Study the Effect of Wormwood (*Artemisia absinthium* L.) Ethanolic Extract against Aluminum Chloride Causing Memory Impairment in Rats

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مجلة البحوث في مجالات التربية النوعية

معرف البحث الرقمي DOI: 10.21608/JEDU.2024.311415.2096

المجلد العاشر. العدد54 . سبتمبر 2024

الترقيم الدولي

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

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

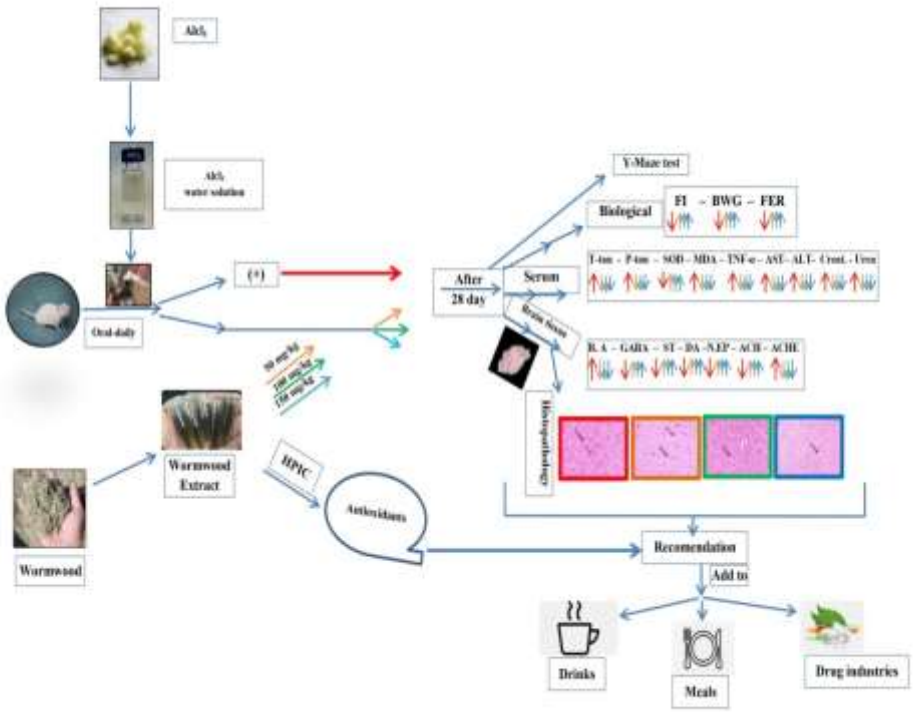
موقع المجلة http://jrfse.minia.edu.eg/Hom

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

Abstract

The purpose of this study is to know the effect of wormwood (*Artemisia absinthium* L.) extract against aluminum chloride which causes memory impairment in rats. Thirty male albino rats were used and divided into two main groups. The first main group (6 rats) fed on basal diet only as a negative control group, while the second main group (24 rats) received aluminum chloride (175 mg/kg B.W), dissolved in distilled water, orally throughout the experiment to cause oxidative stress and memory impairment. Whereas they were divided into four subgroups as follows: The second group was treated as a positive control group and fed the basal diet. The third group is an infected group and fed on the basal diet in addition to ethanolic wormwood extract at a dose of 50 mg/kg BW, orally. The fourth and fifth groups were fed on the basal diet and received ethanolic wormwood extract at doses of 100 and 150 mg/kg BW, respectively, orally using stomach tubes. The wormwood content of active substances was estimated using HPLC. At the end of the experiment, rats were slaughtered and serum samples were taken to conduct some analyses such as some liver enzymes and some kidney functions, total tau, phospho tau, tumor necrosis factor-α, malondialdehyde and superoxide dismutase. The brain was also extracted to estimate dopamine, serotonin, GABA, beta-amyloid, and norepinephrine, as well as to conduct a histopathological examination **.** Y-Maze test was also done . The results showed the positive effect of wormwood, as the levels of dopamine, serotonin, GABA, acetylcholine, norepinephrine and superoxide dismutase increased, while the levels of total tau, phospho tau, beta-amyloid, acetylcholinesterase , malondialdehyde, and tumor necrosis factor-α decreased. Biological assessments such as body weight, feed intake, and feed efficiency ratio also improved. The results of the histopathological examination of the brain supported the results of the chemical analyses. The study recommended using wormwood to improve memory and oxidation status in the body.

Keywords : aluminum chloride, acetylcholinesterase, oxidative stress, neurotoxicity.



Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that gradually affects the brain and impairs thinking, cognitive abilities, and the capacity to carry out basic daily tasks **(Jicha and Carr, 2010)**. In the world, it ranks as the sixth leading cause of death **(Xu *et al*., 2016)**. The World Alzheimer's Report states that there are roughly 50 million AD sufferers globally at the moment, and by 2050, that number is expected to rise to over 139 million **(Alzheimer's Association, 2017)**. One of the biggest obstacles to developing a conclusive treatment for AD is the lack of a clear etiology for the disease. However, a number of risk variables, including oxidative stress, infectious agents, aging, genetics, neuro-inflammation, head trauma, depression, deterioration of anatomical routes, mental processes, and environmental elements such as aluminum poisoning, are linked to AD **(Zhang *et al*., 2021 and Dey and Singh, 2022)**.

According to recent research, consuming aluminum is one of the most important reasons of AD **(Sanajou *et al*., 2023)**. Antacids, food additives, skincare, cosmetics, kitchenware, baby formulae, milk products, juice and marine foods are among the items that allow this metal to enter the body. Additionally, aluminum has been found in drinking water as a result of the water treatment process. It has been naturally found in weathering rocks and soils or is released from them as a result of acid rain brought on by pollution **(Alasfar and Isaifan, 2021 and Niu, 2023**).

The relationship between metals, neurodegenerative diseases, and oxidative stress raises the possibility of a novel treatment approach including the use of metal chelators and free radical scavengers **(Sienes Bailo *et al*., 2022)**. In this regard, natural phytochemicals derived from plants and their derivatives have been extensively employed in the search for neuroprotective medicines against neurodegenerative illnesses such as AD **(Das *et al*., 2024)**. We employed *Artemisia absinthium* in this investigation.

Wormwood *(Artemisia absinthium* L.*)* is a perennial herbaceous and pungent plant that is a member of the *Asteraceae* family of plants **(Bora and Sharma, 2010)**. According to studies conducted in vitro and in vivo, wormwood has been shown to have free radical scavenging action **(Astghik, 2003 and Canadanovic-Brunet *et al*., 2005)**. Wormwood has been found to contain azulenes, flavonoids, tannins, phenolic acids and lignans, as well as bitter sesquiterpenoid lactones and essential oil (**Szopa *et al*., 2020)**.

Wormwood has yielded a number of flavonol-3-glycosides, such as derivatives of quercetin, isorhamnetin, patuletin, and spinacetin. Wormwood extracts have demonstrated robust antioxidant and antiradical properties in vitro, with significant concentrations of total flavonoids and total phenolic components **(Canadanovic-Brunet *et al*., 2005)**.

Wormwood is extensively utilized in meals, cosmetics, and drug industries because of its antioxidant potential **(Aeineh *et al*., 2023)**. Notable uses for wormwood include antiulcer **(Shafi *et al*., 2004)**, antibacterial **(Moslemi *et al*., 2012)**, antimalarial

(Mohammadian *et al*., 2016), hepatoprotective **(Sagástegui *et al*., 2020),** antioxidant **(Mohammed, 2022)**, antitumor **(He *et al*., 2023)** and neuroprotective **(Rashidi *et al*., 2023)**.

The presence of thujone and its equivalents in wormwood has been shown in earlier publications to have certain neurotoxic consequences when used over an extended period of time, despite the herb's wonderful medicinal benefits. Wormwood used in large doses can lead to headaches, nausea, vomiting, cramps in the intestines, and dizziness. According to **Batiha *et al*. (2020)**, wormwood essential oil should not be used by expectant moms, nursing mothers, anyone with allergies, hyperacidity, or those suffering from peptic ulcers. According to **El Deen (2022),** wormwood can be taken in amounts up to 10% of the diet without endangering the kidneys or liver. Also, **Kauser *et al*, (2023)** determined that wormwood extract loaded polymeric nanoparticles' LD50 (an estimate of the amount of poison that, under controlled conditions, will be a lethal dose to 50% of a large number of test animals of a particular species) cut-off value will be 500 mg/kg.

Therefore, the goal of this study was to ascertain the effectiveness of wormwood against $AlCl_3$ toxicity, which causes memory impairment in rats.

Materials and Methods

Materials

The dried wormwood was obtained from a local herb seller in Shebin El-Kom, Menofia, Egypt. The Menoufia University, Shebin El-Kom, Egypt's Agricultural Plant Department conducted taxonomic confirmation identified the plant materials as wormwood.

Corn starch, sucrose, wheat bran, and corn oil were bought from market in Shebin El-kom, Menoufia, Egypt. From the Cairo Corporation for Chemical Trade in Cairo, Egypt, casein, vitamins, minerals, choline bitartrate, and L-cysteine were procured. Sigma Chemical Company provided the anhydrous aluminum chloride ($AlCl_3$).

Thirty male albino rats (Sprague Dawley strain) were purchased from the Medical Insects Research Institute in Dokki, Cairo, Egypt. The rats weighed roughly 180± 10g. This

experiment has received ethical approval from Menoufia University's Institutional Animal Care and Use Committee **(IACUC) (Reg. No., MUFHE /F/NFS/ 22/24).**

Methods

Preparation of ethanolic extract

Wormwood blooming tips were allowed to air dry in the shade before being finely pulverized in an electric blender. After that, 20 g of flower powder was extracted for 8 hours using 150 mL of 80% ethanol in a Soxhlet extractor. A rotary evaporator was used to evaporate the residue. Until they were used, the dried extracts were kept at 4°C. Saline was used to dissolve the extracts **(Ene-ojo *et al*., 2013)**.

Wormwood extract phenolic compounds

Using the technique outlined by **Rao and Nagaraju (2003)**, the polyphenolic compounds of wormwood were separated and analyzed for phenolic and flavonoid compounds by HPLC in the food safety and control laboratory at Cairo University.

Diet components

The components of the basal diet were produced in accordance with **Reeves *et al*. (1993)**.

Experimental design:

Thirty adult male Sprague Dawley strain albino rats weighing 180±10g were given a week to adjust to their new surroundings. They were kept up in compliance with the **OECD (2008)** requirements. The animals were kept in separate housing with free access to food and water, as well as a 25 °C temperature and 12-hour light/dark cycle. Following their acclimatization, the rats were split into two primary groups: The first group of six rats was used as a negative control and was fed a baseline diet. Throughout the trial, aluminum chloride (175 mg/kg B.W) was given orally to the second group of 24 rats and dissolved in distilled water. Due to its high rate of induction, this aluminum chloride dosage schedule was chosen based on prior reports **Mcgheer and Mcgheer (2001)**. Rats from the second main infected group were split into four subgroups. One subgroup was maintained as a control group and fed a basal diet along with $AlCl_3$ until the end of the experiment. The other three subgroups received daily treatments of 50, 100, and 150 mg/kg of

wormwood ethanolic extract **(Yazdani *et al*., 2013),** respectively, along with $AlCl_3$ for a period of 28 days.

Biological evaluation:

These formulae were used to determine the feed efficiency ratio (FER) and body weight gain (BWG) according to **Chapman *et al*. (1959):**

BWG = (Final weight - Initial weight)

$$\textbf{FER} = \frac{\textbf{Grams gain in body weight}}{\textbf{Grams feed consumed}}$$

Behavior study : Y-Maze test:

According to **Foyet *et al*. (2015),** behavioral activities such as memory loss, age-related cognitive decline and spatial learning were assessed in the animals using the Y maze. After receiving their last doses of wormwood, the rats were taken into the behavioral analysis room, given three hours to acclimate, and then subjected to the Y-maze test. The instrument was a white wooden labyrinth with three arms, numbered A through C, that were 40 cm long, 15 cm wide, and 30 cm tall. Each rat from a different group was allowed five minutes to make their fast way around the maze after being placed in one arm . Each rat was placed at random at the end of an arm, and it had eight minutes to explore the maze at its own pace. This was divided into two testing sessions of 2 minutes each , with each session ending until the rat reached the food reward or 8 minutes later. Ethanol (70%) was used to thoroughly clean the maze in between each animal in order to lessen smell cues.

Blood , tissue samples collection and histopathological examinations :

Each rat's hepatic portal vein was used to obtain blood samples, which were then transferred into dry, sterile centrifuge tubes. The plastic vial containing the serum was sealed and kept frozen at -20ºC **(Schermer, 1967)** . The brains of the dissected rats were removed, rinsed in saline, and cut in half in the sagittal plane. One half was fixed with 10% formalin for histological examination. The brain tissues were serially diluted with alcohol after being fixed for 24 hours in 10% formalin saline in order to

cause dehydration. Brain tissues were stained with hematoxylin and eosin (H and E) so they could be seen under a light microscope **(Grafström *et al.*, 2008)**. The cortex and hippocampus of the other half were removed, and the tissues were quickly frozen at -80 °C to get them ready for homogenization. For fifteen minutes, the homogenate was centrifuged at 3000 rpm and 4 °C. The supernatant was then separated, portioned equally, and refrigerated in an Eppendorf tube in preparation for the biochemical test. Brain tissue was utilized for the measurement of β-amyloid levels **(Olsson *et al.*, 2005)**, levels of gamma-aminobutyric acid (GABA) which were measured by **Lasley *et al.* (1984),** dopamine (DA) and serotonin (S.T.) were measured by **Sasa and Blank (1977),** acetylcholine esterase (AChE) and acetylcholine (ACH) were estimated by **Carageorgio *et al.* (2005) and Cheney *et al.* (1989)**, and norepinephrine was estimated by **Yoshitake *et al.* (2006)**. In serum, phosphorylated tau, and serum tau were determined according to **Shekhar *et al.* (2016)**. Superoxide dismutase (SOD) were evaluated according to **Nandi and Chatterjee (1988)**. **Giera *et al.* (2012)** identified malondialdehyde (MDA), while **Acharya *et al.* (1996)** identified tumor necrosis factor-α (TNF-α). The methods of **Tietz (1976) and Yound (1975)** were used to estimate the amounts of aspartate amino transferase (AST) and alanine amino transferase (ALT), respectively. Serum urea and creatinine were measured in accordance with **Patton and Crouch (1977) and Schirmeister (1964)**

Statically analysis:

One-way ANOVA was used to statistically evaluate the data using a computerized version of the COSTAT program. A one-way ANOVA test was used to assess the effects of different treatments; significance between groups was indicated at ($P \leq 0.05$) **Snedecor and Cochran (1967)**.

Results and discussion

The most important phenolic compounds found in wormwood ethanolic extract (WEE)

Table 1 shows the most important phenolic compounds found in wormwood. As shown in Table 1, the most abundant

compounds in wormwood are gallic acid, chlorogenic acid, catechin , coffeic acid , rutin , ellagic acid , vanillin, naringenin , querectin and cinnamic acid .

These results from the analysis of wormwood were in agreement with **Canadanovic-Brunet *et al*. (2005)** who found that the high concentration of phytochemicals found in wormwood, including total flavonoids and phenolic compounds, may contribute to its antioxidative activity.

Furthermore, wormwood has been shown to contain organic and phenolic acids, including coumaric, syringic, vanillic, salicylic and chlorogenic acids. Wormwood may also contain other substances such as quercetin, apigenin, flavone, catechin, myristin, and artemetin, all of which have the ability to suppress free radicals (**Bora and Sharma, 2010 and Amin *et al*., 2022)**.

The presence of flavonoids (quercetin and rutin) and phenolic substances (coumaric acid, gallic acid, syringic acid, vanillic acid, chlorogenic acid and salicylic acid) in wormwood demonstrated the plant's ability to prevent oxidative stress-related disorders **(Craciunescu et al., 2012 and Ali and Abbasi, 2013)**.

According to the previous analysis, wormwood contains chlorogenic and rosmarinic acids. The characteristics of chlorogenic acid include neuroprotection, antioxidant and anti-inflammatory effects **(Bezerra *et al*., 2024)** so wormwood can be used as therapeutic agents or adjuncts in the treatment of sporadic AD due to the neuroprotective properties of chlorogenic acids. According to **Noguchi-Shinohara *et al*. (2020)**, rosmarinic acid has antiviral, antibacterial, anti-inflammatory, anticancer, and neuroprotective activities.

Table (1): The most important phenolic compounds found in wormwood ethanolic extract (WEE)

Active compounds	Conc. (µg/g)
Gallic acid	4246.33
Chlorogenic acid	1736.76
Catechin	1352.22
Methyl gallate	23.98
Coffeic acid	374.80

Active compounds	Conc. (µg/g)
Syringic acid	104.44
Rutin	232.24
Ellagic acid	83.67
Coumaric acid	14.52
Vanillin	381.68
Ferulic acid	9.80
Naringenin	241.22
Rosmarinic acid	16.18
Daidzein	3.19
Querectin	95.94
Cinnamic acid	52.25
Hesperetin	12.95

Effect of wormwood ethanolic extract (WWE) on feed intake (FI), feed efficiency ratio (FER) and body weight gain (BWG) of rats with impaired memory

The impact of wormwood ethanolic extract (WWE) on feed intake (FI), feed efficiency ratio (FER) and body weight gain (BWG) of rats with impaired memory is displayed in Table 2. The results of the table demonstrated that the $AlCl_3$ treated rats showed significantly ($p \leq 0.05$) lower FI (-57.79%), FER (-34.5%) and BWG (-72.11%) compared to the control negative group. On the other hand, values of FI, FER and BWG of rats suffering from impaired memory were significantly ($p \leq 0.05$) increased after receiving WWE (50, 100, and 150 mg/kg BW) for 28 days. The percentage of increases reached 41.96, 66.26 and 95.80% ,33.33, 41.93 and 47.31%, and 87.93, 134.48 and 187.06 % of the control positive group, respectively. It was found that the rate of improvement in FI, FER, and BWG increases with the increase in the dose of wormwood given.

These findings are in line with those of **Bekhedda *et al*. (2020) and Hawash *et al*. (2023)**, who discovered that $AlCl_3$ significantly reduced the rats' BWG, FI, and FER values. This is because aluminum compounds impair gastrointestinal motility in both humans and rats and hinder stomach emptying. The metal's anorectic effect, which prevents serotonin and dopamine from being produced, is another reason for it. These two neurotransmitters play a key role in controlling appetite and the

perception of fullness. Furthermore, **Karami *et al*.'s (2023)** research demonstrated that oxidative stress caused by damage and increased intracellular reactive oxygen species (ROS) production could be the cause of this decrease in weight growth, which could then result in anorexia or decreased food absorption.

According to **Beigh *et al*. (2019) and El Deen (2022),** supplementing with wormwood herb increases growth rate in terms of feed intake, weight gains, and body measurements. The pre-treatment with wormwood aqueous extract demonstrated a preventative effect against acute liver damage caused by aluminum oxide-containing nanoparticles (Al_2O_3 NPs), possibly as a result of enhanced antioxidant capacity, which enhances food intake, digestion, metabolism, and appetite. As a result, rats given wormwood extract showed a rise in weight **(Karami *et al*., 2023)**.

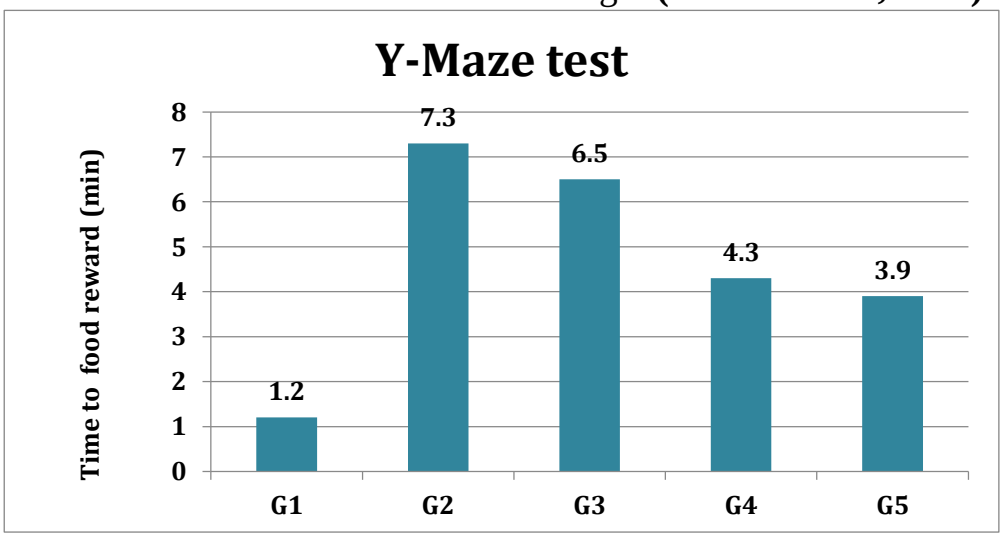


Fig.(1): Effect of wormwood ethanolic extract (WWE) on Y-Maze test of rats with impaired memory

The Y-maze test is frequently used to assess the health of the hippocampus of rats . The results of this study showed that all treated groups performed poorly compared to the negative group. The group that took oral wormwood extract (150 mg / kg BW) was better than the other treatment groups. These outcomes correspond with **Bari et al. (2022)** who reported that the Y-maze test demonstrated that wormwood improves memory loss, increases acetylcholine levels and reduces oxidative stress in rats.

Table (2): Effect of wormwood ethanolic extract (WWE) on feed intake (FI), feed efficiency ratio (FER) and body weight gain (BWG) of rats with impaired memory.

Groups	FI (g/ day)		FER		BWG (g/ day)	
	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	% of change
G1 (-)	29.36 ± 2.31^{a}	-	0.142 ± 0.006^{a}	-	4.16±0.152^{a}	-
G2 (+)	12.39 ± 0.844^{d}	-57.79	0.093 ± 0.007^{b}	- 34.5	1.16± 0.152^{e}	-72.11
G3(WEE 50 mg / kg BW)	17.59 ± 1.49^{c}	41.96	0.124± 0 .022^{ab}	33.33	2.18± 0.320^{d}	87.93
G4(WEE 100 mg/ kg BW)	20.6 ± 1.67^{c}	66.26	0.132 ± 0.021^{a}	41.93	2.72± 0.21^{c}	134.48
G5(WEE 150 mg / kg BW)	24.26 ± 2.07^{b}	95.80	0.137 ± 0.021^{a}	47.31	3.33±0.242^{b}	187.06
LSD	3.34	-----	0.031	----	0.408	-----

Each value is expressed as mean ± SD. Means under the same column with different superscript letters are significantly different ($p \leq 0.05$). G1, normal group; G2, positive group; G3, G4 and G5, groups treated with 50,100 and 150 mg/ kg of WWE, respectively. WWE, wormwood ethanolic extract; FI, feed intake; FER, feed efficiency ratio; BWG, body weight gain.

Effect of wormwood ethanolic extract (WWE) on total tau (T-tau), phospho - tau (P-tau) and beta- amyloid (B.A) proteins of rats with impaired memory

Table 3 shows the effect of wormwood ethanolic extract (WWE) on the proteins total tau (T-tau), phospho-tau (P-tau) and beta-amyloid (B.A.) in rats with memory impairment. Rats treated with $AlCl_3$ had significantly ($p \leq 0.05$) higher levels of T-tau (110.40 %), P-tau (122%), and B.A. (646.48%) in comparison to normal rats. By contrast, feeding rats on WWE (50,100, and 150 mg/kg BW) for 28 days resulted in a significantly ($p \leq 0.05$) lower

T-tau, P-tau, and B.A compared to positive group by -23.24, -30.91 and - 43.75%, -19.46, -29.29 and -48.14%, and -34.47, -50.67, and -76.26%, respectively. It was discovered that as the dosage is increased, the rate of improvement in T-tau, P-tau and B.A improves.

These results are consistent with those of **Li and Wang (2024),** who found that rats with AD caused by $AlCl_3$ exhibited a substantial increase in acetylcholinesterase (ACHE) activity and an enhanced deposition of Amyloid β-Protein (Aβ1) peptides in their brain tissues. This suggests that cholinergic metabolism triggered by $AlCl_3$ may initiate the production of amyloid 1 beta fibrils in brain tissues, thereby exacerbating the circumstances associated with Alzheimer's disease. Al increases amyloid's permeability in the striatum and thalamus by preventing its proteolytic breakdown. This also improves amyloid's deposition and aggregation. Moreover, **Bryliński *et al*. (2023)** provided evidence that Al stimulates the phosphorylation and aggregation of phosphorylated proteins, including tau protein.

Since tau protein in its abnormally hyperphosphorylated state makes up the majority of the tau protein in neurofibrillary tangles, P-tau may be a more specific sign for AD than T-tau, which has been proposed as a generic marker of neurodegeneration **(Wattmo *et al*., 2020)**. The investigation's findings showed that WWE significantly reduced the levels of B.A, P-tau, and T-tau. These medicinal and preventative advantages of wormwood may be attributed to gallic acid and quercetin. Two polyphenol small molecules that are common in natural crops, quercetin and gallic acid, have been shown to inhibit the third microtubule-binding repeat (R3) fragment of human full-length tau in vitro as well as recombinant tau **(Tang *et al*., 2023)**. Currently, one potential treatment approach for tauopathies is to inhibit tau protein aggregation **(Tang *et al*., 2024)**.

Large amounts of caffeic and rosmarinic acids have been found in wormwood, according to research results pertaining to the identification of its add specific components. Research has demonstrated that pretreating PC12 cells (the PC12 cell line is capable of producing, releasing, and storing catecholamines like

norepinephrine and dopamine) with caffeic acid significantly reduced the amount of tau hyperphosphorylation caused by B.A and avoided the increase in intracellular calcium levels that B.A causes **(Sul *et al*., 2009)**. In the brains of hyperinsulinemic rats, caffeine reduced levels of B.A and P tau protein and suppressed the action of glycogen synthase kinase 3 (GSK3), one of the kinases that phosphorylates tau protein **(Chang *et al*., 2019)**. Additionally, caffeine shields PC12 cells from the neurotoxicity caused by amyloid-β **(Gulkari and Maske, 2020)**. The mechanism by which rosmarinic acid significantly lowers amyloid-induced memory loss is its capacity to downregulate tumor necrosis factor (TNF) and nuclear factor- kappa B (NF-κB) expressions. According to **Shekarchi *et al*. (2012)**, rosmarinic acid may reduce the hyperphosphorylation of the tau protein.

According to research by **Taheri *et al*. (2021)**, wormwood hydroalcoholic extract successfully reverses spatial memory deficits and lowers B.A plaque because of its antioxidant and anti-inflammatory properties. It might successfully eliminate the B.A plaque from the hippocampal CA1 area (the CA1 area is involved in input integration and the subiculum aids in memory retrieval).

Table (3): Effect of wormwood ethanolic extract (WWE) on total tau (T-tau), phospho - tau (P-tau) and beta- amyloid (B.A) proteins of rats with impaired memory.

Groups	T-tau (pg/ ml)		P-tau (pg/ ml)		B.A (pg/ mg)	
	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	% of change
G1 (-)	269.03 ± 1.65^{e}	-----	53.39 ± 2.83^{e}	---	150.1±1.94^{e}	-----
G2 (+)	566.06 ± 2.76^{a}	110.40	118.53 ± 1. 33^{a}	122	1120.48± 1.70^{a}	646.48
G3 (WWE 50 mg /kg BW)	434.50 ± 1.99^{b}	-23.24	95. 46 ± 2.15 ^{b}	-19.46	734.21± 2.97^{b}	-34.47
G4(WWE 100mg / kg BW)	391.09 ± 2.24^{c}	-30.91	83.81 ± 1.49^{c}	-29.29	552.64± 2.96^{c}	-50.67
G5 WWE 150 mg / kg BW	318.38 ± 1.63^{d}	-43.75	61.46 ± 2.31 ^{d}	-48.14	265.98±2.56^{d}	-76.26
LSD	3.81	-----	3.81	----	4.52	-----

Each value is expressed as mean ± SD. Means under the same column with different superscript letters are significantly different ($p \leq 0.05$). G1, normal group; G2, positive group ; G3, G4 and G5, groups treated (50,100 and 150 mg/ kg BW) of WWE, respectively. WWE, Wormwood Ethanolic Extract, T-tau, total tau; P-tau, phospho - tau; B.A, beta- amyloid.

Effect of wormwood ethanolic extract (WWE) on gamma aminobutyric acid (GABA), serotonin (ST) and dopamine (DA) of rats with impaired memory

Table 4 shows how wormwood ethanolic extract (WWE) affects the gamma aminobutyric acid (GABA), serotonin (ST) and dopamine (DA) of rats with impaired memory. Rats administered with $AlCl_3$ exhibited significantly ($p \leq 0.05$) decreased GABA (-79.04%), ST (-89.64%) and DA (-92.23%) compared to the normal rats. Conversely, after consuming WWE (50,100, and 150 mg/kg BW) for 28 days, the values of GABA , ST and DA of rats with poor memory were considerably ($p \leq 0.05$) increased compared to the positive group, the increases were 6, 152.88 and 250.92%, 213.22, 343.80 and 604.13% and 322.55, 662.4 and 872.9%, in that order. It was discovered that as the dose is increased, GABA, ST, and DA improve at a faster rate.

These results are consistent with those of other researchers **Ahmed *et al*. (2021)**, **Ogunlade *et al*. (2022)**, and **Hawash *et al*. (2023)** who found that $AlCl_3$ dramatically lowered GABA, ST, and DA. This could be because $AlCl_3$ exacerbated feelings of powerlessness and depression-like behavior. Reduced brain ST levels and hypofunction of the central serotonergic system are closely linked to depression **(Abbas *et al*., 2022)**. According to **Gonçalves and Silva (2007)**, GABA catabolism is increased by enzymatic activity when GABA concentration is decreased as a result of Al. The preferential degeneration of GABAergic neurons in response to exposure to Al may be another explanation.

Rats given WWE showed varying degrees of improvement in GABA, ST, and DA. This is made evident by **Ahangar *et al*. (2011)**, who found that wormwood extract exhibited antidepressant efficacy. The extract's potential combination of phytochemical compounds as well as mechanistic actions such as the inhibition of monoamine oxidase enzyme enzymes, the abrogation of depression, and selective ST reuptake inhibition may be responsible for these effects.

Gallic acid and quercetin are two of the most significant components in wormwood; gallic acid appears to be a promising antidepressant medication option for the management of emotional problems. Gallic acid appears to function in the

synaptic clefts of the central nervous system in two different ways by raising catecholamine and serotonin levels. This antidepressant-like effect also appears to be mediated by extra alpha adrenergic, serotonergic and dopaminergic receptors **(Can *et al*., 2017)**. Additionally, it has been discovered that quercetin and its derivatives, quercetin 4'-O-glucoside, have an antidepressant-like effect on mice. This effect may be attributed to the inhibition of monoamine oxidase A (MAO-A) activity, which prevents brain oxidative stress, and the restoration of serotonin levels **(Hossain *et al*.,2021 and Singh *et al*.,2021)**.

According to **Batiha *et al*. (2020)**, wormwood is thought to have brain-protective properties and to aid in the body's production of the antioxidant glutathione. It mentions that research on animals indicates wormwood may raise serotonin levels and have antidepressant properties. Furthermore, wormwood may help those with neurological conditions like Parkinson's or Alzheimer's since it may have ingredients that lessen delirium, disorientation and confusion **(Szopa *et al*., 2020)**.

Table (4): Effect of wormwood ethanolic extract (WWE) on gamma aminobutyric acid (GABA), serotonin (ST) and dopamine (DA) of rats with impaired memory

Groups	GABA (pg/ mg)		ST(ng/ mg)		DA(ng/ mg)	
	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	% of change
G1 (-)	686.29 ± 2.94^{a}	-----	11.68 ± 1.22^{a}	----	8.56±0.841^{a}	----
G2 (+)	143.84 ± 2.23^{e}	-79.04	1.21 ± 0.30^{d}	-89.64	0.665± 0.157^{d}	-92.23
G3 (WWE 50 mg /kg BW)	152.48 ± 2.50^{d}	6	3.79 ± 1 .23^{c}	213.22	2. 81± 1.13^{c}	322.55
G4(WWE 100mg / kg BW)	363.75 ± 2.15^{c}	152.88	5.37 ± 0.946^{c}	343.80	5.07± 1.11^{b}	662.4
G5 WWE 150 mg/ kg BW	504.77 ±1.68^{b}	250.92	8.52 ± 0.903^{b}	604.13	6.47±1.48^{b}	872.9
LSD	4.254	-----	1.78	----	1.90	-----

Each value is expressed as mean ± SD. Means under the same column with different superscript letters are significantly different ($p \leq 0.05$). G1, normal group; G2, positive group; G3, G4 and G5, groups treated with (50,100 and150) mg/ kg BW of WWE, respectively. WWE, wormwood Ethanolic Extract; GABA, gamma aminobutyric acid; ST, serotonin; DA, dopamine

Effect of wormwood ethanolic extract (WWE) on Norepinephrine (N. EP), acetylcholine (ACH) and acetylcholine esterase (ACHE) of rats with impaired memory

Table 5 displays the impact of WWE intervention on norepinephrine (N. EP) , acetylcholine (ACH) , and acetylcholine esterase (ACHE) in rats with memory impairment. Our positive group showed a considerable ($p \leq 0.05$) decrease in N. EP (-90.69%) and ACH (-69.48%) as compared to normal rats. Rats with poor memory showed significant ($p \leq 0.05$) increases in their N. EP and ACH values after taking WWE (50, 100, and 150 mg/kg BW) for 28 days, as compared to the positive group. The increases were 251.9, 429.39 640.92% and 48.07, 115.07 and 124.07%, in that sequence. In contrast, control positive group showed a considerably ($p \leq 0.05$) higher ACHE (246.01%) than the normal rats .The ACHE values of rats with poor memory were significantly ($p \leq 0.05$) lower than those of the positive group after taking WWE (50, 100, and 150 mg/kg BW) for 28 days. The decreases were -25.04, -44.02 and 57.44% in that order. Group 5 achieved the best result.

These findings concur with those of **Xiu *et al*. (2014)**, who demonstrated that $AlCl_3$ reduced the amount of N. EP in the hypothalamus. This could be because $AlCl_3$ inhibits N. EP 's release and/or uptake across the presynaptic membrane, which causes N. EP levels in the hypothalamus to decrease and those in the serum to increase. **Kaushik *et al*. (2018)** further verified that a major contributing factor to cognitive deficits in Alzheimer's disease is the loss of cholinergic neurotransmitters brought on by AChE's continuous activity. The same conclusion was drawn by **Hawash *et al*. (2023)** who found that the positive control group had higher levels of ACHE and lower levels of ACH after oral administration of $AlCl_3$ than the negative control group.

Rats given ethanolic wormwood extract showed varying degrees of decreases in ACHE and increases in N. EP and ACH levels. **Kharoubi *et al*. (2011)** provide clear evidence that administering plant extract following cessation of poisoning

resulted in the restoration of enzymatic activity (ACHE and MAO) and markedly decreased thiobarbituric acid reactive substances(TBARS) values in the different cerebral areas when compared to the Pb groups. This extract's preventive efficacy can be attributed to its chelating ability and/or antioxidant action, which is predominantly caused by the action of sulfhydryl groups. These findings support the notion that naturally occurring substances high in antioxidants significantly increase enzyme function and lessen oxidative stress **(Ahamed and Siddiqui, 2007)**.

Wormwood can also restore cognitive impairment by modulating neurotransmitter and neuromodulator activity **(Kang *et al*., 2016)**.

It has been demonstrated that wormwood ethanol extract exhibits anticholinesterase activity, protects against lead-induced neurotoxicity, and modifies rat behavior by bringing monoamine oxidase (MAO) and AChE enzyme levels back to almost normal. In mice, wormwood dramatically enhanced cognitive performance and improved brain functions by lowering oxidative stress and releasing molecules related to inflammation and apoptosis **(Zhao *et al*., 2020)**.

Table (5): Effect of wormwood ethanolic extract (WWE) on Norepinephrine (N. EP), acetylcholine (ACH) and acetylcholine esterase (ACHE) of rats with impaired memory

Groups	N.EP (ng/ mg)		ACH (pg/ mg)		ACHE (pg/ mg)	
	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	% of change
G1 (-)	29.55 ± 1.97^{a}	-----	735.99± 2.18^{a}	----	130.67±2.49^{e}	-----
G2 (+)	2.75 ± 0.45^{e}	- 90.69	224.57 ± 2.30^{e}	-69.48	452. 14± 2.84^{a}	246.01
G3 (WWE 50mg / kg BW)	9.70 ± 1.36^{d}	251.9	332.54 ± 1 .74^{d}	48.07	338. 89± 1.74^{b}	-25.04
G4(WWE 100mg/ kg BW)	14.59 ± 1.92^{c}	429.39	482.99 ± 1.66^{c}	115.07	253.08± 1.68^{c}	-44.02
G5 WWE 150 mg /kg BW	20.42 ±1.56^{b}	640.92	503.20 ± 0.907^{b}	124.07	192. 39±2.34^{d}	-57.44
LSD	2.83	-----	3.324	----	4.11	-----

Each value is expressed as mean ± SD. Means under the same column with different superscript letters are significantly different ($p \leq 0.05$). G1, normal group; G2, positive group; G3, G4 and G5, groups treated with (50,100 and150) mg / kg BW of WWE, respectively. WWE, Wormwood Ethanolic Extract**,** N.EP, Norepinephrine; ACH, acetylcholine; ACHE, acetylcholine esterase.

Effect of wormwood ethanolic extract (WWE) on malondialdehyde (MDA), superoxide dismutase (SOD) and tumor necrosis factor alpha (TNF-α) of rats with impaired memory

Table 6 shows the effects of wormwood ethanolic extract (WWE) intervention on malondialdehyde (MDA), superoxide dismutase (SOD) and tumor necrosis factor alpha (TNF-α) in rats with memory impairment. In comparison to the control negative group, rats treated with $AlCl_3$ exhibited a substantial ($p \leq 0.05$) decrease in SOD (- 80.98%), as well as a significant increase in malondialdehyde (782.27%) and tumor necrosis factor (369.96%). On the other hand, after consuming WWE (50, 100, and 150 mg/kg BW) for 28 days, rats with poor memory had significant ($p \leq 0.05$) increases in their SOD values in contrast to the positive group. In that order, the increases were 114.02, 254.71, and 337.79%. Also, when rats with poor memory took WWE (50, 100, and 150 mg/kg BW) for 28 days, their MDA and TNF values were considerably ($p \leq 0.05$) lower than those of the positive group. The decreases were, in that order, -27.27, -68.03and -80.20% and -2.44, -41.59 and-61.23%. The best result was achieved by group 5.

These results are consistent with those of previous studies that found that $AlCl_3$-induced Alzheimer rats possessed noticeably greater levels of the inflammatory cytokines IL-6, IL-1β and TNF-α. This indicates that oxidative stress is involved, as is the subsequent induction of cellular damage that may set off the production of inflammatory cytokines, which in turn cause damage to tissue and organs through the induction of immune activation, T-cell and B-cell hyperactivity, and the development of autoantibodies **(Umare *et al*., 2014)**. According to **Bryliński *et al*. (2023)**, aluminum is thought to be a proinflammatory and proapoptotic agent that upregulates a number of cytokines in different organs, including interleukin-1β and tumor necrosis factor α (TNFα). Furthermore, the outcomes are consistent with those of **Milnerowicz *et al*. (2015)**, who found that exposure to metals such as aluminum raised TNFα. When these cytokines are overexpressed, leukocyte recruitment is prompted, which

enhances the release of cytokines that promote inflammation and heightens the inflammatory reaction.

Because of its lipophilic properties, $AlCl_3$ broke down blood-brain barrier tight junctions, penetrated brain tissues, and significantly ($p < 0.05$) damaged the cellular membranes of neurons, astrocytes, and glial cells as well as the brain vasculature cells in vivo. This resulted in lipid peroxidation, which increased the production of MDA and NO because $AlCl_3$ can produce reactive oxygen species **(Auti and Kulkarni, 2019 and Lu *et al*., 2020).**

Rats fed wormwood extract showed increases in SOD and varied degrees of reductions in MDA and TNF levels. According to research by **Bora and Sharma (2010)**, extracts from wormwood herb may be able to prevent stroke by lowering oxidative stress in behavioral disorders and the degree of brain damage.

Additionally, according to **Bora and Sharma (2011),** wormwood has been suggested in the past to have protective properties against oxidative stress in the brain. A decrease in lipid peroxidation linked to the restoration of natural antioxidant enzymes like SOD has been used to show that wormwood methanolic extract has neuroprotective qualities. The synergy of the chemicals in the plant controls wormwood's antioxidant activity **(Gonzalez-Coloma *et al*., 2012)**. Wormwood (50 mg/kg) treatment may decrease oxidative damage by raising total thiol levels in the serum **(Mohammadian *et al*., 2016).**

The secondary metabolites of wormwood, such as flavonoids and sesquiterpene-type substances, and their involvement in the suppression of inflammatory regulators such as ST, prostaglandins, histamine, and bradykinins may be responsible for the extracts' anti-inflammatory characteristics **(Hadi *et al*., 2014)** and via preventing the expression of pro-inflammatory mediators such as TNF-α, cyclooxygenase-2 (COX-2), prostaglandin E-2 (PGE2), inducible nitric oxide synthase (iNOS), factor nuclear factor-kappa-B (NF-κB), and cyclooxygenase-2 (COX-2) **(Batiha *et al*., 2020).**

Wormwood's phenolic components restore endogenous antioxidants, such as glutathione (GSH) and superoxide dismutase

(SOD), and decrease lipid peroxidation, or thiobarbituric acid-reactive substances (TBARS) **(Sharifi-Rad *et al*., 2022)**.

Twelve primary common peaks were identified from the UPLC fingerprints of wormwood extracts, which showed strong anti-inflammatory and antioxidant properties to various degrees in different batches. By using correlation analysis to identify the most promising active compounds, P5 (isochlorogenic acid A), P6 (isochlorogenic acid C) and P3 (chlorogenic acid), were further verified for their exceptional anti-inflammatory activities **(Wubuli *et al*., 2024).**

Table(6):Effect of wormwood ethanolic extract (WWE) on malondialdehyde (MDA), superoxide dismutase (SOD) and tumor necrosis factor alpha (TNF-α) of rats with impaired memory

Groups	SOD (U/ L)		MDA (nmol / ml)		TNF-α (pg/ ml)	
	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	% of change
G1 (-)	183.42 ± 0.99^{a}	---	0.773± 0.121^{c}	----	34.43± 2.56^{e}	-----
G2 (+)	34.87 ± 2.62^{e}	- 80.98	6.82 ± 1.90^{a}	782.27	161. 81± 2.36^{a}	369.96
G3 (WWE 50 mg / kg BW)	74.63 ± 1.44^{d}	114.02	4.96 ± 1 .08^{b}	-27.27	157. 86± 1.53^{b}	-2.44
G4 (WWE 100 mg / kg BW)	123.96 ± 1.87^{c}	254.71	2.18 ± 0.32^{c}	-68.03	94.5± 2.28^{c}	-41.59
G5 (WWE 150 mg / kg BW)	152.66 ±2.39^{b}	337.79	1.35 ± 0.50^{c}	-80.20	62. 73±1.59^{d}	-61.23
LSD	3.56	-----	1.84	----	3.84	-----

Each value is expressed as mean ± SD. Means under the same column with different superscript letters are significantly different (p≤ 0.05). G1, normal group; G2, positive group; G3, G4 and G5, groups treated with (50,100 and 150 mg/ kg BW) of WWE, respectively. WWE, wormwood ethanolic extract, SOD, superoxide dismutase; MDA, malondialdehyde; TNF-α, tumor necrosis factor alpha.

Effect of wormwood ethanolic extract (WWE) on some kidney functions (urea and creatinine) and some liver enzymes (ALT and AST) of rats with impaired memory

The impact of wormwood ethanolic extract (WWE) on urea, creatinine, ALT, and AST in rats with memory impairment is displayed in Table 7. The group treated with $AlCl_3$ had higher values of urea (68.40%), creatinine (225%), AST (109.28), and ALT (181.96%) compared to normal rats. Rats fed on WWE (50, 100, and 150 mg/kg BW)for 28 days had significantly ($p \leq 0.05$) lower urea, creatinine, ALT, and AST by -6.79, -12.99 and -19.17%, -5.288, -20.67 and -31.25 %, -15.25,- 18.42 and -30.37%

and -3.34, -2538 and -42.85%, respectively compared to control positive group. It was found that the rate of improvement in urea, creatinine, ALT, and AST increases with dosage of wormwood.

These findings concur with those of **Abdel-Wahab (2012)**, who suggested that cellular deterioration and modifications in the permeability of hepatic cell membranes could be the cause of increased liver enzymes in the plasma following $AlC1_3$ treatment.

According to **Mokrane *et al*. (2020)**, exposure to $AlCl_3$ might cause gravely detrimental alterations in the redox status and other biochemical properties of liver and kidney tissues. According to **Geyikoglu *et al*. (2013)**, alterations in serum urea levels could be connected to problems with metabolism. Furthermore, an increase in serum AST, ALT, and ALP activities suggests that liver dysfunction may be the cause of the elevated urea levels in the plasma of $AlCl_3$-treated mice **(Afolabi *et al*., 2023)**.

The results of the study demonstrated that WWE considerably ($p \leq 0.05$) lowered the levels of AST, ALT, creatinine, and urea. These therapeutic and prophylactic benefits may be linked to the presence of flavonoids and polyphenols, which have potent hepatoprotective and antioxidant properties and inhibit the production of harmful metabolites of $AlCl_3$ **(Amat *et al*., 2010)**. Because of its antioxidative, anti-inflammatory, and anti-apoptotic properties against a variety of liver illnesses, quercetin (one of the active compounds in wormwood) has been described as a promising hepatoprotective chemical **(Li *et al*., 2018)**. The results are in line with previous studies that discovered quercetin to be hepatoprotective against liver damage caused by tertiary butyl hydroperoxide (t-BHP) **(Salem and Kharshoum, 2016)**.

Wormwood hydroalcoholic extract improves hepatic function and reduces markers of oxidative stress while consistently stimulating and maintaining the structural form of the hepatocellular membrane, which lowers blood AST and ALT activity. According to **Mohammadian *et al*. (2016)**, there are three possible hepatoprotective mechanisms: calcium channel blocking, free radical scavenging activity, and reduction of the liver microsomal drug-metabolizing enzyme.

Being the most effective methanolic extract, ethyl acetate extract of wormwood may have antioxidant properties that may prevent renal and liver damage brought on by diclofenac in rats. Wormwood was shown to lower increased blood levels of urea, creatinine, ALT, AST, and ALP; however, the methanol extract was more successful, with a daily dose of 200 mg/kg **(Sagástegui *et al*., 2020)**.

Shikimic acid is a naturally occurring phenolic compound with antioxidant properties **(Al-Malki 2019)**. According to **Lee *et al*. (2020)**, shikimic acid that was extracted from wormwood had renoprotective benefits, as evidenced by a decrease in high serum creatinine levels and by the histological healing of kidneys in mice who had suffered renal damage from cisplatin. Wormwood was found to considerably lower increased serum levels of kidney functions (creatinine, urea, and uric acid) and liver functions (ALT, AST, ALP, albumin, and total bilirubin) **(El Deen, 2022)**.

Table (7): Effect of wormwood ethanolic extract (WWE) on some kidney functions (urea and creatinine) and some liver enzymes (ALT and AST) of rats with impaired memory

Groups	Urea(mg/ dl)		Creatinine (mg /dl)		ALT(U/ L)		AST (U/ L)	
	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	% of change	Mean ± SD	of % change
G1 (-)	29.97 ± 1.85^{d}	------	1.28± 0.215^{d}	------	57.96± 2.62^{d}	------	65.49± 1.95^{e}	-------
G2 (+)	50.47 ± 1.54^{a}	68.40	4.16 ± 0.305^{a}	225	121. 3± 2.61^{a}	109. 28	184. 66± 2.31^{a}	181.96
G3 (WWE 50 mg/kg BW)	47.04 ± 2.43^{b}	-6.79	3.94 ± 0 .148^{a}	-5.288	102. 79± 2.12^{b}	-15.25	178. 49± 2.27^{b}	-3.34
G4(WWE 100 mg/kg BW	43. 91 ± 1.45^{bc}	-12.99	3.3 ± 0.264^{b}	-20.67	98.95± 4.14^{b}	-18.42	137.78± 3.10^{c}	-25.38
G5 (WWE 150 mg/kg BW)	40.79 ±1.28^{c}	-19.17	2.86 ± 0.152^{c}	-31.25	84. 46± 1.99^{c}	-30.37	105.52 ±2.59^{d}	-42.85
LSD	3.20	-----	0.410	----	5.10	-----	4.51	

Each value is expressed as mean ± SD. Means under the same column with different superscript letters are significantly different ($p \leq 0.05$). G1, normal group; G2, positive group; G3, G4 and G5, groups treated with 50,100 and 150 mg / kg BW of WWE, respectively. WWE, wormwood ethanolic extract, ALT, Alanine transaminase; AST, Aspartate transferase

Histopathological examination of the cerebral cortex:

Histopathological examination of cerebral cortex of rats from group 1 exhibited the normal histological architecture (photos 1). In contrariwise, cerebral cortex of rats from group 2 showed histopathological lesions demonstrated as necrosis and pyknosis of neurons with formation of flame like neurofibrillary tangles (photo 2). Meanwhile, cerebral cortex of rats from group 3 revealed degeneration of some neurons and neuronophagia (photo 3). Furthermore, cerebral cortex of rats from group 4 described only degeneration of some neurons (photo 4). On the other hand, cerebral cortex of rats from group 5 showed slight cellular edema and degeneration of some neurons (photo 5).

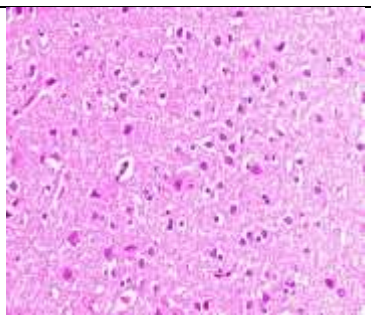


Photo (1): Cerebral cortex of rat from group 1 (control negative group) showing normal histological architecture (H & E X 400).

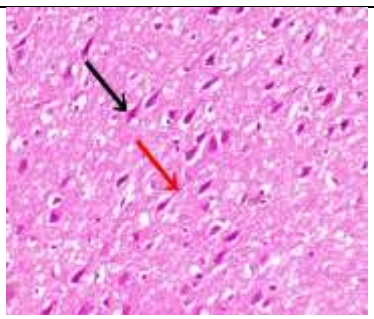


Photo (2): Cerebral cortex of rat from group 2 (positive control group) showing necrosis and pyknosis of neurons (black arrow) with formation of flame like neurofibrillary tangles (red arrow) (H & E X 400).

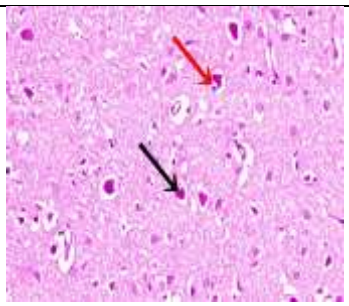


Photo (3): Cerebral cortex of rat from group 3 (WWE 50 mg/kg BW) showing degeneration of some neurons (black arrow) and neuronophagia (red arrow) (H & E X 400).

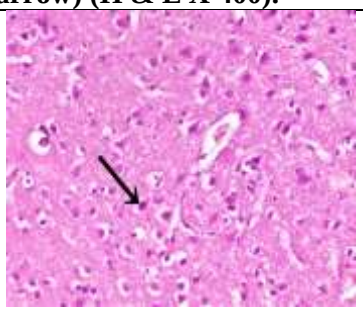


Photo (4): Cerebral cortex of rat from group 4 (WWE 100 mg/kg BW) showing degeneration of some neurons (black arrow) (H & E X 400).

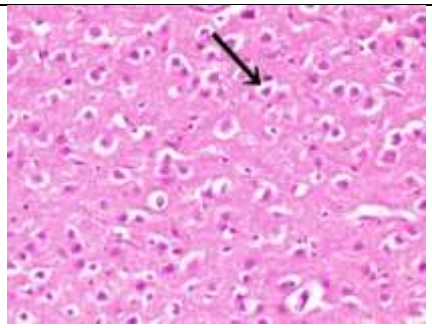


Photo (5): Cerebral cortex of rat from group 5 (WWE 150 mg/kg BW) showing slight cellular edema (black arrow) (H & E X 400).

This result was in line with was consistent with the findings of **Liaquat *et al*. (2019)**, who observed that the cerebral cortex neurons in the rats intoxicated with $AlCl_3$ were irregularly shaped, loosely packed, and darkly stained. Furthermore, compared to the groups treated with aluminum chloride, the histological investigation of the cerebral cortex, cerebellar area, and hippocampus of the negative control group showed normal neurons, according to **Hawash *et al*. (2023)**.

Conclusion :

The current study showed that $AlCl_3$ has severe neurotoxic effects, such as oxidative stress and memory impairment, that contribute to Alzheimer's disease. But because wormwood extract contains important components like gallic acid, catechin, para-hydroxybenzoic acid, cinnamic acid, syringic acid, ferulic acid, vanillic acid, chrysin, and protocatechuic acid, it also has the potential to be used therapeutically to prevent and treat Alzheimer's disease and memory impairment caused by $AlCl_3$. This is because it improves neurotransmitters, reduces inflammatory cytokines like TNF-α, B.A, P-tau, and T-tau, and increases the antioxidant capacity of SOD in enhancing memory impairment and shielding neurons from oxidative damage, gets rid of free radicals that cause neurodegenerative diseases, and ultimately provides a barrier to the brain against the effects of Alzheimer's.We draw the conclusion that wormwood extract therapy may be able to lessen or avoid the negative effects of aluminum buildup on the brain, particularly in those who are more susceptible to $AlCl_3$.

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دراسة تأثير المستخلص الإيثانولي للشيح ضد كلوريد الألومنيوم المسبب لضعف الذاكرة فى الفئران

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تهدف هذه الدراسة الى معرفة تأثير مستخلص الشيح ضد كلوريد الألومنيوم المسبب لضعف الذاكرة لدى الفئران. تم استخدام ثلاثين فأرًا ذكرًا تم تقسيمهم الى مجموعتين رئيسيتين. المجموعة الرئيسية الأولى (6 فئران) تم تغذيتها على الوجبة الأساسية فقط كمجموعة ضابطة سالبة، بينما المجموعة الرئيسية الثانية (24 فأر) تلقت كلوريد الألومنيوم (175 ملجم / كجم وزن الجسم)، مذابًا في الماء المقطر، عن طريق الفم طوال التجربة لإحداث الإجهاد التأكسدي وضعف الذاكرة وتم تقسيمها إلى أربع مجموعات فرعية على النحو التالي: المجموعه الثانيه عوملت كمجموعه ضابطة موجبه وتغذت على الوجبه الاساسية ، المجموعه الثالثة هى مجموعه مصابة وتتغذى على الوجبة الأساسية بالاضافة الى المستخلص الكحولى للشيح بجرعة 50 ملجم لكل كجم من وزن الفأر عن طريق الفم أما المجموعتين الرابعة والخامسة فتغذت علي الوجبة الأساسية و مستخلص الشيح بجرعات ١٠٠ و150 ملجم لكل كجم على التوالى عن طريق الفم باستخدام انبوب المعدة ، وتم تقدير محتوى الشيح من المواد الفعالة باستخدام كروماتوغرافيا السائل عالي الأداء، وفي نهاية التجربة تم ذبح الفئران وأخذ عينات من مصل الدم لإجراء بعض التحاليل مثل بعض انزيمات الكبد ووظائف الكلى والتاو الكلي والفوسفو تاو والسوبر أكسيد ديسميوتيز والمالونديالدهيد وعامل نخر الورم، كما تم استخراج المخ لتقدير الدوبامين والسيروتونين وحمض جاما أمينوبوتيريك وبيتا أميلويد والنورايبيرفيرين ، وكذلك لإجراء الفحص النسيجي المرضي كذلك تم عمل اختبار المتاهة. وأظهرت النتائج التأثير الإيجابي للشيح ، حيث ارتفعت مستويات الدوبامين والسيروتونين وحمض جاما أمينوبوتيريك والأستيل كولين والنورايبيرفيرين وسوبر أكسيد ديسميوتيز، بينما انخفضت مستويات التاو الكلي والفوسفوتاو والبيتا أميلويد والأستيل كولين استريز والمالونديالدهيد وعامل نخر الورم. كما تحسنت التقييمات البيولوجية مثل وزن الجسم والمتناول من الطعام ومعدل الاستفادة من الغذاء. ودعمت نتائج الفحص النسيجي للدماغ نتائج التحاليل الكيميائية. وأوصت الدراسة باستخدام نبات الشيح لتحسين الذاكرة وحالة الأكسدة في الجسم.

الكلمات المفتاحية: كلوريد الألومنيوم ، الأستيل كولين استريز، الإجهاد التأكسدي ، السمية العصبية