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Original research

Protective effect of curcumin against acetamiprid - induced neurotoxicity in male albino rats

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Abstract:

Acetamiprid (ACMP) is a widely used neonicotinoid that is frequently favored in pest control. After imidacloprid, it is the most commonly manufactured neonicotinoid. It was established that ACMP exhibits brain toxic impact at sub-lethal doses. Curcumin (Cur) a natural polyphenol has been conveyed to possess neuroprotective activity by reducing oxidative stress. The purpose of this study was to look into the neuroprotective role of curcumin against acetamiprid induced neuro-toxicity. In the current study, seventy adult male albino rats were divided into two main groups 20 days and 40 days each of them subdivided into 5 groups consist of: control, vehicle (DMSO), Cur, ACMP and ACMP +Cur group. The current study found that acetamiprid administration resulted in a significant increase ($p<0.01$) in nitric oxide levels (NO) with histopathological changes in brain hippocampus tissue. Curcumin co-administration with acetamiprid significantly reduced ($p<0.01$) nitric oxide levels and protected against acetamiprid-mediated structural changes in the hippocampal tissue.

Keywords: Curcumin, Acetamiprid, brain, Nitric oxide.

1- Introduction

Acetamiprid (ACMP) is an organic compound that is one of the most effective neonicotinoid insecticides for crop protection in the world **(Sanyal et al., 2008).** ACMP is highly soluble in water, porous to soil, and possibly toxic to humans. Inhaling it can cause headaches, dizziness, vertigo, nausea, and vomiting **(Todani et al., 2008)**. ACMP toxicity is attributed to its action on nicotinic acetylcholine receptors (nAChRs), specifically the α4β2 subtype, which are members of a ligand-gated ion channel superfamily that causes rapid excitatory cholinergic neurotransmission **(Bromilow and Chamberlain, 1995; Bonmatin et al., 2015).** Acetamiprid may cause oxidative stress, resulting in the production of ROS or RNS and other related toxic effects **(El-Gendy et al., 2010; Duzguner and Erdogan, 2012; Ge et al., 2015).**

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Nitric oxide (NO) is a short-lived endogenous free radical **(Esplugues, 2002).** An increase in NO levels is caused by an abnormal nitric oxide synthase (NOS) **(Stevanovic et al., 2009).** It has been proposed that NO has neurotoxic effects at particularly high concentrations because it mediates glutamatergic neurotoxicity, which is involved in several pathological conditions such as stroke, trauma, and epilepsy, neuronal cell death, and certain neurodegenerative diseases **(Dawson et al., 1991).**

Plants with antioxidant properties have gained prominence in the treatment of oxidative stress-related neurodegenerative diseases in recent years. Curcumin (Cur), an active yellow pigment derived from these antioxidant plant specimens, is the active component of turmeric **(Bisht et al., 2007).** Cur has recently been studied for its potential pharmacological, prophylactic, or therapeutic use as an anti-inflammatory, anticarcinogenic, antiviral, antifungal, antiparasitic, anti-mutagenic, anti-infectious, and antioxidant compound **(Chen et al., 2006; Perez-Arriaga et al., 2006).** It functions as an antioxidant by scavenging free radicals such as peroxyl, hydroxyl, and nitrogen dioxide **(Das and Das, 2002).** Curcumin has a high NO scavenging activity because it inhibits NOS **(Sumanont, et al. 2004).**

In light of this literature, the current study was designed to assess curcumin's neuroprotective effect against acetamiprid (ACMP)-induced oxidative stress and histopathological changes in the rat brain.

2-Materials and methods:

2.1-Chemicals

Acetamiprid (ACMP) with CAS Number: 160430-64-8, was purchased from ***central laboratory of pesticides (agriculture research Centre) from Cairo***. Curcumin extract was purchased from (Sigma Aldrish Co, USA). All other chemicals were of the highest commercial purity.

2.2-Animal Selection

Seventy adult male albino rats (weighing 140 ± 20 g) were gotten from the Serum and Vaccine Laboratory- Helwan Farm. Animals were kept in a well-ventilated clean cage maintained under a 12-h of light-dark cycle at 25 ± 2º C with a relative wetness of 50 ± 5 %. Rats were held for approximately one week before the experiment begins to allow for acclimatization to laboratory conditions. The rats were fed a pellet diet as well as water. Care of the animals and experimental procedures were approved by the Animal Ethical Committee of Aswan University, Egypt, in accordance with the guide for the care and use of laboratory animals.

2.3-Experimental design and treatments

Rats were randomly divided into two major groups based on period (20 and 40 days). Each group was subdivided into five groups (Control, Vehicle, Curcumin, Acetamiprid, ACMP + Cur), 7 rats each. The control group was given a daily dose of saline solution orally. Vehicle (Veh) group received a daily oral dose of 33% DMSO. The Curcumin (Cur) group was given a daily oral dose of 100 mg/kg body weight of Cur (Ding et al., 2016). Acetamiprid (ACMP) group was given a daily oral dose of 20 mg/kg body weight of ACMP (half the dose used by Dhouib et al. 2017). ACMP + Cur –group was given a daily oral dose of 100 mg/ kg body weight. Then theywere given 20 mg/kg body weight ACMP in combination.

2.4- Estimation of nitric oxide levels

The levels of nitric oxide were determined in the homogenate of the brain cortex according to the method of **Montgomery and Dymock (1961).**

2.5- Histological studies

Brains from all groups were collected, washed in sterile saline, and stored in 10% neutral phosphate-buffered formalin (PH=7.0). For microscopic preparations, specimens were gradually dehydrated in ethyl alcohol (50-99 percent), cleared in methyl benzoate, and embedded in molten paraffin wax at 58-62 degrees Celsius. Tissue sections 5µm in thickness were prepared and stained with hematoxylin and eosin **(Gabe, 1976).**

2.6- Statistical analysis

Data of nitric oxide levels were conveyed as means ± S.E. Differences between means were confirmed by one-way analysis of variance ANOVA followed by the Student Newman-Keuls T-test using Minitab 19 software so that the data obtained can be compared and statistically evaluated. Statistical significance was considered when $p < 0.05$.

3-Results and discussion

3.1- Nitric oxide (NO) levels

From the results of this study, ACMP-administration increased NO level in the cortical homogenate compared with control group (Table 1). The increase or stimulation in NO was **109.7**% and **180.8**% at 20 and 40 days respectively. Statistically, this stimulation was significant ($p<0.01$). Similar results, ACMP exposure resulted in oxidative stress and an increase in NO production in the brain **(Duzguner and Erdogan, 2012).** Furthermore, **Akaber et al. (2016)** showed that ACMP caused a significant increase in the levels of NO compared to negative control group. Elevated nitric oxide (NO) leading to disorganization of the membrane**. Knowles and Moncada (1994)** also reported that Abnormal NOS activation during ACMP administration increases NO levels, which contributes to the deterioration of intracellular signaling mechanisms.

The same table (Table 1) when curcumin was given to ACMP-administered rats, it reduced or inhibited the increase of NO level at 20 and 40 days by 32.2% and 102.49% respectively. Statistically, this reduction or inhibition of curcumin to the NO level was significant ($p<0.01$). In the same line, **Thiyagarajan and Sharma (2004)** revealed that curcumin reduced NO levels in treated rats and was associated with peroxy nitrite scavenging by inhibiting xanthine oxidase and inducible NOS. Furthermore, **Fatih et al. (2019)** demonstrated that curcumin treatment normalized NO levels in acetamiprid. Previous Studies are in accordance with our data investigated that curcumin could inhibit NOS hyper activation and the subsequent increase in hippocampal NO (**Gilhotra and Dhingra, 2010; Wei et al., 2010**).

3.2-Histopathological findings

I-Normal control group

High power examination of hippocampus of control group showed that it displayed as a bilateral incurved seahorse-shaped structure that referred to cornu ammonis (CA) and dentate gyrus (DG) (Fig.1). In addition, the same figure shows that the cornu ammonis (CA) area divided into 4 subdivisions: CA1, CA2, CA3 & CA4 regions.

Cornu Ammonis had five layers (CA1 to CA4): stratum alveolus, stratum oriens, stratum pyramidale, stratum radiatum, and stratum lacunosum-moleculare. The middle dark zone was formed by the stratum pyramidale. It housed the hippocampus's primary excitatory neurons. There were also a few interneurons in this layer. The stratum pyramidale in CA1 was made up of small sized pyramidal neurons arranged in 4-5 compact layers of cells, the majority of which had

vesicular nuclei and visible nucleoli. Likewise, neuroglia and blood capillaries were detected in normal structure in both stratum oriens and stratum radiatum layers of CA1 (Fig.2).

Table (1): The effect of curcumin on nitric oxide (NO) levels in homogenates of brain cortex of control and different treated rats

Measurements / Groups	Nitric oxide levels (nmole/mg tissue)	
	20 days	40 days
Control	1.6114 ±0.0207	1.6114 ±0.0207
Vehicle	1.6142 ±0.0249*	1.6264 ±0.0163*
Curcumin	1.6718 ±0.0128*	1.6802 ±0.0116*
Acetamiprid % of control	3.3794 ±0.0548# 109.7%	4.5258 ±0.0727# 180.8%
ACMP + cur % of Acetamiprid	2.555 ±0.0439## 32.2%	2.235 ±0.101## 102.49%

Values are means ± S.E. of 6 animals in each group.
* Non-significant compared with control group (p>0.05).
# Significant compared with control group (p<0.01).
Significant compared with acetamiprid group (p<0.01).

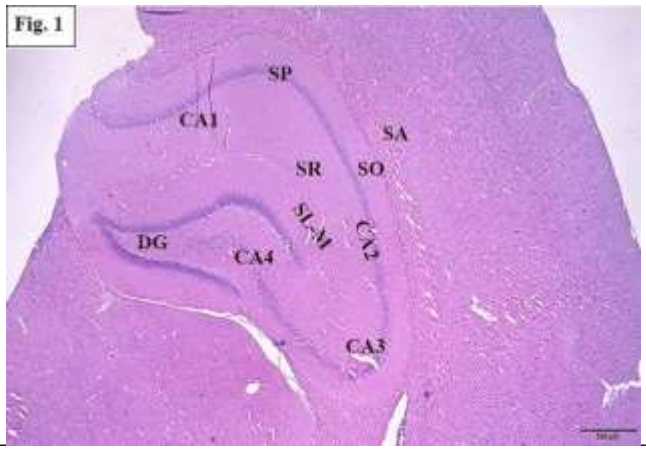


Fig. 1: Photomicrograph from control group section viewing the different areas of the hippocampal formation. Cornu Ammonis regions (CA1, CA2, CA3 & CA4), Dentate gyrus (DG), Stratum alveolus (SA), Stratum oriens (SO), Stratum pyramidale (SP), Stratum radiatum (SR), Stratum lacunosum-moleculare (SL-M). Scale bar: 500µm

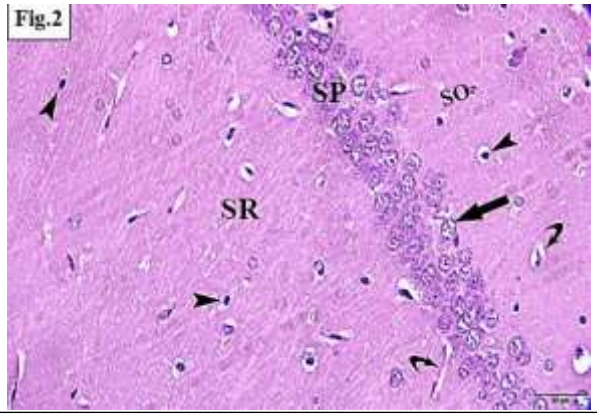
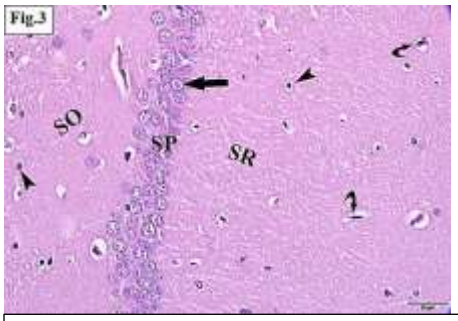
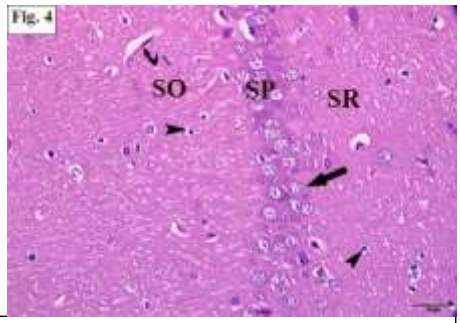


Fig. 2: High magnification of control group section showing pyramidal cells (thick arrows) of Stratum pyramidale (SP) of CA1 region, neuroglia (arrow head), blood capillaries ( ). Stratum oriens (SO), Stratum radiatum (SR). **Scale bar: 50µm**

II- Veh- treated groups

Comparing with control group, histological examinations of the sections of Veh - groups at 20 and 40 days (Figs.3 & 4 respectively) revealed histological integrity of the CA1 area of the hippocampus. The stratum pyramidale of CA1 is formed of closely packed small pyramidal cells arranged in 4-5 layers with large vesicular nuclei and prominent nucleoli. In both stratum oriens and stratum radiatum layers of CA1 healthy shapes of glial cells and blood capillaries were noticed.

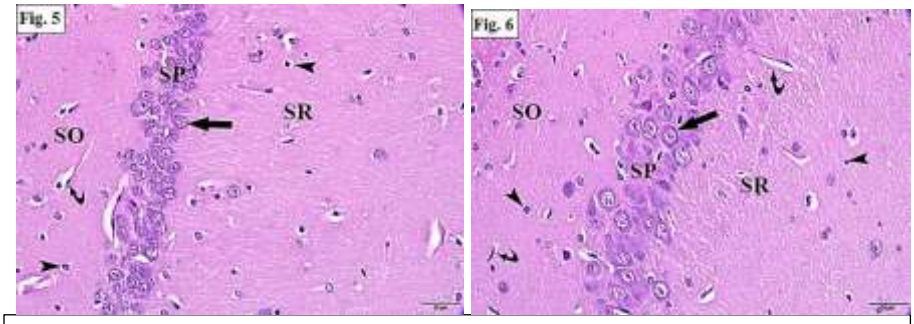




Figs. (3&4): High magnification sections of 20 &40 days respectively of Veh-treated group showing normal pyramidal cells (thick arrows) of Stratum pyramidale (SP) of CA1 region, neuroglia (arrow head), blood capillaries ( ). Stratum oriens (SO), Stratum radiatum (SR). **Scale bar: 50µm**

III- Cur- treated groups

After the end of both 20 & 40 days (Figs.5 & 6, respectively) following treatment of rats with curcumin, microscopic examination of CA1 area of the hippocampus displayed no histological alterations contrasted with those of the control group. The stratum pyramidale of CA1 comprised of small pyramidal cells were arranged in 4–5 compact layers and had large and centrally located pale nuclei with prominent nucleoli. The same figures revealed healthy structure of glial cells and blood capillaries in both stratum oriens and stratum radiatum layers of CA1.

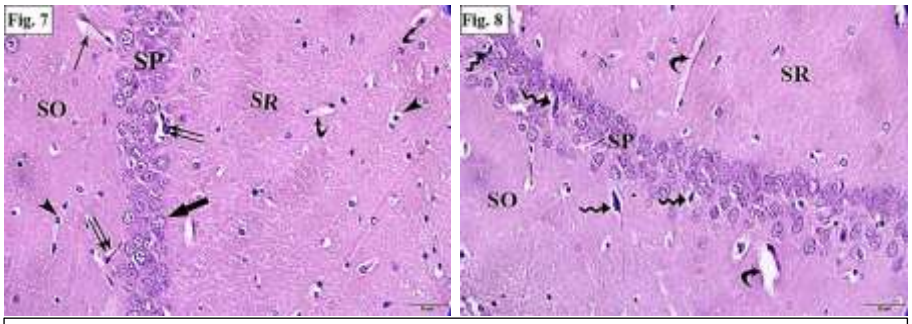


Figs. (5& 6): High magnification sections of 20&40 days respectively of Cur-treated group showing structural integrity of pyramidal cells (thick arrows) of Stratum pyramidale (SP) of CA1 region, neuroglia (arrow head), blood capillaries (↷). Stratum oriens (SO), Stratum radiatum (SR). **Scale bar: 50µm**

IV- ACMP- treated groups

In comparing with control group, light microscopic examination of the hippocampal sections of 20 days of ACMP- administered group exhibited slight histopathological changes. These changes included dilatation of blood capillaries (Fig.7).

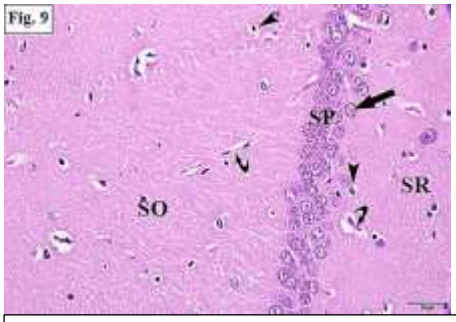
Otherwise, light microscopic inspection of the hippocampal sections at 40 days of ACMP-administered group showed more histopathological alterations in CA1 than 20 days. The stratum pyramidale showed atrophied and shrunken neurons with hyper chromatic nuclei. Dilatation of blood vessels with irregular outlines was also noted (Fig.8).

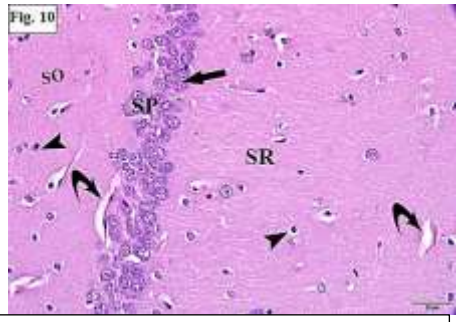


Figs. (7&8): High magnification sections of 20 & 40- days at respectively of ACMP-administered-group revealing atrophied and shrunken cells with hyperchromatic nuclei (↝) and the of blood vessel (↷) showed irregular outlines. Pyramidal cells (thick arrows) of Stratum pyramidale (SP), neuroglia (arrow head), Stratum oriens (SO), Stratum radiatum (SR). **Scale bar: 50µm**

V- ACMP +Cur- treated groups

Comparing with ACMP- treated group, the investigation of the hippocampal sections at both 20 & 40 days of ACMP+ Cur-treated group revealed that the hippocampal integrity retained its normal form to large extent comparing with ACMP administered group. The stratum pyramidale with 4-5 compact layers of pyramidal neurons showed an improvement in stratum pyramidale of CA1. Normal neurons, with large vesicular nuclei and prominent nucleoli and normal distribution of the glial cells and normal appearance of blood capillaries were detected (Figs.9& 10, respectively).





Figs. (9&10): High magnification sections of 20 & 40- days at respectively of ACMP+Cur administered-group displayed normal structure of stratum pyramidale (SP) with 4-5 compact layers of small pyramidal cells (thick arrow) of CA1 region, most with vesicular nuclei and observable nucleoli. Also, glial cells (arrow head) in normal form and blood capillaries (↷) were noticeable in both Stratum oriens (SO) and stratum radiatum (SR) layers. **Scale bar: 50µm**

Pesticides cause oxidative stress, which causes the formation of free radicals and changes in the antioxidant system. The generation of free radicals causes DNA damage, protein degradation, LPO, and finally damage to various vital organs such as the brain resulting in pesticide-mediated toxicity **(Abdollahi et al., 2004; Khan et al., 2005; Lopez et al., 2007).** The findings of the present study are in accordance with different studies **(Yasmina et al., 2018; Morteza et al., 2020; Meilin et al., 2020)** that showed atrophied cells with pyknotic nuclei were increased especially in medium and high doses of ACMP.

Additionally, the current study revealed that pre-treatment of curcumin to ACMP-administered group provided protection against hippocampal disorders as confirmed by preservation of the hippocampal structure to its normal form. The results of this study are consistent with different studies (**Sumanont, et al., 2006; Issuriya, et al., 2014; Kübra and Dilek , 2020; Yasmina et al., 2021**) that confirmed the protective role of curcumin against neurotoxicity induced by ACMP and the efficacy of curcumin to restore the normal histological architecture in the dentate gyrus and hippocampus. In the same line, **Kübra and Dilek, (2020)** found that pretreatment with curcumin increased the number of cells in hippocampal sections with clearly visible cell and nucleus boundaries. Similarly, **Namgyal et al. (2020)** revealed that curcumin had effectively arrested the degeneration of the hippocampal neurons**.**

Conclusion

The study clearly demonstrated the chronic exposure to acetamiprid used in this study was able to induce neurotoxicity by abnormalities in NO level and hippocampus brain area in adult male rats. Furthermore, the co-administration of curcumin showed improvements in neurological disorders caused by acetamiprid.

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