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Some Brain Dysfunctions induced by Acrylamide and possible Mitigating Role of Alpha-lipoic Acid in Adult Rats

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Abstract:

Background: It is well known that acrylamide is a neurotoxic that causes several pathological alterations in the central and peripheral nervous systems. As well as the ALA is a dual antioxidant and pro-inflammatory agent. Fifteen adult male rats were used in this study, and assigned randomly into three equal groups. Rats of the first group, control (CCG), were administered tab water for 35 days by gavage needle. In the second group, acrylamide group (ACG), rats were given acrylamide (ACR) 5mg/kg B.W by gavage needle for 35 days. In the third group, acrylamide plus alpha lipioc group (ALG), rats had acrylamide (ACR) 5mg/kg B.W. plus alpha lipioc acid (ALA) 100mg/kg B.W. for 35 days by gavaging as well

Aims: The current study was conducted to investigate the neurotoxic effect of the acrylamide (ACR) and the role of alpha lipioc acid (ALA) to ameliorate the ACR neurotoxicity.

R**esults**: At the end of the study, the behavioural testing was performed and brains of rats were harvested for histopathological examination. The results showed that the oral exposure to ACR induces impairment of rat behaviours, while treatment of ALA reduces such impairments. Moreover, histopathological examination of brain sections of the animals exposed to ACR shows microglial cells aggregation in one side of blood vessels in the brain parenchyma and inflammatory cells around and inside the congested blood vessels. Furtyhermore, proliferation of microglial cells with Alzheimer type II astrocyte were noticed as well. However, the brain sections of ALG administered rats showed a relatively less microglial activation and less inflammatory cells in the examined areas

Conclusions: Overall, alpha lipoic acid mitigated the brain oxidative stress and inflammation induced by acrylamide and restored the structure and normal function of the brains.

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Keyword: Keyword: Acrylamide, Alpha lipoic acid, Brain Dysfunction, Neurobahaviors

Introduction :

Acrylamide (ACR) is produced from food that is rich in carbohydrates and cooked with high temperature. Scientific attention has shed a light on ACR because there is growing concerns about the negative effects of its compounds on veterinary and human public health (Kenwood, 2022). At room temperature ACR is solid substance, melted on 85 $^{\circ}$C, which is the point when polymerization occur and production of polyacrylamide. ACR is water soluble and also it can be dissolved in acetone and alcohols as well (Bušová et al., 2020). ACR is also known as vinyl amide, acrylicamide, ethylene carboxamide, amide, propenamide, and propenoic acid (Roth, 2003). ACR is a significant chemical utilized in numerous industrial and scientific procedures, including the purification of water, the manufacturing of cosmetics, and gel electrophoresis (Kenwood, 2022). It is also yielded from tobacco smoke and foods that are rich in carbohydrates such as potatoes, coffee, and grains that cooked (frying, grilling, or baking) at extremely high temperatures (Luo et al., 2021).

In regard of ACR exposure, it was believed that exposure to ACR occurs partially from food or cigarette smoke and it occurred majorly at work. In addition, ACR polymers can be used as sewage and waste treatment additives, thickeners, flocculants, soil conditioners, increased oil recovery additives, and papermaking aids (Tepe et al., 2019).

Ingested ACR absorbed by digestive system and carried to the other tissues by the bloodstream, where it can interact with DNA, neurons, Hb, and vital enzymes. Ozturk and his team (2023) revealed that ACR exposure leads to nervous system impairments, which represented as skeletal muscle weakness and ataxia, irregular walk patterns anomalies, and peripheral loss of sensation. Furthermore, many pathological alterations were observed in the nervous system as a result of ACR exposure such as apoptosis, which is considered as predominant mechanism in ACR-exposed animals and humans (Ozturk et al., 2023).

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Alpha-lipoic acid (ALA) compound exist intracellularly especially in mitochondria, it is named as 1,2-dithiolane-3-pentanoic acid or thioctic acid (Toker, 2016). ALA is an organosulfur compound synthesized in minor quantities by most plants, animals, and human's cells (Ghibu et al., 2009). ALA produced in small amount inside animal and human body and it is adequate to produce the full action inside the cell. Thus, the dietary sources such as vegetables, fruits are very crucial to get ALA activity (Brufani et al., 2014).

ALA has antioxidant properties because it maintains, enhance the intrinsic antioxidant systems, and preserve products of them or cell accessibility (Shay et al., 2009). The antioxidant activity results from that ALA functioning as a crucial enhancer for many enzymes like pyruvate and a-ketoglutarate dehydrogenase complexes; moreover, it plays and important roles in connecting Kreb's cycle and glycolysis. It also has the ability to be a redox couple in minimal reduction levels in brain and other tissues and cross the blood–brain barrier (Packer et al., 2010). Several other important antioxidants such as glutathione, vitamin C, and vitamin E can be generated from ALA because it can act as an enzymatic cofactor (Maglione et al., 2015). Furthermore, ALA can be active in both the membrane and aqueous phases; and thus, it is usually referred as a universal antioxidant. In addition to facilitation of other antioxidants intracellularly, ALA can be free radical quenching and metal-chelating agent (Chen et al., 2012). Furthermore, it participates in glucose and lipid metabolism glucose and gene transcriptional management (Chen et al., 2012; Packer et al., 2010). Not apart from other tissue, ALA in brain act as antioxidant defender thus it protects neural tissue from oxidative stress that caused brain injury such as trauma and subarachnoid haemorrhage. Many researchers suggested that the neuroprotective effect of ALA may resulted from interfering with apoptosis in both caspase-dependent and caspase-independent manner (Castro et al., 2019).

Materials and Methods:

Equipment and instruments

Table (3-1) provides an illustration of the instruments and equipment utilized in the present study.

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Table (1). Instruments, equipment and Chemicals that were used in this study.

No	**Instrument / equipment /Chemicals**	**Company / Country**
1.	Light Microscope	CYAN / Belgium
2.	Microtome Rotary	Kedee / India
3.	Scope image Camera	MEJI / Japan
4.	Elevated plus-maze	Local Made / Iraq
5.	Barnes Maze	Local Made / Iraq
6.	Eosin Stain	Germany
7.	Formalin 10%	India
8.	Hematoxylin	Germany
9.	Ketamine	Malaysia
10.	Liquid Paraffin	Germany
11.	Acrylamide	Riedel-de Haën AG\England
12.	Paraffin Wax	Germany
13.	Alpha Lipioc acid	now/USA
14.	Xylazine	Egypt
15.	Oral Gavage Needle	Instech / USA

Animals and housing

In the present study fifteen mature male Westar rats were used. The ages of animals were 9–11 weeks, and their weights were between 170±20 grams. The rats were housed two weeks prior the experiments to be acclimatized with the new environment. Throughout the experimental trials, rats were kept in plastic cages (3 rats/cage) in a well-ventilated room at the house of laboratory animals of University of Baghdad, College of Veterinary Medicine. Moreover, standard rodent chow and tab

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water were freely accessible to all animals. The housing temperature was maintained at 23.2 °C and the light/dark cycle (12/12 hours) was fixed from 7:00 am to 7:00 pm.

Experimental design

Animals: Fifteen adult male rats were subjected to the experiments of this study. These rats were divided into three equal groups, ten rats per group and assigned as following:

1. Control group (CCG): Rats of this group were intubated with distilled water by gavage needle for 35 days.
2. ACR group (ACG): Animals in this group intubated with acrylamide 5mg/kg B.W. by gavage needle daily for 35 days (Ivanski et al., 2020).
3. ACR and Alpha lipioc acid (ALG) group: Rats in this group intubated with acrylamide 5mg/kg B.W. plus ALA 100mg/kg B.W. daily by gavage needle for 35 days.

Tissue collection

All experimental rats were anesthetized with intramuscular injections of ketamine (60 mg/kg B.W.) and xylazine (40 mg/kg B.W.), at the termination day of trial, then and they were decapitated to extract the whole brain. The left part of the brain was immersed in formalin (10%) and kept in plastic containers for routine histological examination (Humadi and Minnat, 2023).

Neurobehavioral tests

Behavioural study: Elevated plus maze and Barnes maze behavioural tasks were performed once at the end of experiment.

Elevated plus maze (EPM)

The EPM apparatus is a cross-shaped apparatus with arms 84 cm in length and 10 cm wide. The open arms have 2-centemetrs high walls whereas the closed arms have 17 cm high. The device elevated above the floor in high 90 cm from floor.

Each arm entry and duration are recorded and watched for 5–6 minutes. The time duration spent in each arms are used to examine and determine the anxiety behaviour, an increased open arm activity (duration or entries) is a sign of anti-anxiety behaviour. However, when animal spends more time in the closed arms might interpret as more anxiety. The task was done once, , hence there was no training or reward. For a period of five minutes, the animal was kept in the middle between arms and all visits between arms were timed using a timer. After each trial the platform cleaned with a 70% ethanol to prevent any olfactory cues.

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Barnes maze (BM)

The Barnes is circular platform with a diameter of 100 cm, it has many holes on the outer side of the circle. An escape box is positioned under one of these holes. The maze was balanced and installed 90 cm off the ground. The Barnes maze is effective in exploring the spatial memory by applying three phases of testing: habituation, learning (training), and memory. After each trial the platform cleaned with a 70% ethanol to prevent any olfactory cues.

Histopathology

Brain specimens from each group were stored in 10% formalin immediately following animal culling. After 24 h, the fixation solution was changed. 48 h later, the specimens washed with tap water for three to four hours in order to get rid of the formalin solution. Then, the spacemen underwent a number of steps to prepare the tissue for histological study and staining by haematoxylin and Eosin. These steps included drying, cleaning, embedding, blocking, cutting, and, lastly, staining (Bancroft et al., 2013).

Statistical analysis:

The data was analysed with Graph Pad Prism software version 9.1.0 (San Diego, CA, United States) using Two-way ANOVA and One-way ANOVA. Then the Tukey's test was used (*post hoc* testing of statistical significant differences). Number of animals is represented by (n). Data were presented as mean ± standard error (SE). Statistically significant was accepted when ($P<0.05$) (Kim, 2014).

Ethics Statement: Prior the study the ethical approval (Number 12614 at 23/11/2023) was obtained from the committee of animal care and use in the University of Baghdad / College of Veterinary Medicine, Baghdad / Iraq.

Results:

Effect of acrylamide and alpha-lipioc acid on rat's behaviours

Effect of acrylamide and alpha-lipioc on time spent in open arms of EPM:

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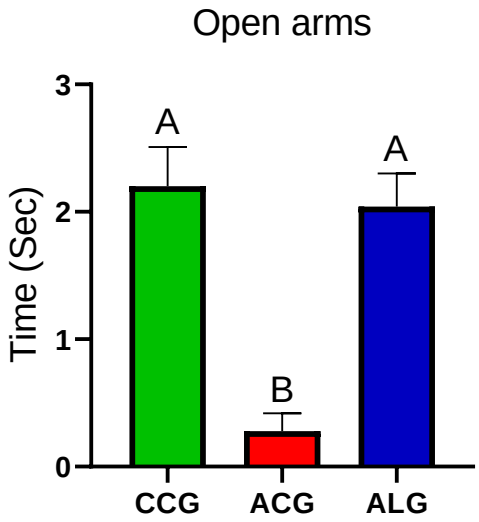

Figure 1: Effect of acrylamide and alpha-lipioc acid on time spent in open arms in anxiety test (EPM) in adult male rats.
***Uppercase letters indicate the significant differences between groups ($p < 0.05$).**
Data presented as mean ± SE

Rats exposure to acrylamide for 35 days led to anxiety like behaviours which representing by spending significantly ($P<0.05$) lower times in open arms rather than other arm in ACG group (0.28±0.06) comparing with CCG (2.20±0.13) and ALG (2.04±0.11), respectively (Figure 1). Whereas, there were no significant ($P>0.05$) differences observed between the control group (CCG) and ALA group in the recorded time that the rats spent in the open arms (Figure 1).

Effect of acrylamide and alpha-lipioc on time spent in closed arms of EPM:

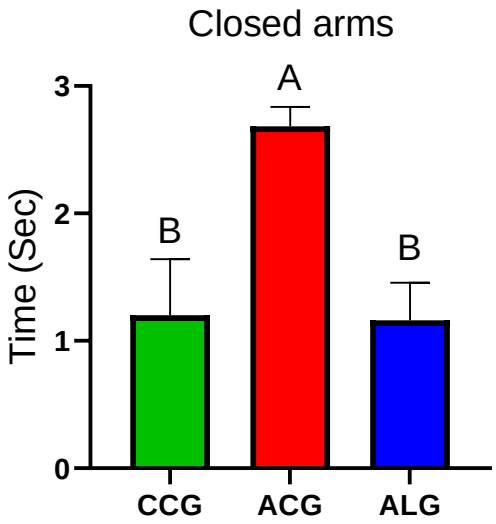

Figure 2: Effect of acrylamide and alpha-lipioc acid on time that the rats spent in the closed arms of anxiety test (EPM).
***Uppercase letters indicate the differences between groups.**
Data presented as mean ± SE

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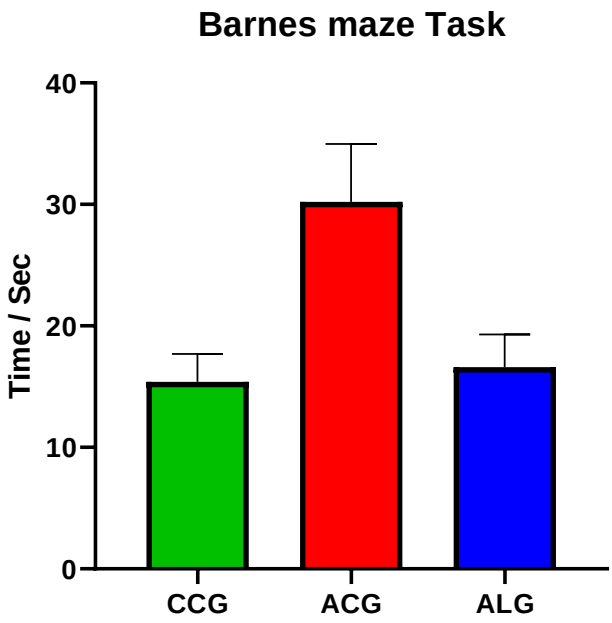
The times spent in closed arms by ACG rats (2.68±0.68) were significantly (P<0.05) higher than CCG group (1.20±0.60) and ALG group (1.16±0.16), at the termination of experiment (i.e., rats in ACG were highly anxious). However, treating rats which exposed to ACR by ALA brought the behaviours of rat close to the normal (Figure 2, see the green and blue columns).



igure 3: Effect of acrylamide and alpha-lipioc acid on spatial memory in adult male rats using Barns maze.
***Uppercase letters indicate the differences between groups.**
Data presented as mean ± SE
N=5 rats per group.

Learning and spatial memory of normal, ACR exposed, and ALA treated rats were examined using Barnes maze task at the end of the experiment (Figure 3). The rats that exposed to ACR were impaired significantly (p<0.05) in terms of spatial memory performance (15.40±1.03) when compared with the other groups. However, ALA daily treatment with 100 mg/kg for 35 days was significantly attenuating the spatial memory impairment in the ACR group caused by ACR (30.20±2.13). Moreover, there was non-significant differences (p>0.05) between CCG group (3.872±0.020) and ALA group (16.60±1.20) at the end of study (Figure 3).

Effect of Acrylamide and alpha-Lipioc acid on structure of rats' brains:

Histological sections that obtained from control animals show no clear lession in brain (Figure 4). Brain sections in of animals exposed to ACR show vacuolation and congested blood vessels in the ependymal cells layer and inflammatory cells around this layer. Moreover, microglial cells aggregation in one side of blood vessels in parenchyma (Figures 5 and 6). Another section of the

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same group shows oligodentrocytes attached to a necrotized neuron with proliferation of these oligodentrocytes, astrocyes and microglial cells. However, treating animal with ALA prevented ACR to exert any histological defect on brain histology (Figure 7).

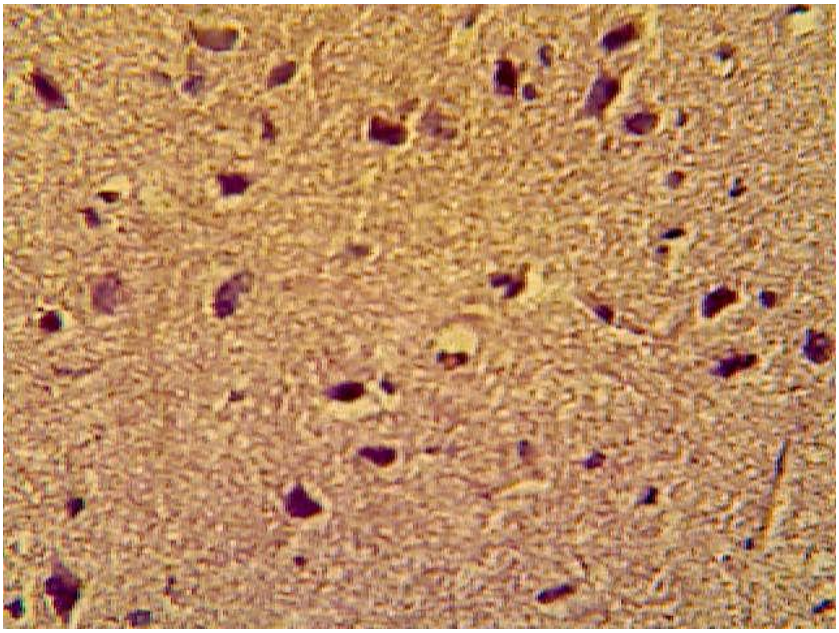

Figure 4: Representative image of cerebral tissue of control animal shows no clear lession (H & E stain 40X).

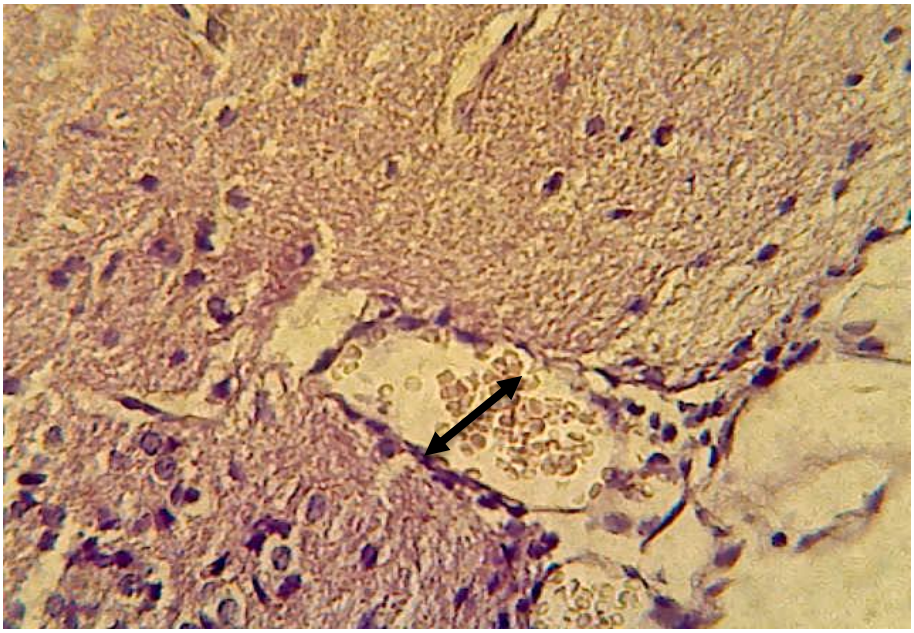

Figure 5: Representative image of cerebral tissue of animals treated with ACR shows inflammatory cells around and within a congested blood vessel (H & E stain 40X).

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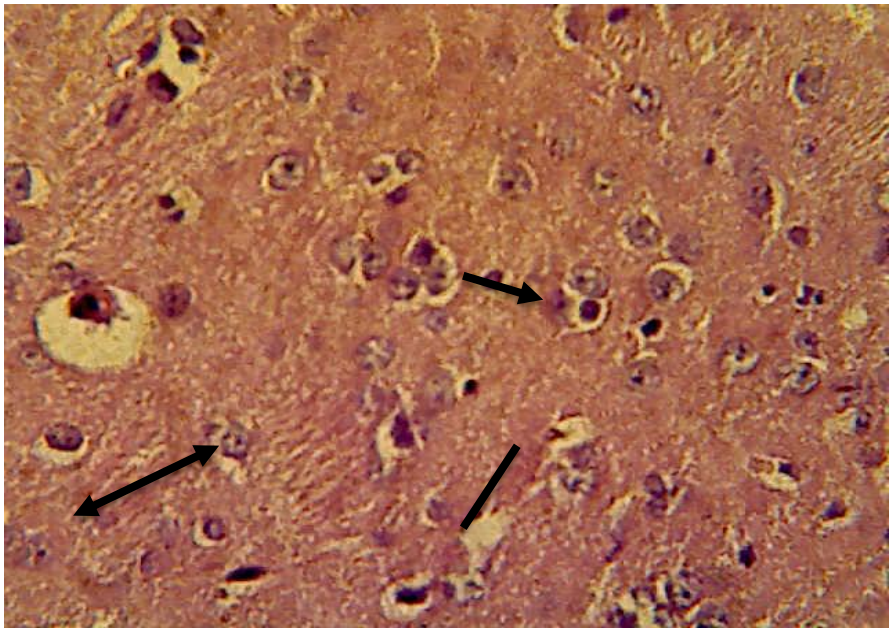

Figure 6: Representative image of cerebral tissue of animals treated with ACR shows oligodentrocytes attached to a necrotized neuron with proliferation of astrocyes , oligodentrocytes and microglia (H & E stain 40X).

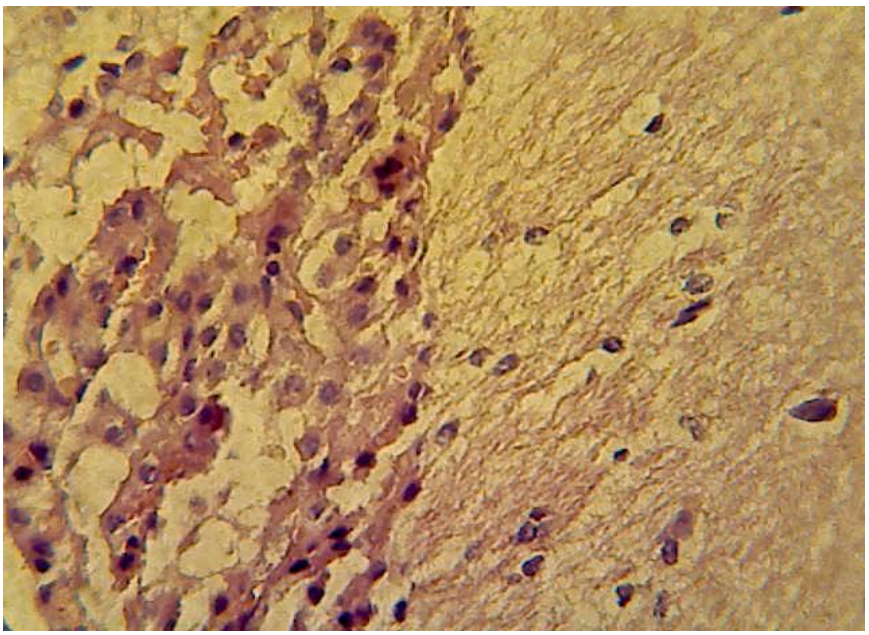

Figure 7: Representative image of cerebral tissue of rats treated with alpha lipoic acid shows no clear lesions (H & E stain 40X).

The current data indicate that the ACR affect certain brain function such as spatial memory and emotions in addition to alteration of the normal cellular architecture of the brain. However, treating

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animals with ALA could retrieve the normal brain functions and structure. It is a growing belief that there is association between ACR and neurodegenerative disorders, and there are a huge body of trails suggested the role of this substance and its role in neurodegenerative developments (Xu et al., 2024).

Any defect to the brain and spinal cord lead to movement disorders and behavioural impairments (Ghaith et al., 2024), which result from ACR exposure in rodents (Park et al., 2021). ACR is also affect the levels of some neurotransmitters such as dopamine and GABA (Gama Amino butyric Acid) levels as these neurotransmitters were diminished significantly as a result of ACR in rats leading to hypolocomotion (Tabeshpour et al., 2019). In addition, rats exposed to ACR displayed altered behavioral indices and decreased body mass. It has been shown that the exposure to ACR can lower GSH (Glutathione) levels and raise MDA (Malondialdehyde) levels, which elevates ROS (Guo et al., 2020). Moreover, it has been established that tissue illness resulted from induced oxidative stress (Ibrahim et al., 2019). Moreover, ACR can result in overproduction of inflammatory factors, oxidative stress and upregulated inflammatory responses then neuronal damage in the peripheral and central nervous system or even death (Goudarzi et al., 2019).

The effects of ACR on brain can be measured by several behavioural tasks such as geotaxis performance, Y- maze, and swimming test. ACR decreased locomotors activity in the Y maze test by decreasing the number of successful entries to consecutive arms (Khyoon and Abdulwahid, 2024).

Alphalipoic acid can penetrate the blood-brain barrier and it is naturally involved in pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (Ahmed et al., 2015). Moreover, it has been implemented in curing of many neuropathic-associated diseases such as diabetes because that the ALA has an ability to chelate iron and has very high safe profile as well as it is known to be global antioxidant (Goraca et al., 2011). Notably, the role of ALA as an antioxidant was clarified by Murad and Al-Okaily (2021) by maintaining the thiol levels and improve the tissue endogenous antioxidants by hydroxy radicals formation which supress antioxidants-containing sulphur (Murad and Al-Okaily, 2021). Surprisingly, results obtained from clinical studies revealed that the cognition of Alzheimer's patients showed some improvement by dietary supplement with ALA (Pei et al., 2023). Moreover, Zhang and colleagues (2024) demonstrated that ALA can ameliorate memory disorders by activation of BNIP3L-(Bcl-2/adenovirus E1B 19 kDa-interacting protein 3-like) mediated mitophagy which leads to improve activity of α-secretase of A disintegrin and metalloproteinase 10 (ADAM10) and elevation of their expression by activating BNIP3L-mediated mitophagy. This effect drives amyloid-β precursor protein (APP) towards a non-pathological pathway (Zhang et al., 2024). Additionally, ALA has been shown to induce a significant reduction in the oxidative damages by different pathways. For instance, You and his team (2025) claimed that ALA can improve the fission and mitophagy in mitochondria by factor HLH-30 (Hemophagocytic Lymphohistiocytosis) transcription. Moreover, this study suggested that ALA suppress the stress by motivate mitophagy and maintain the oxidative balance by insulin-like signalling peptide 19 (INS-19) (You et al., 2025).

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Conclusions:

Exposing rats to dietary acrylamide resulted in impaired cognition and learning, as well as alteration in the brain structure. However, administration of alpaha lipoic acid alongside with ACR can reduce the adverse effects and restore the normal function, and structure of the brain.

Recommendations:

Based on the results of this study, it is recommended that:

1- Investigating the effects of acrylamide on different body's systems.

2-Including different behavioral tests such as motor and sensory behavioural tests in the future studies.

Guidelines for Writing the Recommendations

- **Provide practical suggestions** or clinical applications based on your study's findings.
- May include **future research directions, policy implications, or clinical practice advice**.
- Keep recommendations **concise, specific, and directly tied to your results**.
- This section is **optional** and should only be included when appropriate.

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Authors Contributions: The author of this manuscript has designed, conducted the experiments, drafted and amended all versions of the manuscript and submitted it to this journal for publication.

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