The Possible Protective Roles of Garlic Oil and Rosemary Extract Against neuro and geno/toxicities of Acrylamide on Adult Male Albino Rats

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ABSTRACT

Background: Acrylamide (AA) is a chemical compound that is typically formed in starchy food products during high-temperature cooking. Itis a known lethal neurotoxin and genotoxin. **Aim**: The study was designed to illustrate gait change, biochemical and histopathological alterations besides the genotoxicity of AA on the brain of rats and the possible protection of both garlic oil and rosemary extract when administrated in co-treatment. **Materials &Methods:** Ninety adult male albino rats were divided into 6 groups (15 rats each); negative control, garlic oil group, rosemary extract group, AA group, AA+ garlic oil group, AA+ rosemary extract group. Rats were gavaged orally for six weeks. At the end of experimental period, the gait score of rats was evaluated then, blood samples and brains from the rats were obtained for biochemical, histological and cytogenetic evaluation. **Results:** AA exposed rats exhibited abnormal gait with significant decline in superoxide dismutase (SOD), catalase (CAT), acetylcholine esterase (AChE), deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein contents and an increase malondialdehyde (MDA) with histopathological changes of the brain tissues. Either treatment with garlic oil or rosemary extract improves these changes. **Conclusion**: AA is toxic to the brain of rats. Garlic oil or rosemary extract can ameliorate this toxicity. **Recommendation**: Strict control of AA consumption is urgently needed.

Key words: Acrylamide, garlic oil, rosemary extract, AChE, DNA, RNA.

I- INTRODUCTION

Acrylamide (AA) is a water-soluble vinyl monomer primarily used for the production of polymers that have broad applications in various chemical industries, e.g., water and waste-water management, ore processing, and dye synthesis. It is used extensively in the molecular laboratories for gel chromatograph **(Lebda et al., 2015)**.

Acrylamide is formed in high temperature cooking such as frying, roasting, but boiling and steaming do not typically form AA. It is found mainly in food made from plants such as potato products, grain products or coffee. AA does not form in dairy, meat or fish products **(Al-Sowayan, 2014)**.

Due to AA exposure, free radical and hydroperoxide generation was increased followed by lipid peroxidation (LPO) in animals **(Prasad, 2012)**. Generation of an excess of free radicals (reactive oxygen species [ROS]) may cause biological molecules oxidation, mainly LPO, enzymes oxidation, and DNA base oxidation. Free radicals are the main reason for the pathogenesis of many diseases such as neurodegeneration, diabetes, diseases of cardiovascular system, and neoplasm formation **(Dasari et al., 2018).**

In addition, the metabolic conversion of AA to glycinamide (GA) *via* an epoxidation reaction that is facilitated by cytochrome P450 (CYP2E1) is critical for the genotoxicity of AA, as it was reported to be a more potent mutagen including its ability to bind DNA causing genetic damage. Thus, human exposure to AA through their diet needs to be given

importance without negligence **(Ranjini and Manonmani, 2019).**

Acrylamide acts as a neurotoxic agent. Genetic mutations and cellular transformation were occurred after high levels of AA. AA molecules could reach every organ and tissue in the body and reacts with DNA, neurons, hemoglobin (HB) and enzymes **(Aboubakr et al., 2019)**.

Garlic (Allium sativum) is an important component of the Mediterranean diet and it is commonly used herb for both culinary (as a flavor enhancer) and medicinal purposes. Garlic is rich in bioactive organosulfur compounds such as allicin, alliin, diallyl disulfide, diallyl trisulfide, S-allyl cysteine and S-allyl○ mercaptocysteine (**Shalaby and Hammoda, 2015).**

The biological effects attributed to garlic include induction of endogenous antioxidant in rat tissue organs, stimulation of immune function, enhancement of detoxification of foreign compounds, antimicrobial and antioxidant effects and inhibition of lipid peroxidation (**Salem and Salem, 2016).**

Rosemary (*Rosmarinus officinalis*) is one of household herbs that contains a number of phytochemicals, including rosmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid, and the antioxidants carnosic acid **(Akela et al., 2018)**.

Extracts of rosemary leaves possess a variety of bioactivities in vitro including antioxidant, antibacterial, anti-tumor, antiulcerogenic, antidiuretic, antidiabetic, anti-inflammatory and antithrombotic agents **(Tousson et al., 2019)**.

The aim of the present work was to evaluate and compare the possible protective role of garlic oil and rosemary extract against neuro and geno/toxicities of acrylamide on adult male albino rats.

II-MATERIALS AND METHODS

II. 1.Place of the study

- Faculty of Medicine for Girls Al-Azhar University: Handling of animals and histopathological studies.
- National Research Center in Dokki (Cairo): Biochemical studies.

II.2. Chemicals

Acrylamide was purchased from Sigma–Aldrich Company china as 98% purity in the form of white powder and dissolved in distilled water.

II.3. Plants

- Garlic oil was purchased from El-Captain Company (Cairo, Egypt).
- Rosemary leaves was purchased from Botany Department, Faculty of Science, Zigzag University.

Preparation of Rosemary Extract

Rosemary leaves were washed thoroughly with distilled water the air dried leaves were coarsely powdered. Eight grams (g) of the powder dissolved in 100 ml of distilled water was boiled for 2 minutes. After cooling (about one hour) and passing through filter paper, a clear solution was obtained (about 60ml). During twenty-four hours of preparation, the extract was given to the rats by gastric tube as (10 ml/kg/day, i.e., 2 ml/rat) (**Haloui et al., 2000; El-sherifandIssa, 2015)**.

III.4. Kits

For the measurement of the different parameters, Kits were obtained from Bio diagnostic company and Sigma Company.

II.5. Experimental Animals

The present study was carried out on 90 adult male albino rats with average body weight ranged from (180 to 200 grams). The animals were obtained from Helwan animal breeding farm, Cairo, Egypt.

They were maintained in stainless steel cages in a well-ventilated animal house at normal temperature (22°C ± 5°C) under a 12:12-hour light–dark cycle. They were fed with standard diet and given water. They were kept under suitable conditions for 1 week for adaptation prior to the start of the experiment.

The choice of the rats in this study was due to many metabolic similarities between rat and human **(Gad and chengel, 1992)**.

The handlings of animals were following the rules for the experimental

research ethics approved by Research Ethics Committee at faculty of Medicine for Girls Al-Azhar University.

II.6. Experimental Design

The animals were divided randomly into six groups (15 rats each). All groups received the treatment by the oral route through gastric tube once daily for 6 weeks.

***Group I:** served as negative control and received distillate water ad libitum according to **(El –Sayyad et al., 2013)**.

***Group II:** rats received garlic oil 5 ml /kg body weight according to **(Hassan et al., 2010)**

***Group III:** rats received RE 10 ml /kg body weight according to **(Haloui et al., 2000; El-sherif and Issa, 2015)**.

***Group IV:** rats were administered acrylamide 15 mg /kg body weight according to **(Jangir et al., 2016).**

***Group V:** rats were administered acrylamide + garlic oil (15 mg /kg + 5 ml /kg body weight) respectively.

Group VI: rats were administered acrylamide + rosemary extract (15 mg /kg + 10 ml /kg) respectively.

II.7. Specimens collection

At the end of experimental period (6 weeks), the animals were fasted overnight and then anaesthetized with diethyl ether inhalation and blood samples were collected by direct puncture of retro- orbital venous plexus using glass capillaries in clean dry test tubes. The blood samples were centrifuged at 2000 rpm for 15 minutes, to separate the sera then stored at -20 °C for assessment of biochemical parameters.

After the collection of blood samples all animals were sacrificed by cervical dislocation, their brains were quickly excised, rinsed in ice-cold saline, and used immediately or stored frozen at -80 ºC until analysis.

Brain was removed from rats and were kept in bouin fixation and prepared for histopathological studies **(Shrivastava et al. 2018)**.

II.8.The behavioral index (gait scores) examination

The gait score was examined weekly according to the methods described by **(LoPachin, 2005)**. Rats were placed in a clear Plexiglas box and observed for 3 minutes. Following observation, a gait score was assigned from 1 to 4, where (1) a normal, unaffected gait, (2) is a slightly affected gait (foot splay, slight hind limb weakness, and slight limb spread), (3) is a moderately affected gait (foot splay, moderate hind limb weakness, and moderate limb spread during ambulation), and (4) is a severely affected gait (foot splay, severe hind limb weakness, dragging hind limbs, and inability to rear).

II.9.Biochemical analysis:

a- MDA level as lipid peroxidation marker and antioxidant enzymes in form of superoxide dismutase (SOD) and catalase (CAT):

- **Quantitative estimation of MDA:** According to **Ohkawa et al. (1979)**. The absorbance was read at 543 nanometer (nm) by spectrophotometer.
- **Quantitative estimation of SOD:** According to the **Nishikimi et al. (1972).** The absorbance was read at 560 nm by spectrophotometer.
- **Quantitative estimation of CAT:** According to the **Aebi (1984**). The absorbance was read at 510 nm by spectrophotometer.

b- Quantitative estimation of brain acetylcholinesterase (AchE): According to **the Henry (1974)**. The absorbance was read at 450 nm by spectrophotometer.

II.10.Cytogenetic analysis:

Quantitative estimation of total content of DNA, RNA and protein in brain tissue: method described by **Dische and Schwartz (1954), Dische (1957)** and **Kaplan and Szalbo (1983)** respectively. The absorbances were read at 600 nm, 660nmn and 550 nm respectively by spectrophotometer.

II.11.Histopathological examination:

Brains sections were stained with H&E stain: According to **Kieranan (2001)**.

II.12.Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version (20). All data were presented as mean standard deviation (SD).

For Statistical differences among the experimental groups were assessed by ANOVA & independent T- test. Significant was defined at $p<0.05$.

III-RESULTS

III.1.The behavioral index (gait scores) examination

In the first three weeks, there were no visible neurological abnormalities in the walking pattern in all groups of this study.

In the fourth week, seven rats from acrylamide treated group (group IV) showed slightly splay of hind limbs, while the rats in other groups showed normal gaits (no visible neurological abnormalities in the walking pattern).

In the fifth week, in acrylamide-treated group (group IV), five rats showed slight abnormal gait, one rat showed moderate abnormal gait with moderate degree of foot splay, and limb abduction while nine rats showed severe affected gait with severe hind limb spread, abduction and external rotation and the rats dragged their feet as they walked (**Figure 1)**.Whereas, acrylamide + garlic oil treated group (group V) showed two rats with slight affected gait.

Furthermore, in rats of acrylamide + rosemary extract group (group VI), one rats showed slight affected gait while other rats were still normal.

In the sixth week, in acrylamide treated group (group IV) two rats showed moderate affected gait and thirteen rats showed severe affected gait. Whereas in acrylamide + garlic oil treated group three rats showed slight affected gait.

In addition, rats in group of acrylamide + rosemary extract three rats showed slightly affected gait while other rats were still normal.

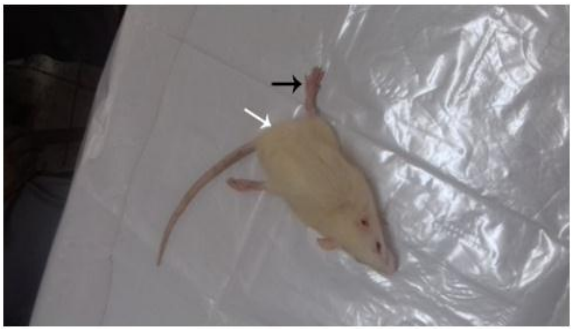

Fig. (1): Photo of rat after six-weeks acrylamide treatment (from group IV) showing splayed hind legs, anddisrupted in body posture. Black arrows indicate splayed leg, white arrow indicate abdomen rubbing to the ground.

III.2.Biochemical analysis

a- MDA level and superoxide dismutase (SOD) and catalase (CAT) activities

The data in **tables (1&2) and figures (2, 3& 4)** recorded that, there were no significant differences ($P>0.05$) in MDA level, percent of inhibition of SOD and CAT activity in the serum of garlic oil treated group and rosemary extract group as compared to negative control group. Whereas, There were high significant ($P<0.001$) increase in serum MDA levels, increase the percentage of inhibition of superoxide dismutase and decrease in CAT activity in the serum of acrylamide treated group, acrylamide + garlic oil group and acrylamide +rosemary extract group compared to negative control group.

However, co-administration of garlic oil and rosemary extract with acrylamide revealed significant decrease in MDA, decrease in percent of inhibition of SOD and increase CAT activity in the serum as compared to the AA treated group, with no significant differences between the possible protective role of garlic oil and rosemary extract on sub chronic toxicity by AA as regards MDA levels, percentage of inhibition of SOD and CAT activity in the serum.

Table (1): Comparison between different studied groups regarding mean level of MDA, percentage of inhibition of SOD and catalase activity in serum of adult male albino rats (ANOVA test).

Groups n=15rats/group	MDA in serum nmol/ml	% of inhibition of SOD in the serum(u/l)	Catalase activity in serum(u/l)
Negative Control			
Mean±SD	9.40±0.72	23.90±1.58	833.85±35.96
Range	8.39-10.56	21.61-26.77	769.58-881.38
Garlic oil			
Mean±SD	9.35±0.71	23.72±1.55	839.51±34.05
Range	8.33-10.49	21.42-26.45	778.52-887.46
Rosemary Extract			
Mean±SD	9.32±0.73	23.54±1.50	845.83±35.01
Range	8.27-10.48	21.29-26.23	781.25-893.72
Acrylamide			
Mean±SD	25.96±1.80	93.83±2.69	272.02±30.16
Range	22.96-28.59	89.97-98.11	219.67-311.52
Acrylamide+garlic oil			
Mean±SD	11.12±1.01	29.11±2.18	718.91±29.83
Range	9.69-12.69	25.97-32.48	666.38-762.72
Acrylamide + Rosemary Extract			
Mean±SD	11.08±1.00	28.53±2.59	725.12±31.55
Range	9.65-12.64	24.20-32.25	668.20-768.43
ANOVA test	415.572	1986.716	494.657
p-value	**<0.001****	**<0.001****	**<0.001****

**= High significant at p <0.001; MDA= malondialdehyde; SOD = superoxide dismutase; n = number; SD = standard deviation; ANOVA=Analysis of variance.

Table (2): Comparison between each two studied groups regarding MDA, percentage of inhibition of SOD and catalase activity level in serum of adult male albino rats (Independent t-test).

Groups n=15rats/group	MDA in serum nmol/ml			% of inhibition of SOD in the serum(u/l)			Catalase activity in serum(u/l)		
	Change%	**t-test**	**p-value**	**Change%**	**t-test**	**p-value**	**Change%**	**t-test**	**p-value**
Negative Control vs. Garlic oil	↓0.540	0.167	0.869	↓0.780	0.278	0.784	↑0.680	-0.379	0.709
Negative Control vs. Rosemary Extract	↓0.790	0.242	0.811	↓1.540	0.559	0.583	↑1.440	-0.791	0.438
Negative Control vs. Acrylamide	↑176.240	-28.375	<0.001**	↑292.530	-74.310	<0.001**	↓67.380	39.700	<0.001**
Negative Control vs. Acrylamide+garlic oil	↑18.300	-4.606	<0.001**	↑21.800	-6.410	<0.001**	↓13.780	8.159	<0.001**
Negative Control vs. Acrylamide + Rosemary Extract	↑17.950	-4.532	<0.001**	↑19.350	-5.054	<0.001**	↓13.040	7.538	<0.001**
Acrylamide vs. Acrylamide+garlic oil	↓57.170	23.877	<0.001**	↓68.970	61.987	<0.001**	↑164.290	-34.939	<0.001**
Acrylamide vs. Acrylamide + Rosemary Extract	↓57.300	23.962	<0.001**	↓69.600	58.034	<0.001**	↑166.570	-34.427	<0.001**
Acrylamide+ garlic oil vs. Acrylamide + Rosemary Extract	↓0.300	0.078	0.938	↓2.010	0.575	0.572	↑0.860	-0.474	0.640

P-value>0.05 Insignificant; ** = highly significant (P<0.001); Vs=versus; MDA= malondialdehyde; SOD = superoxide dismutase; n = number.

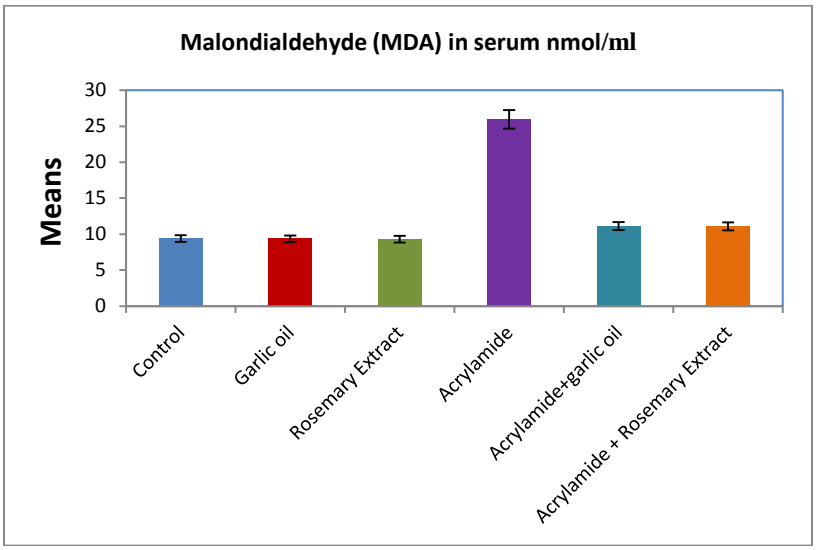

Fig. (2): Column chart showing mean level of malondialdehyde (MDA) in the serum of adult male albino rats in studied groups.

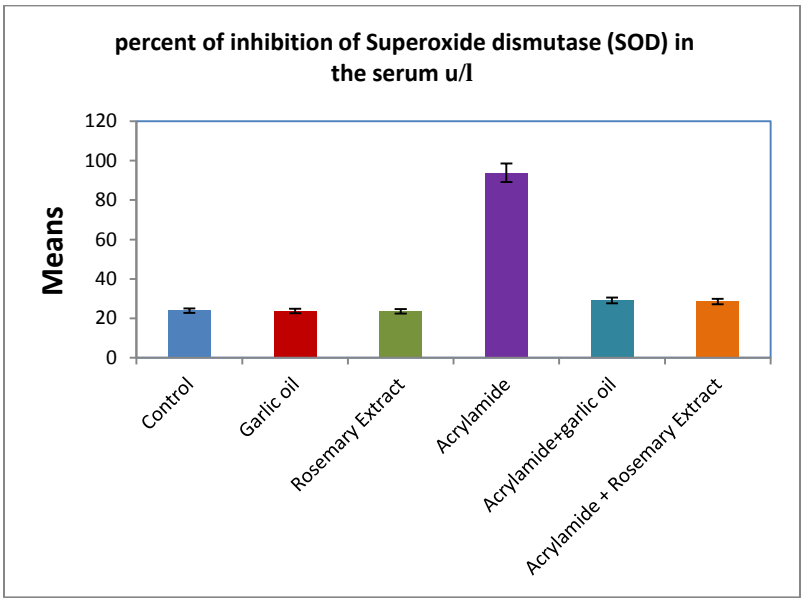

Fig. (3): Column chart showing mean level of percent of inhibition of superoxide dismutase (SOD) in the serum of adult male albino rats in studied groups.

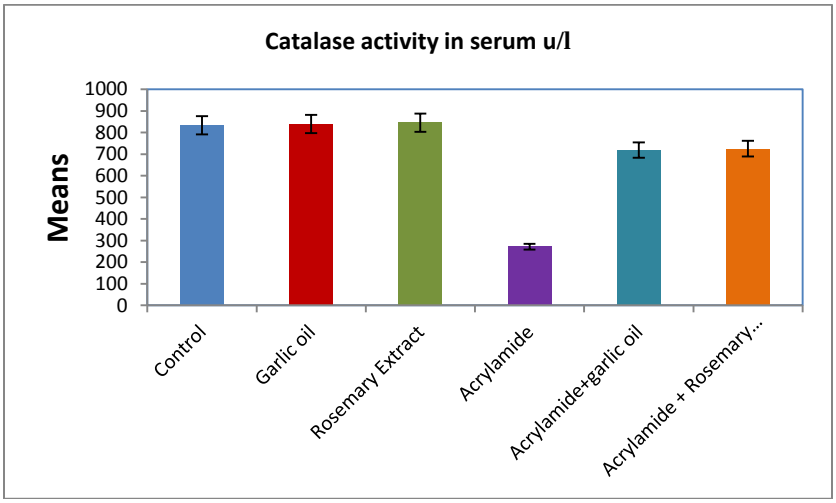

Fig. (4): Column chart showing mean level of catalase (CAT) activity in the serum of adult male albino rats in studied groups.

b) Acetylcholinesterase activity

There were no significant differences (P>0.05) in acetylcholinesterase enzyme in the brain tissue in garlic oil treated group and rosemary extract group as compared to the negative control group. Whereas, there were high significant decreases (P<0.001) in activity of acetylcholinesterase enzyme in the brain tissue of acrylamide treated group, AA +garlic oil group and AA + rosemary extract group as compared to the negative control group.

But, co-administration of AA+ garlic oil and AA + rosemary extract caused high significant increase (P<0.001) in activity of acetylcholinesterase enzyme in the brain tissue as compared to the AA treated group, with no significant differences between the possible protective role of garlic oil and rosemary extract on sub chronic toxicity by AA as

regards acetylcholinesterase enzyme in the brain tissue **tables (3&4) and Fig. (5).**

Table (3): Comparison between different studied groups regarding mean values of acetylcholinesterase enzyme in the brain tissue (U/L) of adult male albino rats (ANOVA test).

Groups n=15rats/group	Acetylcholinesterase enzyme in brain tissue U/L
Negative Control	
Mean±SD	8045.39±296.74
Range	7624.29-8584.41
Garlic oil	
Mean±SD	8067.05±297.68
Range	7652.13-8591.23
Rosemary Extract	
Mean±SD	8079.75±296.54
Range	7671.09-8609.05
Acrylamide	
Mean±SD	2927.46±145.30
Range	2697.97-3116.32
Acrylamide+garlic oil	
Mean±SD	7156.34±280.23
Range	6674.39-7546.47
Acrylamide + Rosemary Extract	
Mean±SD	7170.67±281.64
Range	6681.21-7550.63
ANOVA test	594.746
p-value	**<0.001****

**= High significant at p <0.001; S.D. = standard deviation; n=number; ANOVA=Analysis of variance.

Table (4): Comparison between each two studied groups regarding acetylcholinesterase enzyme in the brain tissue of adult male albino rats (Independent t-test).

Groups n=15rats/group	Acetylcholinesterase enzyme in brain U/L		
	Change%	**t-test**	**p-value**
Negative Control vs. Garlic oil	↑0.270	-0.171	0.866
Negative Control vs. Rosemary Extract	↑0.430	-0.272	0.789
Negative Control l vs. Acrylamide	↓63.610	51.374	<0.001**
Negative Control l vs. Acrylamide+garlic oil	↓11.050	7.224	<0.001**
Negative Control vs. Acrylamide + Rosemary Extract	↓10.870	7.091	<0.001**
Acrylamide vs. Acrylamide+garlic oil	↑144.460	-44.433	<0.001**
Acrylamide vs. Acrylamide + Rosemary Extract	↑144.940	-44.408	<0.001**
Acrylamide+garlic oil vs. Acrylamide + Rosemary Extract	↑0.200	-0.120	0.906

P-value>0.05 Insignificant*;* ****** = highly significant (P<*0.001*); Vs= versus; n=number.

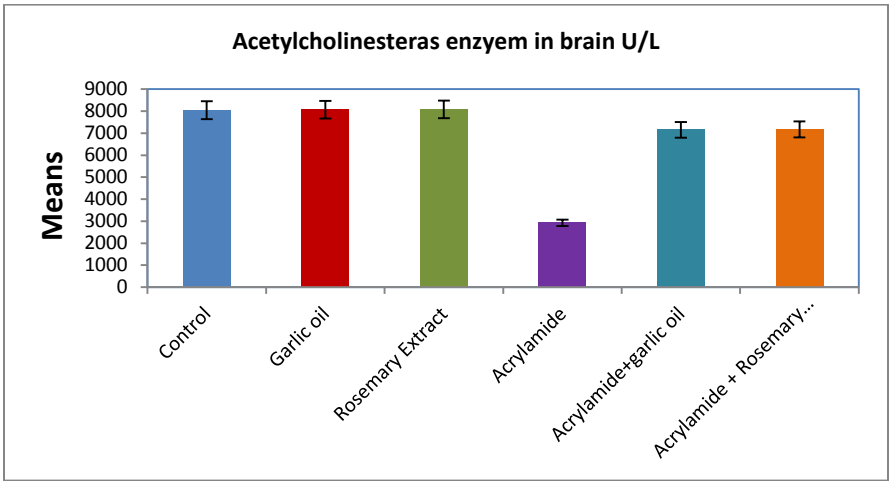

Fig. (5): Column chart showing mean level of acetylcholinesterase enzyme in the brain tissue of adult male albino rats in studied groups.

III.3. Cytogenetic analysis

The total content of DNA, RNA and protein in brain tissue:

Regarding comparison between negative control group and other groups, there were no significant differences (P>0.05) in total contents of DNA, RNA and protein in brain tissue of garlic oil treated group and rosemary extract group. Whereas, There were high significant decreases (P<0.001) in percent of total contents of DNA, RNA and protein in brain tissue of acrylamide treated group, AA + garlic oil group and AA + rosemary extract group as compared to the negative control group.

However, co-administration of AA+ garlic oil and AA + rosemary extract caused high significant increase (P<0.001) in the total content of DNA, RNA and protein in brain tissue as compared to acrylamide treated group, with no significant differences between the possible protective role of garlic oil and rosemary extract on sub chronic toxicity by AA as regards total contents of DNA, RNA and protein in brain tissue **Tables (5&6) and Figures (6, 7 & 8)**.

Table (5): Comparison between different studied groups regarding mean values of total contents of DNA mg/ g tissue, RNA mg/ g tissue and protein in brain g/g of adult male albino rats (ANOVA test).

Groups n=15rats/group	Total contents of DNA in brain mg/ g tissue	Total contents of RNA in brain mg/ g tissue	Total contents of protein in brain g/g
Negative Control			
Mean±SD	0.63±0.03	0.36±0.02	9.81±0.99
Range	0.60-0.67	0.32-0.40	7.92-11.29
Garlic oil			
Mean±SD	0.64±0.03	0.36±0.02	9.84±0.97
Range	0.59-0.68	0.33-0.40	8.01-11.30
Rosemary Extract			
Mean±SD	0.64±0.03	0.36±0.02	9.85±0.97
Range	0.60-0.68	0.33-0.40	8.03-11.31
Acrylamide			
Mean±SD	0.18±0.06	0.18±0.02	3.91±0.63
Range	0.00-0.22	0.16-0.20	2.91-5.03
Acrylamide+garlic oil			
Mean±SD	0.57±0.03	0.29±0.02	7.86±1.08
Range	0.51-0.61	0.27-0.31	6.55-9.64
Acrylamide + Rosemary Extract			
Mean±SD	0.57±0.03	0.29±0.02	7.91±1.09
Range	0.51-0.61	0.27-0.31	6.62-9.69
ANOVA test	240.817	141.304	62.584
p-value	<0.001**	<0.001**	<0.001**

**= High significant at p <0.001; DNA=deoxyribonucleic acid; RNA =ribonucleic acid; n = number; SD = standard deviation; ANOVA=Analysis of variance.

Table (6): Comparison between each two studied groups regarding total contents of DNA mg/g tissue, RNA mg/g tissue and protein in brain g/gin the brain of adult male albino rats (Independent t-test).

Groups n=15rats/group	Total contents of DNA in brain mg/ g tissue			Total contents of RNA in brain mg/ g tissue			Total contents of protein in brain g/g		
	Change%	**t-test**	**p-value**	**Change%**	**t-test**	**p-value**	**Change%**	**t-test**	**p-value**
Negative Control vs. Garlic oil	↑0.370	-0.196	0.847	↑0.590	-0.217	0.830	↑0.300	-0.070	0.945
Negative Control vs. Rosemary Extract	↑0.720	-0.382	0.707	↑1.300	-0.478	0.638	↑0.480	-0.113	0.911
Negative Control vs. Acrylamide	↓70.880	21.915	<0.001**	↓48.930	21.035	<0.001**	↓60.090	16.716	<0.001**
Negative Control vs. Acrylamide+garlic oil	↓9.710	4.651	<0.001**	↓19.410	8.320	<0.001**	↓19.890	4.417	<0.001**
Negative Control vs. Acrylamide + Rosemary Extract	↓9.260	4.475	<0.001**	↓18.700	7.910	<0.001**	↓19.360	4.289	<0.001**
Acrylamide vs. Acrylamide+garlic oil	↑210.110	-18.137	<0.001**	↑57.790	-15.997	<0.001**	↑100.720	-10.438	<0.001**
Acrylamide vs. Acrylamide + Rosemary Extract	↑211.640	-18.328	<0.001**	↑59.190	-16.049	<0.001**	↑102.070	-10.549	<0.001**
Acrylamide+garlic oil vs. Acrylamide + Rosemary Extract	↑0.490	-0.195	0.847	↑0.890	-0.377	0.710	↑0.670	-0.114	0.910

P-value>0.05 Insignificant; ****** = highly significant (P<0.001); Vs= versus; DNA = deoxyribonucleic acid; RNA = ribonucleic acid; n = number.

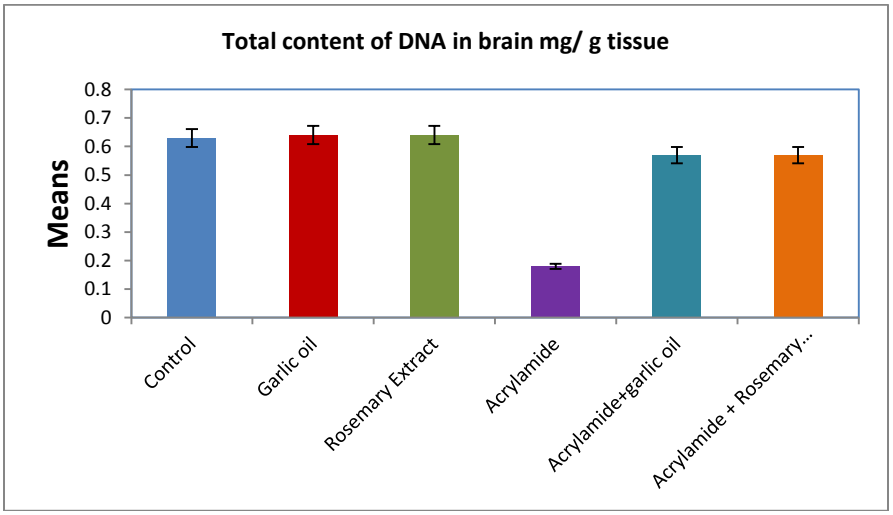

Fig. (6): Column chart showing mean level of total content of deoxyribonucleic acid (DNA) mg/g tissue in the brain of adult male albino rats in studied groups.

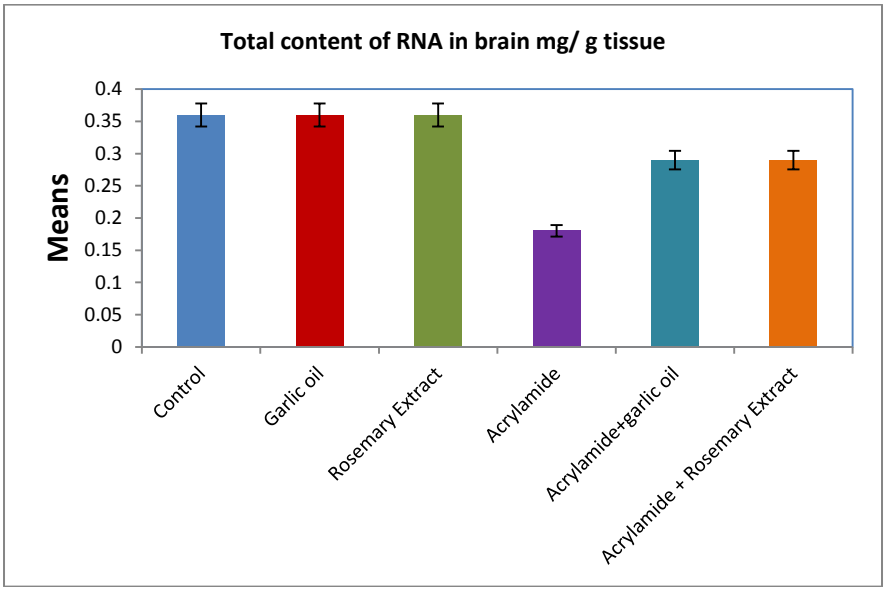

Fig. (7): Column chart showing mean level of total content of ribonucleic acid (RNA) mg/g tissue in the brain of adult male albino rats in studied groups.

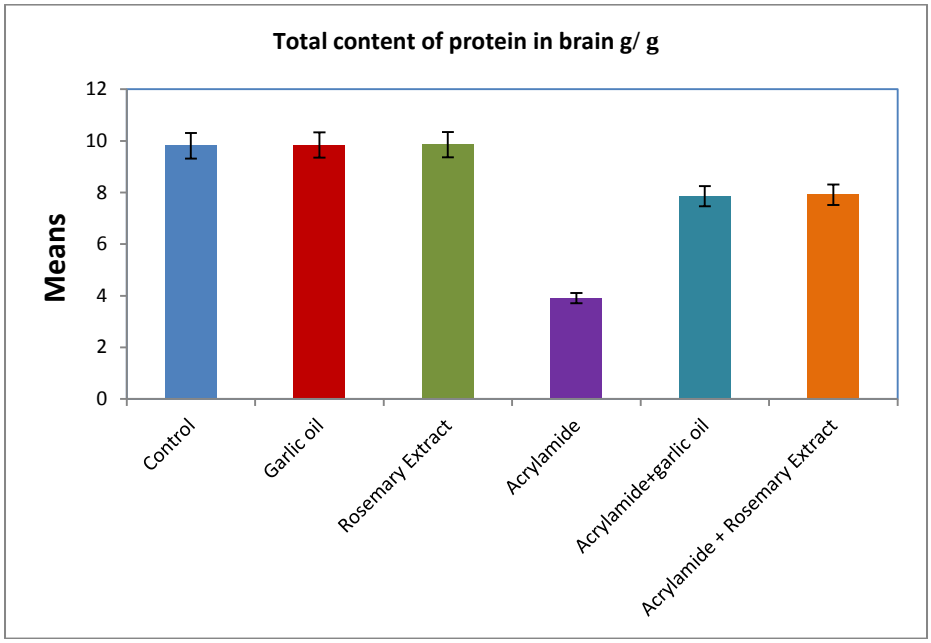

Fig.(8): Column chart showing mean level of total content of protein g/g in the brain of adult male albino rats in studied groups.

III.4.Histopathological analysis:

Light microscopic examination of the brain sections in control, garlic oil and rosemary extract showed no histopathological alteration with normal histological structure of the pia matter covers the molecular layer followed by external granular layer, external pyramidal, the pyramidal cells, granular cells with rounded open face nuclei and neuropil (the

pink stained background) **(figures 9,10,11&12)**.

On the other hand, Light microscopic examination of the brain sections in acrylamide treated rats showed shrunken pyramidal cells surrounded by empty spaces. Apoptotic cells having small darkly stained nuclei and little acidophilic cytoplasm, surrounded by empty space are also seen. Mononuclear cellular infiltration can be observed. Dilated and congested blood vessels can be detected and there is area of hemorrhage **(figures 13, 14&15)**.

Furthermore, the Combined treatment of AA+ garlic oil and AA + rosemary extract, considerably reduced the severity of tissue lesions caused by acrylamide **(figures 16&17)** respectively.

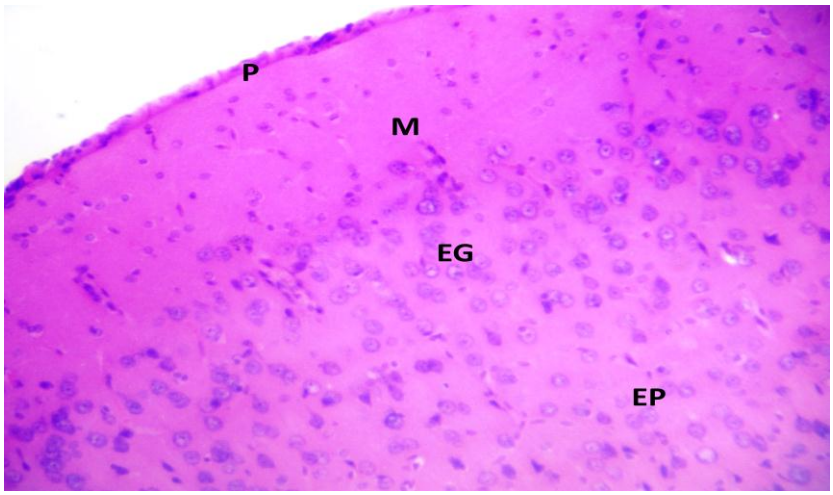

Fig. (9): Aphotomicrograph of section in the cerebral cortex of adult male albino rat from control group showing the pia matter (P) covers the molecular layer (M) followed by external granular layer (EG), external pyramidal (EP) **(H&E X200)**.

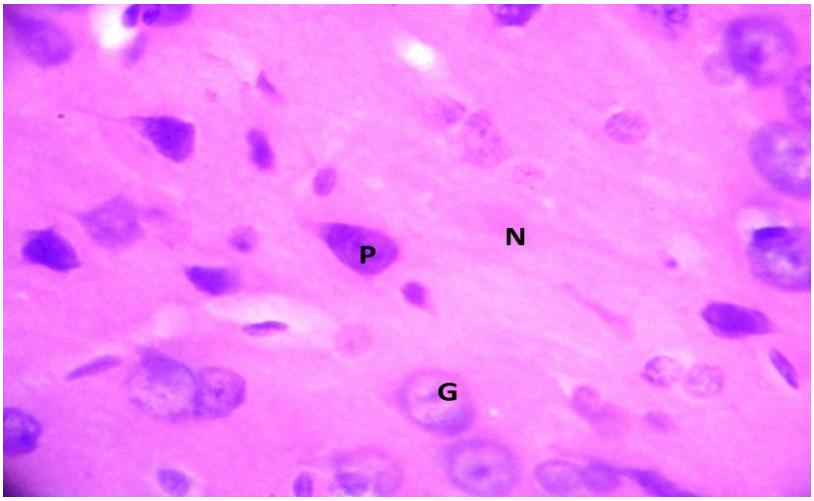

Fig. (10): Aphotomicrograph of section in the cerebral cortex of adult male albino rat from control group showing the pyramidal cells (P). Granular cells (G) with rounded open face nuclei are also seen. The pink stained background is the neuropil (N) **(H&E X400)**.

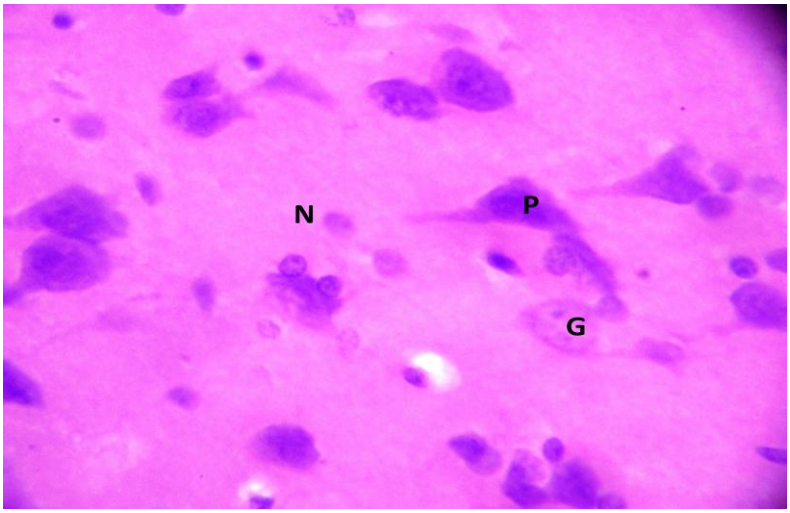

Fig. (11): Aphotomicrograph of section in the cerebral cortex of adult male albino rat from garlic group showing the pyramidal cells (P). Granular cells (G) with rounded open face nuclei. The pink stained background is the neuropil (N) **(H&E X400)**.

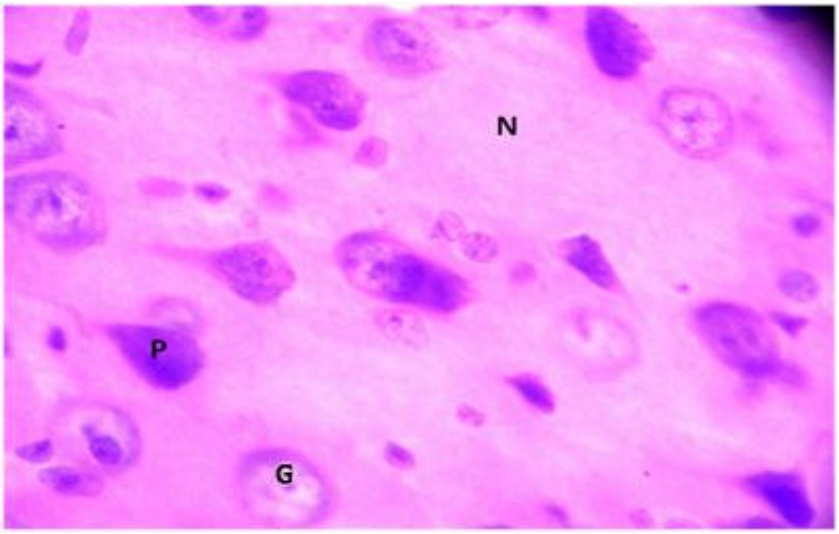

Fig. (12): A photomicrograph of section in the cerebral cortex of adult male albino rat from rosemary group showing the pyramidal cells (P). Granular cells (G) with rounded open face nuclei. The pink stained background is the neuropil (N) **(H&E X400)**.

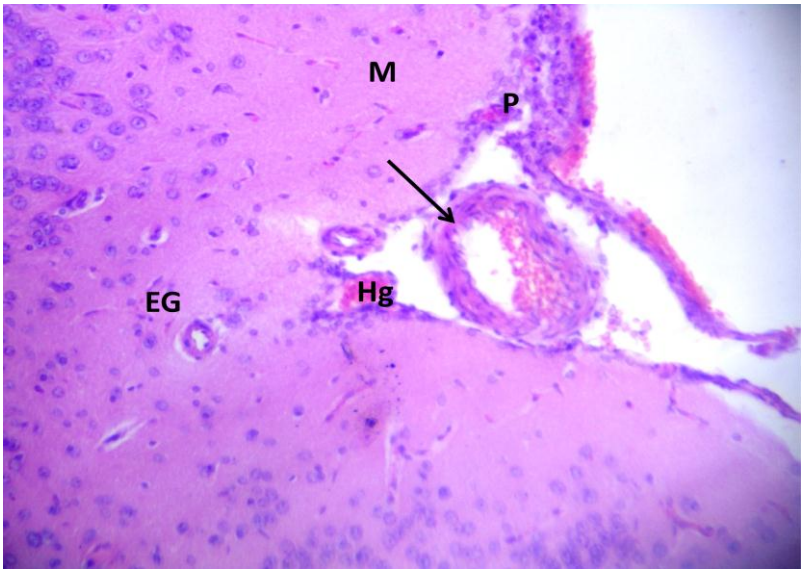

Fig. (13): Aphotomicrograph of section in the cerebral cortex of adult male albino rat from acrylamide group showing the pia matter (P), covers the molecular layer (M) followed by external granular layer (EG). Dilated and congested blood vessels can be detected (arrow). Also, area of hemorrhage (Hg) can be seen **(H&E X200)**.

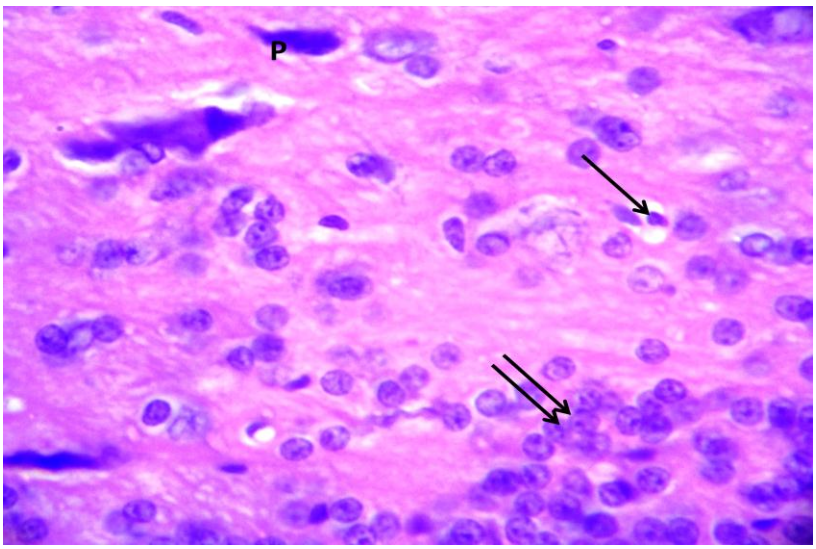

Fig. (14): A photomicrograph of section in the cerebral cortex of adult male albino rat from acrylamide group showing shrunken pyramidal cells (P) surrounded by empty spaces. Apoptotic cells (arrow) having small darkly stained nuclei and little acidophilic cytoplasm, surrounded by empty space are seen. Mononuclear cellular infiltration (double arrows) can be observed **(H&E X400)**.

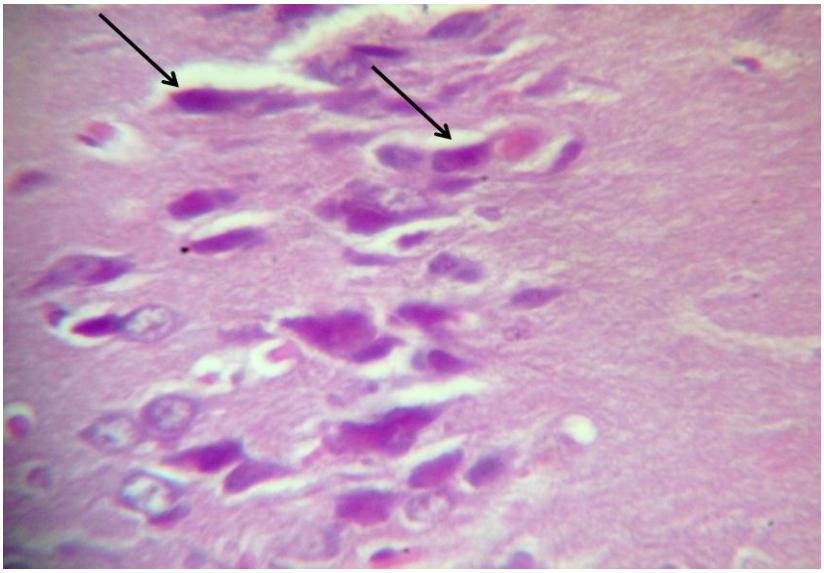

Fig. (15): Aphotomicrograph of section in the cerebral cortex of adult male albino rat from acrylamide group showing multiple shrunken pyramidal cells (arrows) surrounded by empty spaces **(H&E X400).**

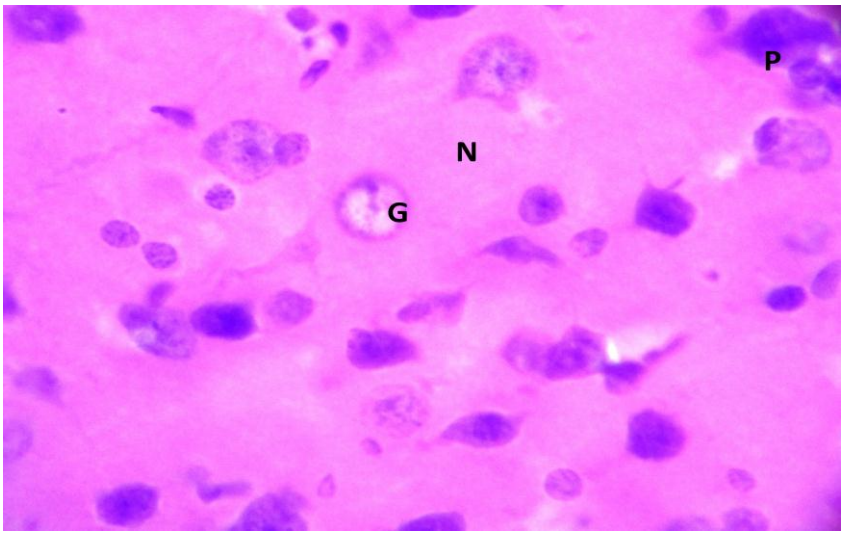

Fig. (16): Aphotomicrograph of section in the cerebral cortex of adult male albino rat from acrylamide+garlic group showing reduced the severity of tissue lesions caused by acrylamide. The pyramidal cells (P) and granular cells (G) with rounded open face nuclei are seen. The pink stained background is the neuropil (N) **(H&E X400)**.

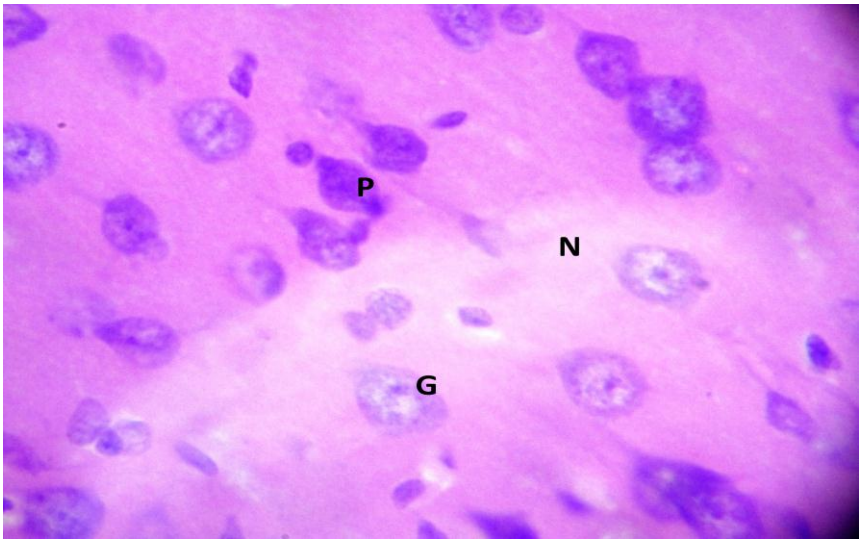

Fig. (17): A photomicrograph of section in the cerebral cortex of adult male albino rat of acrylamide+ rosemary group showing reduced the severity of tissue lesions caused by acrylamide. The pyramidal cells (P) and granular cells (G) with rounded open face nuclei are seen **(H&E X400)**.

IV- DISCUSSION

Acrylamide has been characterized as a carcinogen to animals and might create a risk to human health. Its acts as a neurotoxin agent. Genetic mutations and cellular transformation were occurred after high levels of AA. Its molecules could reach every organ and tissue in the body and reacts with DNA, neurons, hemoglobin and enzymes **(Aboubakr et al. 2019)**.

The aim of the present work was to evaluate and compare the possible protective role of garlic oil and rosemary extract against neuro and geno/toxicities of acrylamide on adult male albino rats.

Exposure to AA (15 mg/kg for 6weeks) in the present study show severe affected gait with severe hind limb spread, abduction and external rotation and the rats dragged their feet as they walk.

The mechanism underlying acrylamide-induced neuronal injury is related to acrylamide-induced apoptosis in the cerebral cortex of rats **(Li et al. 2008).**

Moreover, **Hammad et al. (2013)** added that acrylamide could inhibit the axonal energy production; change in the rate, quantity and deposition of anterograde transported materials; and disruption of cytoskeletal structure and function. Based on the role of transmembrane ion shifts in cell injury, acrylamide might cause distal axonopathy by disrupting subaxonal distribution of Ca^{+2}, K^{+} and Na^{+}.

The present results are in agreement with that of **Mehri et al. (2016)**, who reported that exposure to AA (50 mg/kg, IP) induced progressive gait abnormalities in the rats.

Furthermore, **Al-Gholam et al. (2016)** revealed that administration of acrylamide to rats showed a significant increase in gait score from day 14 to day 21.

Lashein et al. (2018) showed abnormal neurobehavioral and morphological changes in mice treated with acrylamide. The changes include hind limb dysfunction, abnormal gait, ataxia, increased landing of the limbs and weakness of the muscles.

In the present study co-administrations treatment of AA and garlic oil show slightly affected gait compared to AA treated rats. This result is in accordance with that of **Amin et al. (2016)** who showed that Co-treatment of rats with garlic oil and acrylamide resulted in mild improvement in neurological abnormalities in the walking pattern.

In the present study co administration of acrylamide and rosemary extract show slightly

affected gait while other rats are still normal compared to AA treated rats.

This result is in agreement with that of **Al-Gholam et al. (2016)** who observed significant decreased (P<0.05) in gait score when rats treated by rosemary with acrylamide, and this was significantly low at day14.

In the current study, oral administration of acrylamide to the adult male albino rats for 6 weeks induce a state of oxidative stress represent by a significant elevation of malondialdehyde level as lipid peroxidation marker in serum with a significant reduction activity of serum antioxidant enzymes (superoxide dismutase and catalase).

These results are supported by that of **EL-Kholy et al. (2018)** who reported that oral administration of acrylamide suppressed SOD, CAT, glutathione peroxidase (GSH-Px) activities and reduced glutathione (GSH) content, while there was an elevation in MDA level. SOD activity depletion was attributed to its inhibition by accumulation of H2O2. They added that, reduction of SOD activity and the rise of MDA level could be signs of oxidative stress.

Abo-El-matty et al. (2018) revealed that AA administration resulted in significant reductions in brain SOD and CAT and significant increase in malondialdehyde level in the brain compared with normal healthy rats. They reported that the significant decrease in the activity of brain SOD might be attributed that to the excess production of reactive oxygen species (ROS) as AA causes brain damage *via* ROS more than any other organ.

The obtained elevation in MDA level and reduction in the activities of antioxidant enzymes could explained by **Zhao et al. (2015)** who stated that the production of reactive oxygen species (ROS) by acrylamide, caused suppression of cellular defense system hence the cells are easily susceptible to oxidative attack through altering the membrane integrity and fatty acid composition. Mitochondria are the main target for the acrylamide

In the current study, concomitant administration of garlic oil (GO) and acrylamide treated rats induce significant improvements in the lipid peroxidation marker and antioxidant enzymes activity.

The antioxidant action of GO could explained by scavenging or neutralizing of free radicals **(Ban et al. 2007)**, interacting with oxidative cascade and preventing its outcome, oxygen quenching and making it less available for oxidative reaction, inhibition of cytochrome P450 **(Ho et al. 2010)**.

Abd-Elhamid et al. (2014) added that diallyldisulfide and diallyltrisulfide present in GO had ability in modulating the oxidative stress and detoxifying enzyme system.

Alsenosy and Abd El-Aziz (2019) stated that garlic has antioxidant properties, as confirmed by the reduction of MDA levels as well as the elevation of the SOD and glutathione peroxidase activities, and can be considered one of the most potent antioxidant agents, protecting the cell against ROS destructive damage.

In the current study, concomitant administration of rosemary extract and acrylamide treated rats induce significant improvements in the lipid peroxidation marker and antioxidant enzymes activity.

Several biological activities of R. *officinalis* extracts are probably linked to their ability to reduce the oxidative damage caused by free radicals, as *R. officinalis* may act as free radical scavengers but additionally might play a role by regulating the activity and/or expression of certain enzymatic systems implicated in relevant physiological processes like apoptosis, or xenobiotic-metabolizing enzymes in liver (**Mahmoud and Bahr 2015).**

These results are in agreement with that of **Cui et al. (2018)** who reported that rosmarinic acid (RA) increased SOD activity and decreased MDA levels in ischemic brain tissue for 24 hours, suggesting RA can scavenge ROS instantly by increasing endogenous antioxidant enzyme activity and reducing lipid peroxidation.

Acetylcholinesterase (AchE) is a key enzyme of the cholinergic transmission in CNS by promoting hydrolysis of the neurotransmitter Acetylcholine (Ach) released at the nerve endings to mediate transmission of the neural impulse across the synapses **(Kopa´nska et al. 2015)** .

Concerning acetylcholinesterase, the result of this work revealed a significant decrease in activity of acetylcholinesterase enzyme in the brain tissue of acrylamide treated group as compared to the control group (group I).

These results fully agree with that of **Shrivastava et al. (2018)** who stated that the activity of AChE significantly decreased in the brain of rats after acrylamide administration. They attribute the decrease in the activity of AChE might be due that acrylamide induced synaptic dysfunction, which involved in the adduction of presynaptic protein thiol groups and subsequent reduction in neurotransmitter release.

In addition, **Dasari et al. (2018)** observed that acetylcholine esterase activity dropped significantly ($P < 0.05$) in brain of rats at the 13th and 27th days post-ingestion of acrylamide (50 mg/300 ml) through drinking.

In the current study there was a high significant increase e.g. improvement in activity of acetylcholinesterase enzyme in the brain tissue of AA+ garlic oil group as compared to the AA treated group.

This result is confirmed by that of **Kotb et al. (2016)** as they showed that garlic has significant protection against malathion intoxication demonstrated inhibition in acetyl cholinesterase (AChE) activity.

This result could be explained by **Shaheen and Yousafzai (2017)** who reported that garlic contains two main classes of antioxidant i.e. flavonoids and diallyl sulphide, trisulphide and allyl-cysteine so garlic prevents oxidative stress by scavenging radicals, which is the reason that it has mitigated the toxicity of acrylamide in the present study.

The result of this study was contradicted with that of **Ghareeb et al. (2010)** who found that coadministration of garlic powder (1.5%) with acrylamide solution (3.33 mL kg1 body weight) to rats for 40 days did not ameliorate inhibition of AChE activity. This inconsistency may be due to different type and dose of garlic preparation, different route of exposure and different duration of exposure.

In the present study, there was a high significant increase i.e. improvement in activity of acetylcholinesterase enzyme in the brain tissue of AA and rosemary extract group as compared to the AA treated group.

This result could be explained by **Hozayen et al. (2014)** who reported that rosemary has the potential to quench free radicals, inhibit lipid peroxidation, and improve the antioxidant status in rat tissue. This is the reason that it has mitigated the toxicity of acrylamide in the present study.

The result of the present study is in contrast to that of **Abdel-Kader et al. (2010)** who revealed that oral administration of *rosmarinus officinalis* (rosemary) extract with a dose of 582.4 mg/kg. (0.5 ml solution/rat) for 4 weeks resulted in a significant reduction of acetylcholine esterase activity in all tested brain areas. This in contrast may be due to different dose of rosemary extract and different duration of exposure.

Concerning deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein contents of rat brain in the current study, there was high significant reduction in DNA, RNA and protein contents in the brain of rats treated by acrylamide compared to negative control group.

The decrease of DNA and RNA could be explained by **Balaban et al. (2013)** who concluded that AA increases the vulnerability of cells to oxidative damage, thus leading to DNA and RNA breaks.

The result of the present study could be explained by **Aboubakr et al. (2019)** who concluded that genotoxicity mainly occurred indirectly as a result of oxidative stress.

Glycidamide was a mutagenic metabolite of AA which has a potent genotoxic agent. AA induced DNA damage and oxidative changes in rat brain due to the high-affinity of glycinamide to form DNA adducts.

The recorded results in the present work are confirmed by similar results of **Al-Sowayan (2014)** who found that there was significant decrease in quantitative level of DNA and RNA in AA treated groups (12mg, 24mg and 36mg/kg b.w.) and chips group (fed on low packets of potato chips 65 gm each) comparing with control.

Ranjini and Manonmani (2019) reported that, The Human hepatocellular liver carcinoma cell line (HepG2) treated with AA and glycinamide (GA) showed an increase in DNA degradation.

Elkomy et al. (2018) and Hammad et al. (2013) reported significant decreases of the total protein and albumin, levels following acrylamide administration in rats.

However, concurrent administrations of garlic oil with acrylamide in the current study caused significant improvement in DNA, RNA and protein contents in the brain.

The present results are in agreement with that of **Mirfardi and Johari (2015)** who found that Garlic extract protects DNA in the testes from the damages caused by free radicals and cyclophosphamide metabolites.

Abd-El-Fattah et al. (2018) stated that fat treated group with choline and garlic oil showed significant increase ($P \leq 0.05$) of serum total protein compared to fat treated group. They reported that the elevation of total protein and albumin levels in the treated groups could be attributed to their antioxidant effects against ROS.

In the current study, the co-administration of rosemary extract and acrylamide induce significant improvements in the total contents of DNA, RNA and protein contents in the brain.

The ameliorative effect of rosemary extracts in the present study could be related to its ability to donate electrons to reactive radicals, converting them to more stable and on reactive species, therefore preventing them from reaching biomolecules, such as lipoproteins, polyunsaturated fatty acids, DNA, amino acids, proteins and sugars, in susceptible biological systems **(El-sherif and Issa 2015).**

These results are in agreement with that of **Mahmoud and Bahr (2015)**who reported that, rats treated with rosemary extract and manganese chloride ($MnCl_2$**)** showed marked reduction in DNA fragmentation (in liver and brain tissues) in line with elevation in total protein content (in liver and brain tissues) toward the normal control group.

Tousson et al. (2019) reported that, co-treatment of rosemary with etoposide showed a significant increase in total protein and albumin levels as compared to etoposide treated groups.

The histopathological lesions observed in the present results are in corroboration with the observed biochemical and cytogenetic changes, where there is alternation of normal histological structure of the brain tissue in the form of shrunken pyramidal cells surrounded by empty spaces. Apoptotic cells having small darkly stained nuclei and little acidophilic cytoplasm, surrounded by empty space is also seen. Mononuclear cellular infiltration can be observed. Dilated and congested blood vessels can be detected and there is area of hemorrhage.

The results of this work were in agreement with that of **Roodi et al. (2018)** who stated that the brain of treated rats revealed ischemic cell change, hyperemia, hemorrhage and edema in cerebrum; ischemic cell change, hyperemia, and hemorrhage in cerebellum tissue.

Recently, **Aboubakr et al. (2019)** stated that AA treatment induced a wide spread degeneration/necrosis in pyramidal neurons of rat hippocampus as well as perineuronal edema.

Regarding co administration with garlic oil to acrylamide-treated rats in current study, it was noted that it ameliorate these histopathological effects.

These results are in harmony with that of **Soliman et al. (2018)** who reported that that garlic has a protective effect against formaldehyde (FA) induced neuronal damage. The intensity of neurodegenerative changes was less in combined FA and garlic treated group than that in the FA-treated group.

In current work, administration of acrylamide with rosemary extract resulted in considerably reduced the severity of tissue lesions caused by acrylamide to the extent that in some treated brain tissues, no notable tissue lesions were detectable.

The results of the present study agreed with that of **Mahran and Arisha (2018)** who stated that co-administration of aqueous rosemary extract (ARE) and monosodium glutamate (MSG) to rats showed an obvious degree of improvement in the histopathological changes of the cerebellar layers compared with monosodium glutamate treated animals

V- CONCLUSION

- Considering the results obtained from the present study, it can be concluded that exposure of rats to acrylamide induces a state of oxidative stress, which results in increase of MDA and decrease of SOD and CAT. It will also lead to DNA damage and AchE-dropped activities, revealing that acrylamide shows significant perturbation of chemostress markers of biological cell and causes brain degeneration in rats. In addition, both garlic oil and rosemary extract treatments appear almost equally able to improve acrylamide-associated biochemical, cytogenic and histopathologic changes in rat brain.

VI- RECOMMENDATIONS

- Strict control of AA consumption is urgently needed. Regular monitoring of the level of AA in environment and baby foods.
- Regular administration of garlic oil and rosemary extract might reduced toxic effects of acrylamide.
- Further studies to evaluate each parameter included in this work separately for longer times and large scale number of rats and also re-evaluation the affection of AA on other systems of the body.
- To study the beneficial effects of garlic oil and rosemary extract on human health and its use as an adjuvant agent in the prevention and treatment of chronic diseases.

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الدور الوقائى المحتمل لزيت الثوم ومستخلص إكليل الجبل ضد السمية العصبية والوراثية للأكريلاميد على ذكورالفئران البيضاء البالغة

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الملخص العربى

الأكريلاميد هو مركب كيميائي يتكون عادة في المواد الغذائية النشوية أثناء طهيها عند درجة حرارة عالية. والذى يعتبر من أحد السموم العصبية والوراثيةا المميتة. **الهدف من البحث**: صممت الدراسة لتوضيح التغيرات فى مشية الفئران والتغيرات الكيميائية الحيوية والنسيجية (الهستوباثولوجية) بالإضافة إلى السمية الوراثية للأكريلاميد على مخ الفئران والدور الوقائي المحتمل لكل من زيت الثوم ومستخلص إكليل الجبل عند إعطائهما مع الأكريلاميد. **طرق البحث المستخدمة:** تم تقسيم تسعين من ذكور الفئران البيضاء البالغة إلى ٦ مجموعات (١٥ فأر فى كل مجموعة) ؛ المجموعة الضابطة السالبة، مجموعة زيت الثوم ، و مجموعة مستخلص إكليل الجبل ، مجموعة الأكريلاميد، مجموعةالأكريلاميد وزيت الثوم ،مجموعة الأكريلاميد ومستخلص إكليل الجبل. وقد تم إعطاؤهم العلاج بالفم. وفي نهاية الفترة التجريبية تم تقييم مشية الفئران ثم الحصول على عينات من الدم ومخ الفئران لتقييم التغيرات الكيميائية الحيوية والنسيجية والجينوخلوية. **النتائج**: أظهرت الفئران التي تعرضت للأكريلاميد مشية غير طبيعية مع انخفاض كبير في فوق أكسيد ديسموتيز، الكاتاليز، أستيل كولين استيريز، الحمض النووي، الحمض النووي الريبي ومحتويات البروتين وزيادة المالونالدهيدمع اضطراب في الشكل الطبيعي لأنسجة المخ. أما العلاج باستخدام زيت الثوم أو مستخلص إكليل الجبل فقد أدى إلى تحسين هذه التغييرات. **الخلاصة**: الأكريلاميد له تأثير سام على المخ. ويمكن لزيت الثوم أو مستخلص إكليل الجبل تحسين هذه السمية. **التوصية**: هناك حاجة ماسة للسيطرة الصارمة على استهلاك الأكريلاميد لما له من اثار ضارة.