerontology international, 19(7), 571–576.

Upadhyaya, S.; Gangachannaiah, S. and Chandrashekar, P. L. (2019): Effect of Piper betel leaf extract on learning and memory in Aluminium chloride induced Alzheimer’s disease in Wistar rats. Biomed. pharmacol. J.; 12(3): 1425-1431.

Xie, Y.; Yang, W.; Chen, X. and Xiao, J. (2014): Inhibition of flavonoids on acetylcholine esterase: binding and structure–activity relationship. Food Funct.; 5(10): 2582-2589.

Zifko, U. A.;Yacob, M., Braun, B. J. and Dietz, G. P. H. (2022): Alleviation of Post-COVID-19 Cognitive Deficits by Treatment with EGb 761®: A Case Series. Am. J. Case. Rep. (23).

الخصائص العلاجيه للأعصاب للزبيب الأسود والجنكة ضد الإجهاد التأكسدي وضعف الذاكرة في مرض الزهايمر الناجم عن كلوريد الألومنيوم

أ.م.د/ أمل ناصف زكي ناصف – د/ سماح محمود البنا

قسم التغذية وعلوم الأغذية، كلية الاقتصاد المنزلي، جامعة المنوفية، شبين الكوم، مصر.

الملخص :

مرض الزهايمر هو نوع من الأمراض التنكسية العصبية التي تتفاقم مع مرور الوقت وتقلل بشكل كبير من الوظيفة الإدراكية. تم العثور على الخصائص المرضية للعديد من الاضطرابات التنكسية العصبية التي تنطوي على عمليات تتأثر بالإجهاد التأكسدي. الألومنيوم هو سم عصبي قوي يمكن أن يسبب الإجهاد التأكسدي، والذي يرتبط بالحالات العصبية بما في ذلك مرض الزهايمر. تم تصميم هذه الدراسة لمعرفه الخصائص العلاجيه العصبية للزبيب الأسود المجفف والجنكة ضد الإجهاد التأكسدي وضعف الذاكرة المكانية في مرض الزهايمر.تم استخدام 35 فأرًا ناضجًا من سلاله سبراغ داولي بوزن 150 ± 10 جرام ، وتم تقسيم الفئران إلى مجموعتين رئيسيتين. المجموعة الرئيسية الأولى (عددها = 5 فئران) كمجموعة ضابطه سالبه (سليمه) وتم تغذيتها بنظام غذائي قياسي فقط. المجموعة الرئيسية الثانية(30 فأرًا) تم إعطائهم كلوريد الالومنيوم عن طريق الفم 100 مجم / كجم، وزن الجسم / يوم) لمدة 30 يوم لإحداث مرض الزهايمر. ثم تم تقسيمها إلى ست مجموعات فرعية. المجموعة الفرعية (1) والتي تعتبر مجموعة الضابطة الموجبة تم تزويدها بنظام غذائي أساسي لمدة 28 يوم . المجموعة الفرعية (2)، تم اعطاء الفئران الريفاستيجمين عن طريق الفم بجرعة 0.25 ملجم / يوم وتم تغذيتها على النظام الغذائي الأساسي. المجموعة الفرعية (3) أعطيت نظام غذائي أساسي مع 10% الزبيب الاسمر المجفف من النظام الغذائي. المجموعة الفرعية (4) أعطيت نظام غذائي أساسي مع 20% الزبيب الاسمر

المجفف من النظام الغذائي. تم إعطاء المجموعة الفرعية (5) نظام غذائي أساسي يحتوي على 10% الجنكة من النظام الغذائي. تم إعطاء المجموعة الفرعية (6) نظام غذائي أساسي يحتوي على 20% الجنكة من النظام الغذائي. بعد 28 يوم، تم تقدير التحاليل البيولوجية والكيميائية الحيوية والنسيجية. وأظهرت النتائج تثبيط بعض مستويات الناقلات العصبية مثل هيدروجيناز اللاكتات ، وأكسيداز الزانثين ، والأستيل كولينستريز ، والإنترلوكين 6 ، وعامل نخر الورم ألفا ، وبروتين بيتا الأميلويد. ونشاط الأسيتيل كولين والأسيتيل كولينستريز. كما اظهرت تنظيم وتحسين بمستويات الإجهاد التأكسدي كالجلوتاثيون ، ديسموتاز الفائق أكسيد ، الكاتلاز ، السيروتونين، الدوبامين وبروتين نقل الفوسفاتيديل كولين و تم إثباته في نتائج التشريح المرضي للمخ . وكانت افضل النتائج للمجموعات التي تم تغذيتها بـ 20% من الزبيب الاسمر المجفف والجنكة.**الاستنتاج:** إعطاء الزبيب الاسمر المجفف والجنكه بشكل منتظم يقلل من ضعف الذاكرة والإجهاد التأكسدي ويحسن العوامل الكولينية والخلل الدوباميني وفقدان الذاكرة والسمية العصبية ويمكن أن يكون علاجًا فعالًا ضد مرض الزهايمر .

الكلمات المفتاحية: مرض الزهايمر، كلوريد الألومنيوم، أستيل كولينستراز، مستويات الناقلات العصبية، السيتوكينات الالتهابية، الإجهاد التأكسدي.