The effect of Clove and Ginkgo biloba leaf on aluminum chloride-induced Alzheimer's disease in rats.

تأثير القرنفل وأوراق الجنكة بيلوبا على مرض الزهايمر المحدث بكلوريد الألمونيوم فى الفئران

By

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مجلة البحوث في مجالات التربية النوعية

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Abstract

Alzheimer's disease (AD) is a neurological disorder and the leading cause of dementia. The current study aimed to examine whether clove and ginkgo biloba leaf could treat rats with aluminum chloride-induced Alzheimer's disease. AlCl3 (17 mg/kg BW) was administered orally to rats for one month to produce AD. For 30 days, rats were given Ginkgo biloba leaf extract and suspensions (400 mg/kg.BW/day) and clove bud powder extract and suspensions (2mg/kg body wt/day and 800mg/kg body wt/day), as well as combinations of the two. Chemical compositions, minerals, phenolic components, and fatty acid levels were determined for ginkgo and clove. Y-maze test, acetylcholinesterase, MDA, GSH, dopamine, serotonin, nor-epinephrine activity, and brain histological findings were analyzed. The study found that administering dry Ginkgo leaves and clove bud powder extracts or suspensions significantly improved cognitive functions in AD rats, including increased (GSH), and reduced MDA levels in cerebral cortex and hippocampus homogenates. Histological examination also showed improvement. However, utilizing a combination therapy produced better benefits than a single treatment. This study suggests that combining dried ginkgo leaves with clove bud powder can improve AChE levels and reduce oxidative stress in the brain, potentially treating cognitive dysfunction associated with AlCl3-induced Alzheimer's disease.

Keywords: Ginkgo billioba, clove, Alzheimer’s disease (AD), aluminium chloride (AlCl3), phenolic component.

Introduction

Alzheimer's disease (AD) is now the sixth most common cause of mortality globally, up from its previous ranking of seventh **(*Hussein et al., 2020*)**. According to the World Alzheimer's Report, there are 50 million AD sufferers globally presently, and by 2050, there are expected to be over 139 million (***Alzheimer's disease statistics, 2019)***. AD is a debilitating, progressive neurodegenerative disease that has a significant financial and personal impact on individuals, families, and society **(*Calsolaro, et al .,2019*)**.

Early Alzheimer's disease is characterized by abnormalities in the structure and function of the hippocampus. (AD). One of the biggest obstacles to developing a conclusive treatment for AD is the lack of a clear etiology for the disease. Nonetheless, AD is linked to several risk variables, including aging, genetics, neuroinflammation, head trauma, depression, oxidative stress, infectious agents, anatomical route degradation, cognitive activity, and environmental factors including aluminum poisoning **(*Elbini et al.,2021*)**. Aluminum (Al) use has been identified in recent research as the primary etiological component for AD **(*Exley ,2017).***

Food, water, cookware, metal cans, and antacids are among the items that allow this metal to enter the human body **(*Inan and Ayaz, 2018*)**. Aluminum modifies the blood-brain barrier and is deposited in the brain to mediate brain intoxication **(*Mirza et al., 2017*)**. It has been demonstrated that oral aluminum treatment causes accumulation in the hippocampus area, which is thought to be the most important structure involved in memory and learning **(*Deture and Dickson,2019*)**. It is well recognized that neurotransmitters, such as norepinephrine, acetylcholine, serotonin, and dopamine, are important in the pathophysiology of AD. Because of these neurotransmitters' vital roles, changes in their amounts may contribute to the onset of AD **(*Kandimalla, and Reddy, 2017*)**.

The methods used to treat AD are inadequate at the moment. They have many negative effects and can only momentarily enhance cognitive abilities or reduce symptoms. To

address the pathology of AD and treat its symptoms at the same time while minimizing side effects, a new class of medications that can target more targets must be developed **(*Yiannopoulou and Papageorgiou, 2020*)**. Many active ingredients with promising pharmacological efficacy against AD were isolated from medicinal plants in Europe and Asia **(*Uddin et al., 2019*)**.

The aromatic dried petals of the Syzygium aromaticum tree (Myrtaceae family) are known as cloves, and they are used as a spice in almost every cuisine in the world. Clove have a strong traditional heritage and history and are a powerful medicinal herbs. Clove is regarded as the antithesis of every antioxidant discovered to date. Due to its anti-fungal, anti-viral, anti-microbial, anti-diabetic, antithrombotic, anesthetic, anti-stress, pain-relieving, and insect-repelling qualities, clove is used to treat a wide range of illnesses **(*Song et al., 2018*)**. Eugenol, the main ingredient in clove's volatile oil, and flavonoids support the herb's anti-inflammatory properties. Clove has been used medicinally to improve memory retention, as well as to treat depression, lethargy, and brain fog. We were then inspired to look at how Clove might be used to treat mice's cholinesterase activity, total cholesterol, and memory impairments **(*Han and Parker, 2017*).**

Since ancient times, people have utilized the fruits and leaves of Ginkgo biloba (also known as ginkgo) as a food and traditional medicine. For at least the last 2000 years, traditional East Asian medical methods have included ginkgo leaves and other aerial components **(*Camfield et al. ,2016*)**. The Ginkgo tree has a variety of bioactive components, such as flavonoids (flavones, biflavones, flavonols, tannins, and related glycosides) and ginkgolides and bilobalides (terpene trilactones specific to the plant). Studies have looked into the possibility of treating a number of illnesses, especially those involving disorders of the brain and peripheral circulation, with dried green ginkgo leaves. Given the range of preparations and dosages of active chemicals found in Ginkgo natural products, a thorough analysis of these products is necessary to ascertain which, if any, may be helpful in treating dementia and cognitive impairment **(*Wieland et al., 2020*)**. The current investigation attempted to determine whether

clove and ginkgo biloba leaf could treat rats' aluminum chloride-induced Alzheimer's disease.

Materials & Methods

Materials:

-Ginkgo biloba (Ginkgo) fruits and leaves and cloves (Syzygium aromaticum) were purchased from local markets in Egypt.

-Albino rats (Sprague - Dawley Strain) weighting (140-155g) were

purchased from the National Research Center in Giza, Egypt.

-Basal diet includes casein, vitamins, minerals, cellulose and choline chloride were obtained from El-Gomhorya Company.

-Aluminum chloride (AlCl3) and donepezil were purchased from El-Gomhorya Company, Cairo, Egypt.

Methods:

Preparations of cloves (Syzygium aromaticum) and Ginkgo biloba (Ginkgo):

We bought dried plant leaves of Syzygium aromaticum (clove) and Ginkgo biloba (ginkgo) from the Cairo, Egypt, local market. After removing any undesired items like branches, roots, or stones, they were dried at 50 degrees Celsius in an air oven, ground in a blender, and then the powder was sealed in polyethylene bags and stored until needed.

Extracts: Ginkgo biloba (Ginkgo) extracts prepared:

Twenty grams of ground plant leaves were extracted under the following circumstances using one liter of solvent at atmospheric pressure: water at 95 °C for 15 minutes of infusion (GW, YW), acetone–water (3:2 v/v) at 40 °C for 90 minutes of extraction (GA, YA), or 96 percent ethanol at 18 °C for 16 hours of maceration (GE, YE). A Whatmann 1 filter was used to filter the mixture once it had cooled. Every sample was lyophilized and vacuum evaporated. The extracts were kept in a cool, dry, and dark environment **(*Kobus et al., 2009*).**

Extracts from cloves (Syzygium aromaticum):

500 g of cloves were dried, cleaned with distillation water,

and then mixed in a mortar. Plant powder was immersed in 5L of 80% methanol in flasks that were shook at 170 RPM for three days. Paper with a 0.45µm pore size was used to filter the extracts. Using a rotary evaporator set at 40 °C, the methanol from each filtrate was extracted, and it was then frozen in the refrigerator for use in subsequent tests **(*Melesie Taye et al., 2020*)**.

Chemical composition analysis:
Cloves and Ginko were examined for moisture, total protein, total lipid, carbs, ash, and fiber in accordance with ***(AOAC ,2020*)**.

Determination of phenolic compounds:

In Cairo University's food safety and control lab, the phenolic components of ginkgo leaves and clove powder were identified using high-performance liquid chromatography (HPLC) in accordance with the methodology described by ***Agilent ,(2014)***. Equipped with a quaternary pump, the Agilent 1260 Infinity HPLC Series (Agilent, USA) ran at 30ºC using an Akinetex® 5µm EVO C18 100×4.6mm (Phenomenex, USA). A ternary liner elution gradient containing (A) HPLC grade water 0.2% H3PO4 (v/v), (B) methanol, and (C) acetonitrile is used to produce the separation. A 20µL injection volume was used. VWD detector tuned at 284 nm for detection.

Biological study:

45 weaning rats (Sprague-Dawley strain), weighing between 180 and 200 grams apiece, were kept in separate stainless-steel cages under hygienic, regulated conditions. **(*Reeves et al., 1993*)** prepared the basal diet. Nine groups of five rats each were randomly assigned to the following distribution of animals: Group 1: healthy, normal-sized rats. Group 2: the rats in the positive control group received 17 mg/kg of body weight per day of AlCl3 orally **(*Zaher et al., 2020*)**. daily for the duration of the trial, which lasted one month. Group 3: After four weeks of AlCl3 poisoning, rats were given the conventional medication (donepezil 5 mg/kg body weight/day) orally. Group 4: Following a 4-week AlCl3

intoxication, rats were given a basic diet supplemented with 15 grams of dried G. biloba leaf for a duration of 4 weeks. For four weeks, Group 5 rats received a daily oral dose of G. biloba extract (400 mg/kg body weight). Group 6 rats were intoxicated with AlCl3 for 4 weeks before receiving a daily oral dose of clove suspension (800 mg/kg body weight/day). Group 7 rats were intoxicated with AlCl3 for 4 weeks before receiving a daily oral dose of clove extract (2 mg/kg body weight/day). After being intoxicated with AlCl3 for four weeks, Group 8 rats were given 400 mg/kg of Ginko Biloba and 800 mg/kg of clove orally suspensions for four weeks. Group 9: After four weeks of AlCl3 poisoning, rats were given 400 mg/kg of Ginko biloba extract and 2 mg/kg of clove extract orally.

biological assessment:

After rats' experiments, the diet was evaluated based on body weight gain, feed intake, and feed efficiency ratio according to **(*Chapman et al., 1959*).**

Behavioral study: Y-Maze test:

In accordance with ***Foyet et al., (2015*)**, the Y maze test was used to examine the animals' behavioral activities, including spatial learning, age-related cognitive decline, and memory loss. Rats were brought into the behavioral analysis room after their final doses of various medications, allowed to acclimate for three hours, and then put through the Y-maze test. The tool was a white wooden labyrinth with three arms that measured 40 cm in length, 15 cm in breadth, and 30 cm in height, and were designated A through C. After being placed in one arm, each rat from a separate group was given five minutes to move quickly through the maze.Every rat was positioned at random at the end of one arm, and it was given free reign to roam throughout the maze for eight minutes. This was split into two testing sessions of two minutes each, with each session ending until the rat reached the food

reward or eight minutes later. To reduce olfactory cues, 70% ethanol was used to wipe the maze clean in between each animal.

Assessment of monoamine neurotransmitters:

When the experiment came to a conclusion, the rats were fasted for the entire night, blood was drawn from the sublingual vein, the serum was separated, and the blood was frozen at -20 °C for biochemical analysis **(*Downie, 1990*).** Enzyme analysis was used to evaluate the serum concentrations of dopamine, serotonin, and norepinephrine **(*Gaballah,2016*).**

Acetyl cholinesterase (ACHE) activity measurement:

Acetyl cholinesterase activity assay kit from Biosource CO was used to measure Ache activity using the ELISA method **(*Carageorgiou et al.,2005*).**

Malondialdehyde assessment and reduced glutathione:

Additionally, reduced glutathione (GSH) activity and the amounts of malondialdehyde (MDA), a marker for lipid peroxidation, were evaluated in the supernatant **(*Giustarini et al.,2008).***

Histopathological examination:

The brain's tissues were preserved in 10% neutral formalin for 24 hours following dissection, after which they were dried out using increasing alcohol concentrations, washed with xyline, and embedded in paraffin wax. Sections of the tissues were made at a thickness of 406 microns, and hematoxylin and fosin stains were applied **(*Carleton, 1987*)**. Using a light microscope, every tissue was inspected to look for any histopathological changes.

Statistical analysis:

An analysis of variance was performed on the collected data. To compare means, the Duncan multiple range test was employed, with a 0.05% significance level. The Statistical Analysis System's ANOVA technique was used to conduct the analysis **(*SAS, 2008*)**.

Results and discussions

Table (1) presents an evaluation of the nutritional value of clove and G. biloba leaves. Clove exhibited the largest proportions of protein (8.9%), fat (14.8%), and fiber (15.2%). Conversely, ginkgo had the largest levels of moisture (8.7%) and carbs (73.6%). Cloves have a lower quantity of moisture than ginkgo leaves, which could extend their shelf life while being packaged and stored. They assist with reducing the impacts of pollution and fungi.

The findings of **(*Barros et al., 2010*)**, who verified that the dry leaves of Ginkgo were composed primarily of carbohydrates (72.98% g/100 g dw), were in agreement with these results. If not, fat was the macronutrient present in smaller amounts, giving this medicinal plant a more healthful character (4.75 g/100 g dw). Ash and proteins were measured at 10.01 and 12.27 g/100 g dw, respectively.

Table (1) The chemical content of dried ginkgo leaves and clove bud (g/100g)

nutrients	Ginkgo leaves powder%	Clove bud powder%
protein	4.90	8.9
fat	2.24	14.8
Moisture	8.17	6.5
Ash	10.55	6.3
fiber	11.46	15.2
carbohydrates	73.61	63.5

Table (2) Mineral content of dried ginkgo leaves and clove bud (mg/100g)

minerals	Ginkgo leaves powder	Clove bud powder
calcium	6003.1	5.6
sodium	41.9	2.4
potassium	5287.8	1105.5
magnesium	1021.09	258.9
manganese	0.065	0.55

Data on the mineral contents of Ginkgo leaves and clove bud powders are shown in Table 2. It can be seen that the dry leaves of Ginkgo have higher levels of calcium (6003.1 mg/100 g) than the powdered cloves (5.6 mg/100g), followed by potassium (5287.8 mg/100 g) and magnesium (1021.09 mg/100 g). On the other hand, the powdered cloves have lower levels of sodium (2.4 mg/100 g) and manganese (0.55 mg/100 g). The primary difference between these results was the amount of minerals in cloves that varied noticeably, according to a study **(*Kauret al., 2019*)**. These minerals included calcium (5040 mg/kg), magnesium (2504 mg/kg), phosphorus (1504.5 mg/kg), and sodium (244.45 mg/kg).

Table (3) percentage of fatty acid content of dried ginkgo leaves and clove bud powders

Fatty acid	Ginkgo leaves powder%	Clove buds' powder %
Lauric acid C12:0	0.40	0.2
Tridecanoic acid (C13:0)	0.66	0.12
Myristic acid (C14:0)	4.9	1.28
Myristoleic acid C14:1 ω9	0.16	-------
Pentadecanoic acid (C15:0)	0.41	0.22
Palmitic acid (C16:0)	24.9	12.5
Palmitoleic acid C16:1 ω9	1.12	1.5
Heptadecanoic acid (C17:0)	0.66	0.56
Octadecenoic acidC17:1	1.06	0.02
Stearic acid C18:0)	2.12	0.56
Vaccinic acid (C18:1 ω7)	10.0	12.8
Linoleic acid (C18:2 ω6)	4.73	33.9
Linolenic acid (C18:3 ω3)	35.04	5.9
Arachidic acid (C20:0)	1.59	3.2
Eicosenoic acid C20:1	0.40	0.71
Behenic acid (C22:0)	0.89	0.21
TSF	51.12	11.41
TUSF	48.8	88.5

Fatty acids composition of Ginkgo leaves and clove bud powders were cleared in Table 3. Palmitic acid (C16:0) (24.9%) and linolenic acid (C18:3 ω3) (35.04%) were the two main fatty

acids found in ginkgo leaves. The main fatty acids in clove powder were linoleic acid (C18:2 ω6) and palmitoleic acid (C16:1 ω9), which contributed 40.9% and 16.5%, respectively. Higher amounts of saturated fatty acids (51.2%) were found in the dry leaves of ginkgo trees. In clove powder, on the other hand, unsaturated fatty acid was present in greater amounts (88.5%). It was demonstrated that dietary consumption of ω -3 and ω -6 polyunsaturated fatty acids may be beneficial in managing a range of medical diseases, including but not limited to heart disease, diabetes, arthritis, osteoporosis, asthma, colon cancer, breast cancer, and prostate cancer, which are linked to the oxidative damage caused by free radicals. We concluded the conclusion that cloves fatty acid profile shows lipids to be a consistent source of the fatty acids that are necessary for healthy nutrition. The clove is a unique component for nutritional applications due to its high MUFA and PUFA content of fatty acid.

All these results were accepted by ***Maltas et al.,(2011)*** who demonstrated that the most prevalent fatty acids in ginkgo dry leaves were palmitic (C16:0), oleic (C18:1n9), and α-linolenic (C18:3n3) (35.90, 18.03, and 11.18%, respectively). The latter is presently regarded as the ideal fatty acid for food because it has both a high oxidative stability and a hypocholesterolemic impact. In addition to, the highest quantities of fatty acids were found to be saturated (59.15%), followed by polyunsaturated (28.85%) and monounsaturated (12%).

These findings were also supported by ***Ramadan et al., (2013)***, who concluded that oleic and linoleic acids were the primary fatty acids found in cloves. The majority saturated fatty acids were palmitic and stearic acids. The significantly high concentration of MUFA and PUFA was CO. Diabetes and other disorders were also shown to have comparatively reduced levels of g-linolenic acid (GLA, C18:3n-6). It has been demonstrated that MUFA reduces "bad" LDL (low density lipoproteins) cholesterol while preserving "good" HDL (high density lipoproteins) cholesterol from a health perspective. The benefits of polyunsaturated fats (PUFAs) in reducing cardiovascular, inflammatory, and cardiac illnesses, atherosclerosis, autoimmune

disorders, diabetes, and other ailments are documented in an increasing amount of literature.

Since the beginning of human history, people have utilized the fruits and leaves of Ginkgo biloba (also known as ginkgo) as a food and a traditional medicine. Ginkgo biloba leaf extract is commonly used to treat peripheral vascular and cerebrovascular insufficiency as well as "mild-to-moderate" dementia symptoms, including short-term memory loss and changes in attention and mental focus **(*Boveris et al. 2007*).**

Table (4) phenolic compound of dried ginkgo leaves powder (g / 100g)

	Phenolic compound	**Ginkgo leaves powder**
1	Catechol	858.23
2	Chlorgenic	20.81
3	Syringic acid	20.67
4	Catchin	1.52
5	rosemarinic	3426.86
6	o- Coumaric acid	10.49
7	Vanillic acid	6.90
8	Neringein	31.01
9	Cinnamic acid	45.26
10	Ellagic	29.28
11	p- Hydroxy benzoic acid	124.65
12	Ferulic acid	64.76
13	Caffeic acid	1.42
14	Rutin	485.6
15	Benzoic acid	355.21
16	p- Coumaric acid	53.29
17	Resvertol	1065.17
18	Myricetin	2218.47
19	Kampherol	59.50
20	Gallic acid	12.85
21	Pyrogallol	----------
22	Quinol	----------

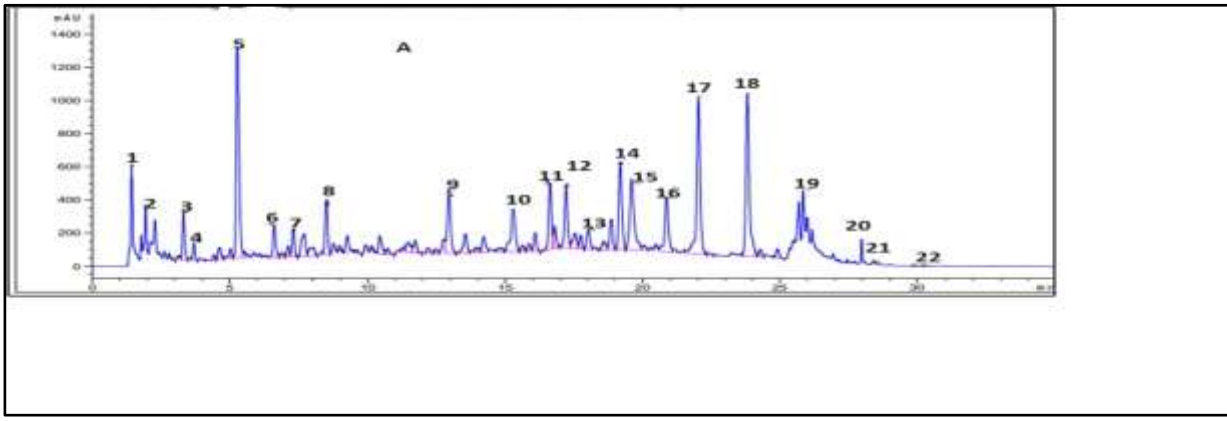


Figure (1) represent phenolic compounds of Ginkgo leaves powder

The phenolic content of dry ginkgo leaves is displayed in Table (4) & figure (1). It was known that rosemarinic (3426.86), myricetin (2218.47), resvertol (1065.17), and catechol (858.23) had a significant amount of phenolic compounds. in addition to several phenolic chemicals such as syringic acid, gallic acid, cinnamic acid, and kampherol. These results were agreed with **(*Ronowicz et al., 2013*)** they approved that the leaves of ginkgo biloba, in particular, are a significant source of chemicals that have antioxidant properties. It has been determined that kaempferol, quercetin, and isorhamnetin are the primary chemicals causing this kind of activity. Free radicals, including peroxide, hydrogen peroxide, hydroxyl radical, and singlet oxygen, can be scavenged and destroyed by these flavonoids. These radicals are linked to several illnesses, including inflammation, atherogenesis, carcinogenesis, and food deterioration. Because of this, ginkgo's naturally produced antioxidants may be useful for a variety of medical uses.

Quercetin and rutinoside were the most prevalent compounds in all of the extracts (211.23 g/gto 498.38 g/g). The two main phenolics in the sample were quercetin (223.99 mg/g) and chlorogenic acid (223.35 mg/g), respectively. Small levels of other chemotaxonomic indicators of G. biloba leaf extracts, including iso rhamnetin, luteolin, kaempferol, and their glycosides, were detected **(*Kobus, et al.,2019*).**

Clove is one of the best sources of phenolic compounds, including gallic acid, eugenol acetate, and eugenol. It has a lot of potential uses in medicine, cosmetics, cuisine, and agriculture. Table (5) & figure (2) shows the phenolic component of dried clove bud powder. It was obvious that quercetin (1250.8) had the highest phenolic content, followed by gallic acid (560.4), catchin (1050.3), and catechol (577.8). These results were agreed with ***Ali, et al.,(2021*)** who confirmed that one of the main plant sources of phenolic chemicals, including flavonoids, cinamic acids, benzoic acids, and hidroxiphenyl propionate, is clove. Clove's primary bioactive ingredient, eugenol, ranges in concentration from 9 381.70 to 14 650.00 mg per 100 g of fresh plant material. Gallic acid is the phenolic acid compound that has the highest concentration (783.50 mg/100 g fresh weight). Higher amounts of other gallic acid derivatives, such as hidrolizable tannins, are found (2 375.8 mg/100 g). The phenolic acids salicylic, ferulic, elagic, and caffeic acids are also present in clove. Clove contains smaller amounts of flavonoids such as kaempferol, quercetin, and its glycosilated derivatives **(*Frohlich ,et al.,2022*).**

Table (5) phenolic compound of dried clove bud powder (g / 100g)

	Phenolic compound	dried clove bud powder
1	trans-Ferulic acid	115.2
2	Syringic acid	130.5
3	Vanillic acid	21.7
4	Quercetin	1250.8
5	Protocatechuic acid	530.9
6	Ferulic acid	79.74
7	Myricetin	18.36
8	Resvertol	20.6
9	Rutin	90.3
10	Catchin	1050.3
11	Caffeic acid	31.06
12	Kampherol	40.3
13	p- Coumaric acid	15.4
14	Gallic acid	560.4
15	Benzoic acid	0.32
16	rosemarinic	0.15
17	Cinnamic acid	0.56
18	Catechol	577.8
19	Chlorgenic	58.35

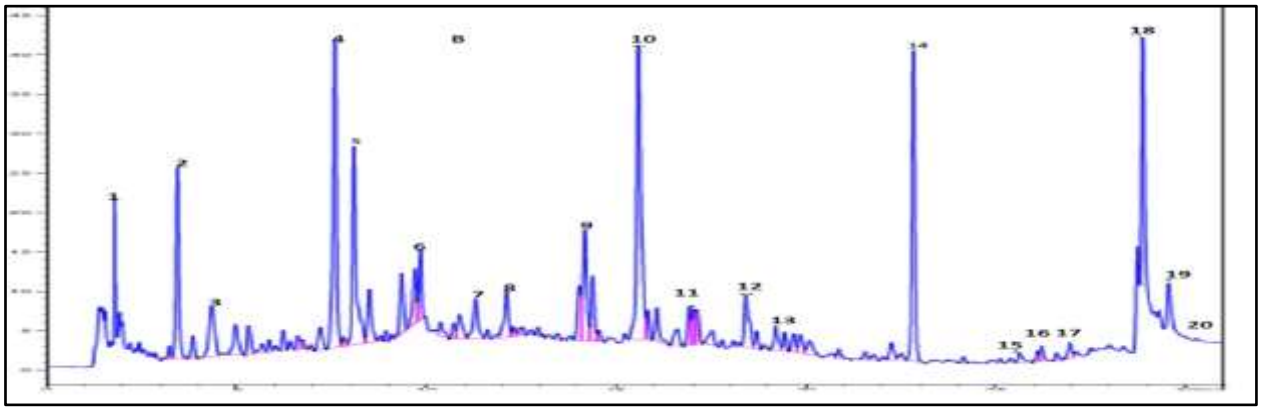


Figure (2) represent phenolic compounds of dry clove bud powder

Table (6) Body weight gain, total feed intake and feed efficiency ratio of Rats with Alzheimer's disease

groups	Initial body gain (g)	Body weight gain (g)	Total feed intake (g)	Feed efficiency ratio
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
G1 **(control -ve)**	143.00 cb ± 7.48	85.00 a ± 13.42	250.83 a ± 40.92	0.34 a ± 0.07
G2 (control +ve)	142.00 cb ± 6.78	15.20 d ± 7.63	175.00 b ± 58.57	0.09 cb ± 0.04
G3 (AL3+ donepezil 5mg/k.gm)	139.00 c ± 6.63	28.00 dcb ± 9.27	192.50 ba ± 53.08	0.16 b ± 0.07
G4 (AL3+ 15 grams of dried G.biloba leaf)	142.00 cb ± 6.78	23.00 dcb ± 9.27	198.33 ba ± 57.15	0.12 cb ± 0.05
G5 (AL3+ G.biloba extract (400 mg/kg body wt)	147.00 cba ± 2.45	15.00 d ± 10.49	221.67 ba ± 52.69	0.06 c ± 0.05
G6 (AL3+ clove (800mg/kg body wt/day) suspension	153.20 a ± 5.19	23.80 dcb ± 10.76	221.67 ba ± 42.39	0.12 cb ± 0.07
G7 (AL3+ clove extract (2mg/kg body wt/day)	143.00 cb ± 6.78	29.00 cb ± 13.19	227.50 ba ± 48.24	0.14 cb ± 0.10
G8 (AL3+ + 400 mg/kg of Ginko Biloba orally + 800 mg/kg of clove (suspension)	150.00 ba ± 8.37	19.00 dc ± 11.58	227.50 ba ± 29.28	0.08 cb ± 0.04
G9 (AL3+ + 400 mg/kg of Ginko Biloba orally + 2 mg/kg of clove) extract	140.00 c ± 7.07	33.00 b ± 5.10	233.33 ba ± 42.39	0.14 cb ± 0.03
F	3.10	25.69	1.43	10.77
Sig.	0.01	0.00	0.21	0.00

Table (6) shows that rats exposed to Alcl3 toxicity had lower feed intake, body weight gain, and feed efficiency (175, 15.20, and 0.09) than the negative control group (250.83, 85, and 0.34, respectively). Rats fed a basal diet supplemented with 400 mg of Ginko Biloba and 2 mg of clove extract demonstrated significant enhancements in values compared to the positive group. Group 9 achieved the best results.

These data were approved by **(*Tsuno et al., 2019*)** Supplementing the AD diet with rivastigmine, dry black raisins, and ginkgo resulted in significant improvements in body weight gain, feed intake, and efficiency ratio compared to the positive control group ($P \leq 0.05$). The group that consumed 20% dry black raisins and ginkgo billoba had the greatest mean value. while, there were no significant differences in body weight increase, feed intake, or feed efficiency ratio between Alzheimer's rats supplemented with 0.25mg rivastigmine and 10% DBR.

The same results agreed with **(*Hassan et al.,2020*)** Metronidazole MET treatment resulted in significant decreases ($p < 0.05$) in feed intake (FI), body weight gain percentage (BWG%), and feed efficiency ratio (FER) compared to control rats. Mixing anise seeds and clove bud extracts with MET significantly increased these measures ($p < 0.05$) compared to rats administered with 0.25mg the medication alone.

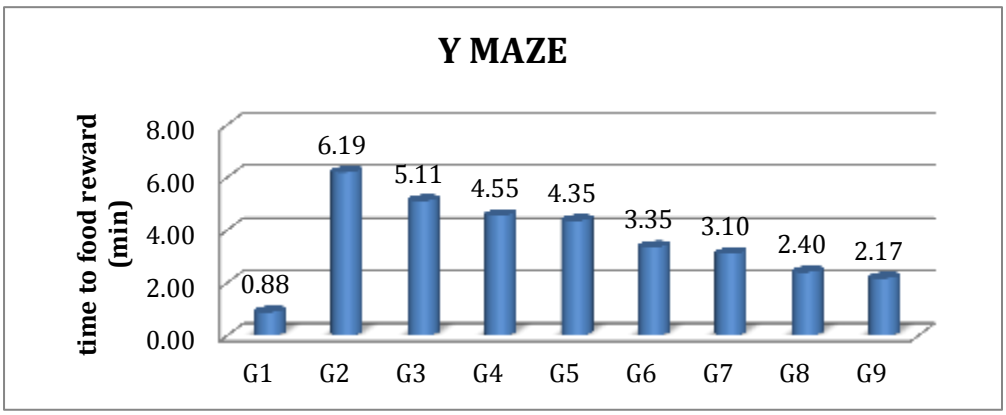


Figure (3) Effects of clove bud powder and dried G. biloba leaves on y maze tests in rats with Alzheimer's disease

The Y-maze test is widely used to evaluate the hippocampal health of rats. In this study all treated groups performed worse than the negative group, according to the results. When compared to the other treatment groups, the group that received oral ginkgo biloba plus clove solution and extract had the best effects. It was evident that these groups had a beneficial protective effect on the memory of rats administered Alzheimer's disease-induced damage. These data were disagreed with **(*Khalil et al., 2020*)**, the number of arm entries was not different statistically significantly between the treatment groups and the control group. In contrast to the AD group, the treatment of B. papyrifera and clove, either separately or together, significantly raises the SAP%. The combination group displayed an increase in the number of arm entries and SAP% in comparison to the B. papyrifera and clove treated groups, but there was no statistically significant difference.

On contrast, these data were approved by **(*Jetti et al.,2016*) ,** they confirmed that the approach assesses arm choice across multiple trials or in a single session. It assumes that weaknesses in alternation reflect poor spatial working memory. G.biloba treatment improved cognitive status, as evidenced by behavioral profiles in the Y maze. The study found that rats intoxicated with AlCl3 had impaired memory and learning ability. However, treating G.biloba, vitamin C, or a combination of the two improved memory loss and spatial recognition as measured by latency time.

Table 7's results showed that groups 8 and 9's norepinephrine levels were significantly lower than those of the positive control group (30.32, 34.35, and 380.39 pg/mg, respectively). The same table's findings demonstrated that groups (8 and 9) had significantly higher dopamine levels than group (2), at 52.07, 65.26, and 9.44 ng/ml, respectively. Additionally, the still group (8,9) performed better on serotonin tests than the positive group (45.74, 47.20, and 4.73 (ng/mg).

Table (7) Effects of dried G. biloba leaves, clove bud powder and their mixtures on the concentration of monoamine neurotransmitters in the serum of rats with AD induced by AlCl3

groups	Norepinephrine (Pg/mg)	Dopamine (ng/ml)	Serotonin (ng/mg)
	Mean ± SD	Mean ± SD	Mean ± SD
G1 **(control -ve)**	3.73 ^{h} ± 0.45	87.48 ^{a} ± 2.01	67.47 ^{a} ± 1.02
G2 (control +ve)	380.39 ^{a} ± 6.83	9.44 ^{g} ± 1.45	4.73 ^{h} ± 0.09
G3 (AL3+ donepezil 5mg/k.gm)	256.52 ^{b} ± 8.91	17.83 ^{f} ± 0.66	17.45 ^{g} ± 0.76
G4 (AL3+ 15 grams of dried G.biloba leaf)	200.80 ^{c} ± 10.38	18.07 ^{f} ± 0.86	22.28 ^{f} ± 1.97
G5 (AL3+ G.biloba extract (400 mg/kg body wt)	162.09 ^{d} ± 4.92	20.33 ^{e} ± 1.57	27.44 ^{e} ± 0.38
G6 (AL3+ clove (800mg/kg body wt/day) suspension	153.11 ^{e} ± 4.95	19.67 ^{fe} ± 0.85	28.60 ^{e} ± 0.49
G7 (AL3+ clove extract (2mg/kg body wt/day)	117.69 ^{f} ± 5.90	24.95 ^{d} ± 1.37	31.21 ^{d} ± 0.54
G8 (AL3+ + 400 mg/kg of Ginko Biloba orally + 800 mg/kg of clove (suspension)	30.32 ^{g} ± 4.07	52.07 ^{c} ± 2.37	45.74 ^{c} ± 1.70
G9 (AL3+ + 400 mg/kg of Ginko Biloba orally + 2 mg/kg of clove) extract	34.35 ^{g} ± 2.18	65.26 ^{b} ± 1.69	47.20 ^{b} ± 1.00
F	2336.64	1862.91	1845.62
Sig.	0.00	0.00	0.00

The data were presented as mean ± S.D.
According to "Duncan" the mean values were arranged in a descending order from "a": "d"

The results of this study demonstrated that oral administration of 400 mg/kg of G. biloba, 800 mg/kg of clove solution, 400 mg/kg of Ginko biloba orally, and 2 mg/kg of clove extract to rats for eight weeks increased the levels of dopamine and serotonin in their serum. These data accepted by ***(Belviranlı and Okudan,2015)*** they have been suggested that the neurotransmitters norepinephrine, dopamine, and serotonin—biogenic amines—are linked to cognitive functions including learning and focus. Numerous investigations have demonstrated that AD is associated with lower brain neurotransmitter levels.

AlCl3 administration disrupted the serotonergic and dopaminergic pathways of the multiple neurotransmitter system.

Clove bud extract has natural phenolic antioxidant qualities that make it a useful treatment for oxidative stress-related illnesses. Numerous health advantages have been attributed to several substances isolated from clove buds extracts, including tannins, ellagic acid, gallic acid, flavonoids, and their glycosides as shown in table (5). These include of aphrodisiac, hypoglycemic, antithrombotic, antiprotozoal, anti-inflammatory, and gastro-protective properties. Clove bud extract has been suggested as a possible therapy for the neurotoxic symptoms of AD because it contains highly bioactive phenolic components **(*Yashin et al.,2017*).**

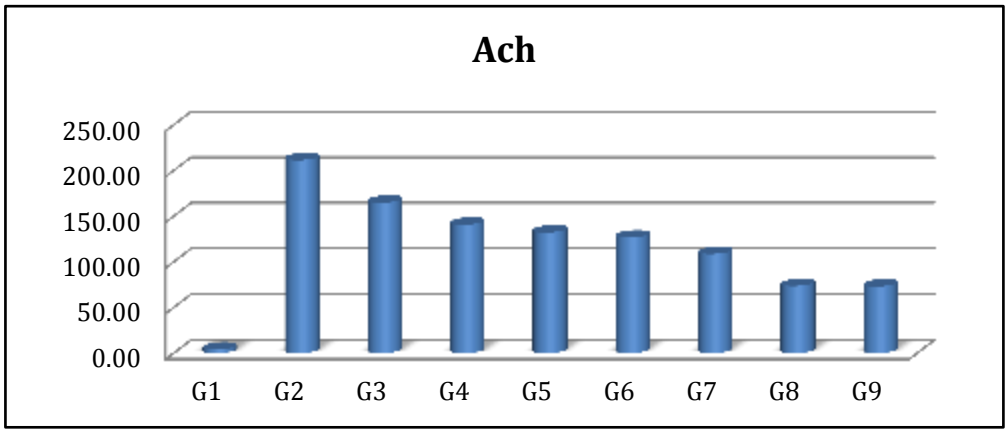


figure (4) Effect of dry G.biloba leaves, clove bud powder and their combinations on acetylcholinesterase activity level in serum of AlCl3-induced AD rats

Figure (4) shows the effects of clove bud powder, dried G. biloba leaves, and their mixtures on the level of acetylcholinesterase activity in the serum of rats administered AlCl3-induced AD. The results demonstrated that the positive group had much higher levels of acetylcholinesterase (ACHE) than the negative group. Furthermore, statistically significant differences were noted between them at $p<0.05$. Conversely, the (ACHE) level is lower in all treated groups than in the positive group. Still higher than the negative group, though. Additionally,

statistically significant differences ($p<0.05$) were noted between them.

These could be connected to diets high in phenolic compounds found in clove buds and dry ginkgo leaves, which have a beneficial effect on the tissue brain rat model of Alzheimer's disease by improving the level of (ACHE). Groups 8 and 9 who received a combination of Ginko Biloba and clove extract, or suspension showed positive results. Additionally, statistically significant differences ($p<0.05$) were found between them.

G.biloba, clove, and their combination enhanced cholinergic neurotransmission and played a protective effect against the breakdown of acetylcholine. As a result, the G.biloba and clove increased the neuroprotective impact by reducing the cholinergic deficiencies brought on by AlCl3 injection. Currently, the most effective method for treating AD, senile dementia, and memory issues is acetylcholinesterase inhibition.

These results agreed with **(*El-Hallouty et al., 2022*)** who reported that Ginko biloba leaf extract is commonly used to treat age-related illnesses, such as dementia brought on by neuronal degeneration and poor memory. The protective properties of Ginko biloba leaf extract have been the focal point of numerous articles in recent years. According to reports, the primary components of Ginko biloba's standardized leaf extract were flavone glycosides, terpenene lactone, and organic acids.

According to the B. papyrifera and clove treatment. increases AChE activity either alone or in combination when compared to the AD group. Clove and B. papyrifera extract's bioactive ingredients function as antioxidants and anti-apoptotic agents, which may be able to stop neurons from dying **(*Aljarari,2023*)**.

Table (8) Effect of dry G.biloba leaves, clove bud powder and their combinations on Glutathione reduced and Malondialdehyde level in serum of AlCl3-induced AD rats

groups	MDA (nmol/gm)	GSH (mg/gm)
	Mean ± SD	Mean ± SD
G1 **(control -ve)**	0.83 i ± 0.02	5.34 a ± 0.10
G2 (control +ve)	5.11 a ± 0.11	0.98 i ± 0.03
G3 (AL3+ donepezil 5mg/k.gm)	4.14 b ± 0.13	1.55 h ± 0.08
G4 (AL3+ 15 grams of dried G.biloba leaf)	3.85 c ± 0.17	1.84 g ± 0.06
G5 (AL3+ G.biloba extract (400 mg/kg body wt)	3.18 d ± 0.03	2.03 f ± 0.09
G6 (AL3+ clove (800mg/kg body wt/day) suspension	2.90 e ± 0.20	2.74 e ± 0.09
G7 (AL3+ clove extract (2mg/kg body wt/day)	2.53 f ± 0.10	3.23 d ± 0.21
G8 (AL3+ + 400 mg/kg of Ginko Biloba orally + 800 mg/kg of clove (suspension)	1.91 g ± 0.03	3.94 c ± 0.08
G9 (AL3+ + 400 mg/kg of Ginko Biloba orally + 2 mg/kg of clove) extract	1.53 h ± 0.29	4.50 b ± 0.19
F	520.50	950.35
Sig.	0.00	0.00

The data were presented as mean ± S.D.
According to "Duncan" the mean values were arranged in a descending order from "a": "d"

Table 8 shows the effects of dried G. biloba leaves, clove bud powder, and their mixtures on the amount of malondialdehyde and glutathione in the serum of rats administered AlCl3-induced AD. Compared to the positive group, which had raised MDA levels of 5.11 nmol/gm, ginkgo and clove extract or suspension (groups 8 and 9) 1.91 and 1.53 nmol/gm had significantly decreased the elevated levels. Besides, to the positive group, group 6 and 7 showed much lower findings, 2.90 and 2.53 nmol/gm, respectively. In comparison to the positive group, which had a level of GSH of 0.98 mg/gm, group (9) had the best results, with 4.50 mg/gm among all treated groups.

These benefits could be attributed to the phenolic antioxidant content of ginkgo and clove bud extract (table 5&6),

which make them an excellent treatment for oxidative stress-related illnesses. Flavonoids, ellagic acid, gallic acid, and tannins are among the compounds that have been linked to several health benefits. These active ingredients have been found to be viable treatments for Alcl3's neurotoxic effects.

These outcomes were accepted by **(*Tahoun, 2017*)** who supposed that Catalase and SOD activities were both markedly reduced by MET exposure. But extracts of clove and anise demonstrated a dose-dependent opposite effect. Two dosages of anise and clove extract considerably decreased the high MDA levels ($p<0.05$). Additionally, the GSH levels in the MET group significantly decreased ($p<0.001$), but the anise and clove extract restored them.

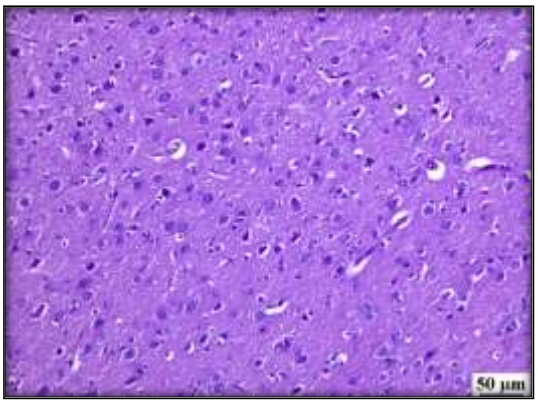
It is unknown if ginkgo billioba (GBS), a Chinese herbal supplement that increases antioxidants, would improve vascular functioning in vascular dysfunction caused by Cs-A. Consequently, the protective effects of GBS against Cs-A-induced vascular dysfunction were investigated in Wistar rats in this work. According to our findings, GBS considerably raised the levels of CAT, SOD, and GSH while lowering MDA **(*Adebayo et al.,2022*)**.

Histopathology results:

Microscopic analysis of brain sections from group 1 (Figs. 5&6) demonstrated normal histology in both the cerebral cortex and all regions of the hippocampus, including CA1, CA2, CA3, CA4, and DG. Group 2 (Fig. 7:9) showed significant histological abnormalities in the cerebral cortex and hippocampus. The cerebral cortex has extensive gliosis and many dark deteriorated neurons. Dark degenerating neurons were found in various locations of the hippocampus. Group 3 showed a significant improvement (Fig. 10:13). The cerebral cortex had less dark deteriorated neurons. In various regions of the hippocampus, neurons appeared to be normal, but in CA1 and CA2, neurons were became worse. Group 4 showed a poor protective effect (Fig. 14&15), with an increased number of dark shrunken degenerative neurons in both the cerebral cortex and various regions of the hippocampus. Moderate improvement was found in group 5 (Fig.

16&17) which is characterized by few deteriorated neurons in the cerebral cortex. Limited protection was found in group 6 (Figs. 18&19), which showed severe gliosis with numerous dispersed degenerative neurons in the cerebral cortex and hippocampus. Group 7 showed moderate improvement (Figs. 20&21). The examination of group 8 (Fig. 22) demonstrated modest gliosis in the cerebral cortex and a few deteriorated neurons in the hippocampus. Group 9 (Figs. 23&24) showed significant improvement, with neurons in the cerebral cortex and various parts of the hippocampus appearing to be normal.

These data were accepted by **(*Dong et al.,2017*)** they demonstrated that Histopathological study of brain tissues from various regions showed improvements in the cerebral cortex and hippocampus. G.biloba treatment resulted in fewer nuclear pyknosis and plagues in the striatum compared to Aricept, the reference medicine. The study found that combining Ginkgo biloba with vitamin C extract increases behavioral abilities, learning and memory, and cures hippocampus neuronal damage caused by AlCl3 injection. Animals treated with ALCl3 for 30 days had memory problems, as demonstrated by longer time to food reward. Vitamin C and G. biloba's antioxidant qualities mitigated the negative effects of aluminum chloride intoxication.



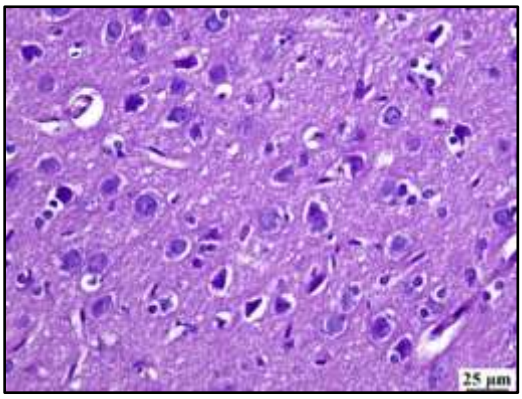
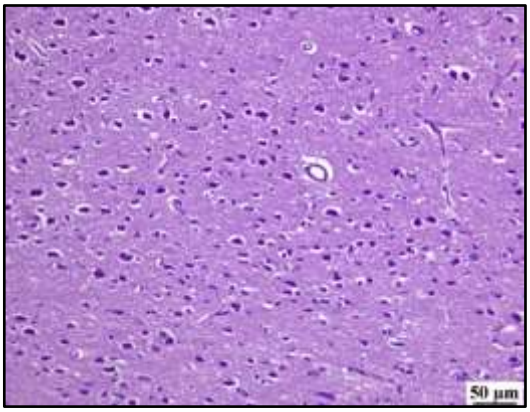
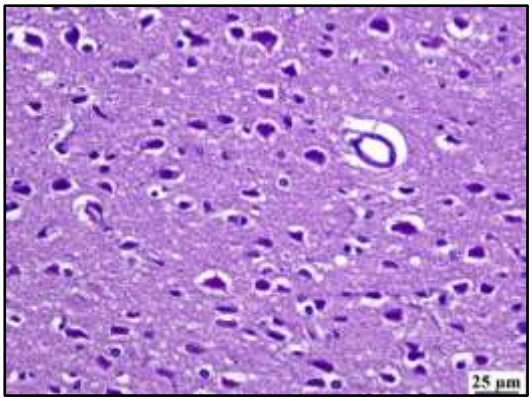


Fig. (5,6) Photomicrograph of brain, group 1, showing normal cerebral cortex (H&E)





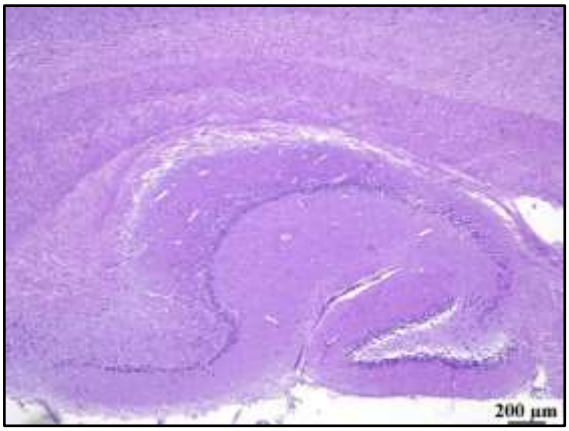


Fig. (7,8,9) Photomicrograph of brain, group 2, higher magnification showing numerous dark degenerated neurons scattered and different hippocampus regions in the cerebral cortex (arrow) (H&E).

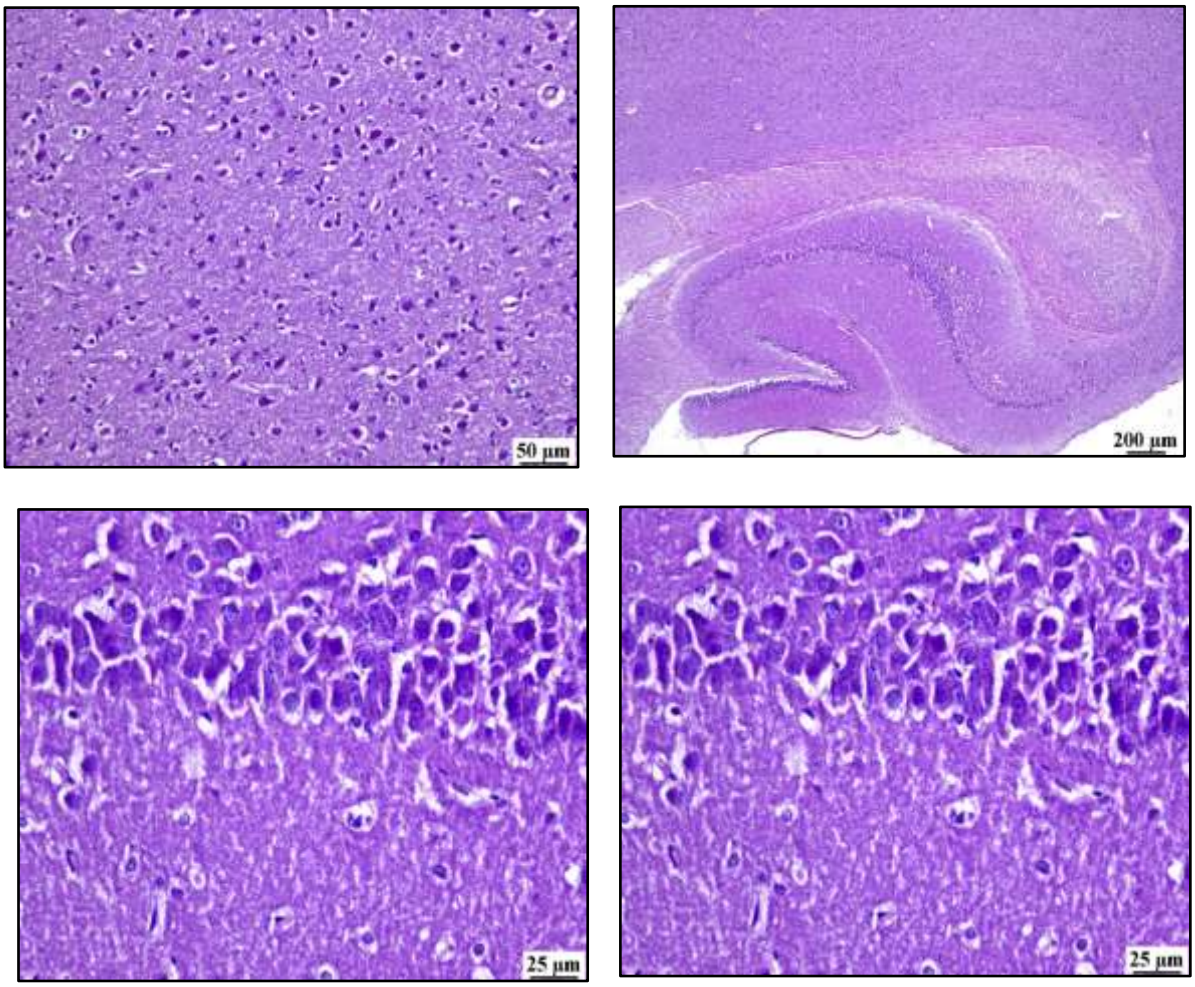
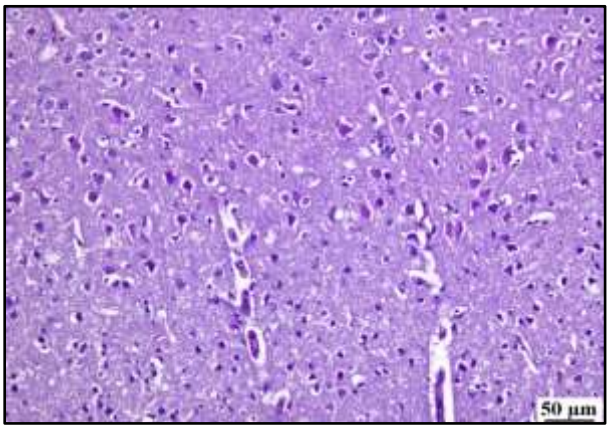


Fig. (10,11,12 &13) Photomicrograph of brain, group 3, showing different regions of the hippocampus and higher magnification showing some degenerated neurons in CA4 region of hippocampus with gliosis (H&E).



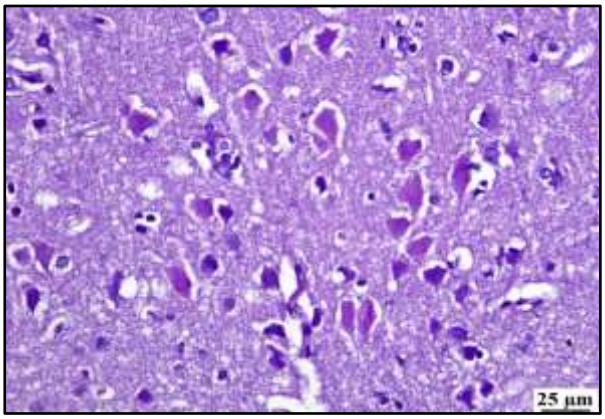
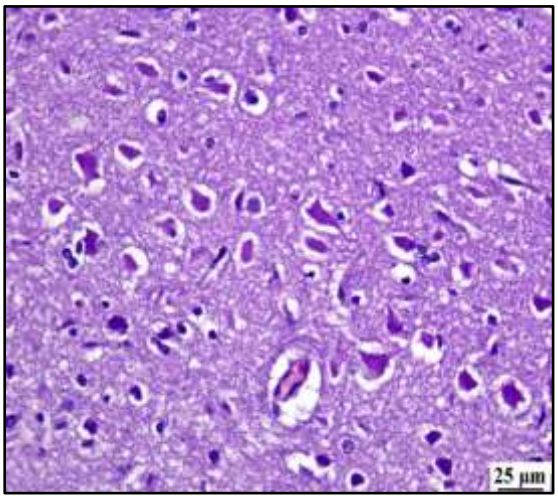


Fig. (14&15) Photomicrograph of brain, group 4, higher magnification showing numerous degenerated neurons scattered in the cerebral cortex associated with diffuse gliosis (H&E).



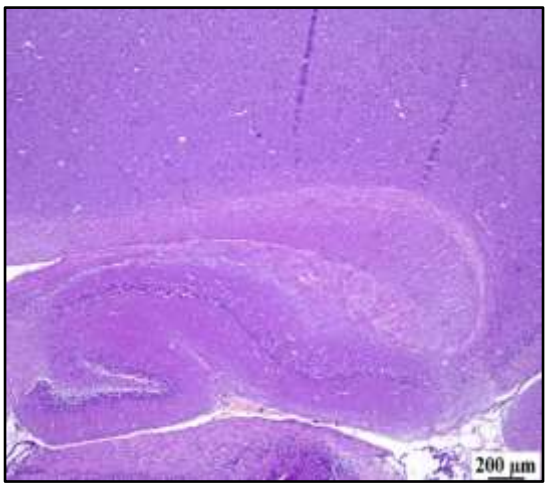


Fig. (16&17) Photomicrograph of brain, group 5 higher magnification showing few degenerated neurons in the cerebral cortex & showing different regions of hippocampus (H&E).

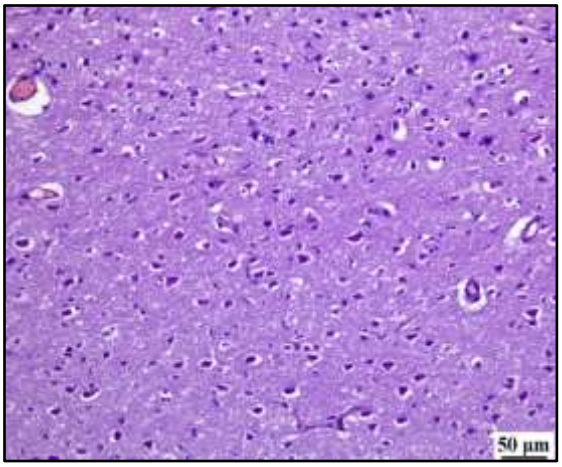
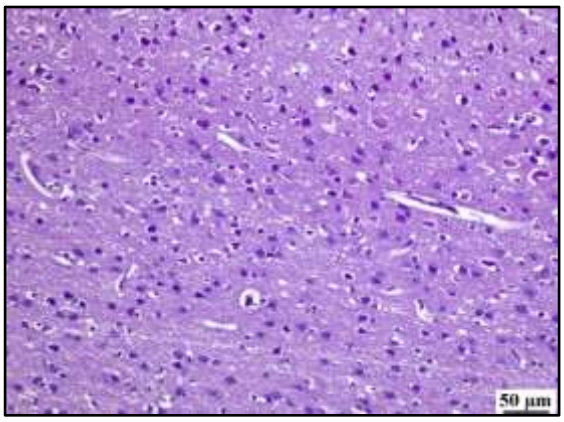


Fig. (18&19) Photomicrograph of brain, group 6 showing different regions of hippocampus and numerous numbers of degenerated neurons in the cerebral cortex (H&E).



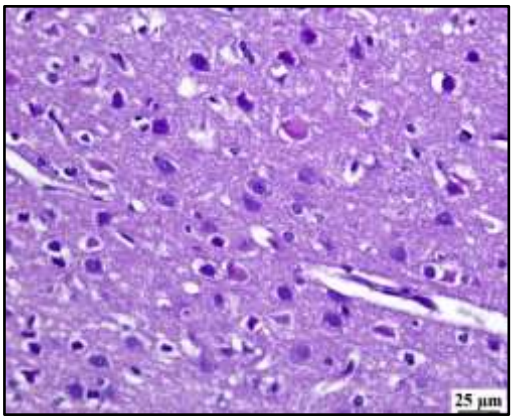


Fig. (20&21) Photomicrograph of brain, group 7 showing variable number of degenerated neurons in the cerebral cortex with moderate gliosis & showing an increased number of degenerated neurons in the cerebral cortex (H&E).

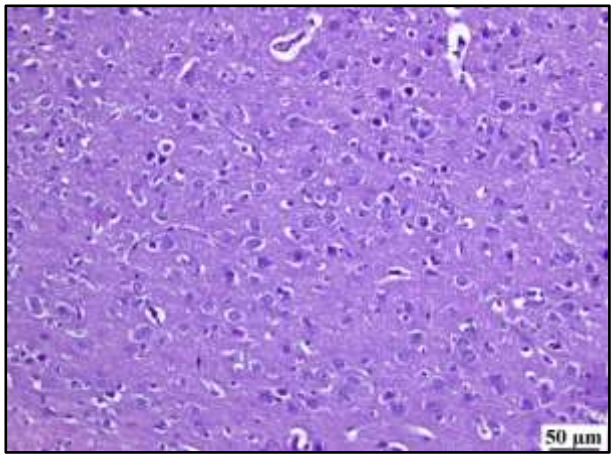
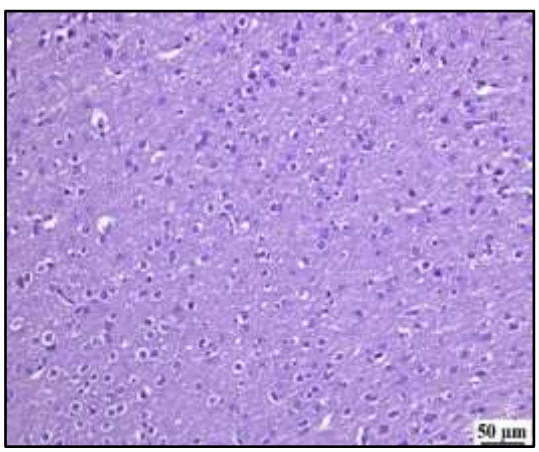


Fig. (22) Photomicrograph of brain, group 8 showing mild gliosis in the cerebral cortex (H&E)



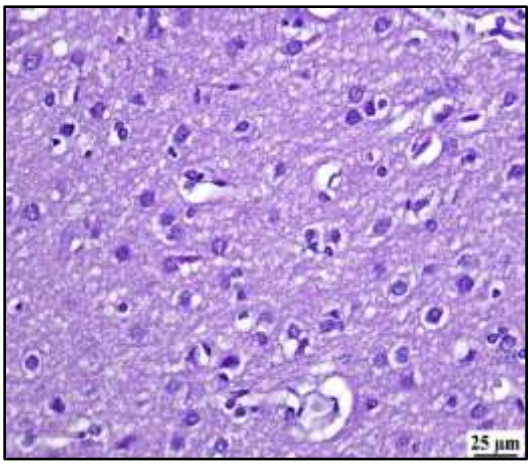


Fig. (23&24) Photomicrograph of brain, group 9 showing apparently normal cerebral cortex (H&E).

conclusion

Based on the study's findings, it can be said that in addition to being used as condiments at home, the spices and herbs under consideration contain sizable amounts of nutrients that, if frequently consumed may be valuable sources of health. Although spices and herbs are utilized in meals in very small amounts, these findings suggest that when taken in in a range of dishes, spices may offer a significant amount of fat, protein, and minerals. To assess product quality at the biochemical and nutritional levels, it is critical to have a comprehensive understanding of all the components that are involved. Numerous bioactive components,

including phenolic compounds—strong antioxidants that actively lower the risk of attenuating cerebral damage in Alzheimer's disease patients—have been found and quantified, particularly in G. biloba and clove. The extract supplements or solutions containing the highest concentration of antioxidants were found G. biloba and clove.

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تأثير القرنفل وأوراق الجنكة بيلوبا على مرض الزهايمر المحدث بكلوريد الألمونيوم فى الفئران

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الملخص العربى

مرض الزهايمر هو اضطراب عصبي ويعتبر هو السبب الرئيسى للخرف. وتهدف الدراسة الحالية إلى دراسة ما إذا كانت أوراق القرنفل والجنكة بيلوبا يمكن أن تعالج الفئران المصابة بمرض الزهايمر الناجم عن كلوريد الألومنيوم. وقد تم إعطاء كلوريد الالمونيوم بنسبة (17 ملغم/كغم من وزن الجسم) عن طريق الفم للفئران لمدة شهر واحد لإحداث مرض الزهايمر. وقد تم إعطاء الفئران مستخلص أوراق الجنكة بيلوبا ومعلقاتها (400 مجم/كجم من وزن الجسم/يوم) ومستخلص مسحوق القرنفل ومعلقاته (2 مجم/كجم من وزن الجسم/يوم و800 مجم/كجم من وزن الجسم/يوم)وتم اعطاء مزيج من الاثنين. كما تم تحديد التركيب الكيميائي والمعادن والمكونات الفينولية ومستويات الأحماض الدهنية للجنكة والقرنفل. بالإضافة الى تحليل اختبار المتاهة Y، أستيل كولينستريز، MDA، GSH، الدوبامين،السيروتونين، نشاط النورإبينفرين، والنتائج النسيجية للدماغ. وجدت الدراسة أن تناول أوراق الجنكة الجافة ومستخلصات أو معلقات مسحوق برعم القرنفل أدى إلى تحسن كبير في الوظائف الإدراكية لدى الفئران المصابة بالمرض، بما في ذلك زيادة (GSH)، وانخفاض مستويات MDA في القشرة الدماغية. وأظهر الفحص النسيجي أيضا تحسنا. ومع ذلك، فإن استخدام العلاج المركب أنتج فوائد أفضل من العلاج الفردي. تشير هذه الدراسة إلى أن الجمع بين أوراق الجنكة المجففة ومسحوق برعم القرنفل يمكن أن يحسن مستويات AChE ويقلل من الإجهاد التأكسدي في الدماغ، مما قد يعالج الخلل المعرفي المرتبط بمرض الزهايمر الناجم عن AlCl3.

الكلمات المفتاحية: الجنكة بيليوبا، القرنفل، مرض الزهايمر (AD)، كلوريد الألومنيوم (AlCl3)، المركبات الفينولية.