Assiut Univ. J. of Zoology **Printed ISSN 1687-4935**
50(1), pp. 1-22(2021)

AMELIORATIVE EFFECT OF THE AQUEOUS EXTRACT OF MUSHROOM (*PLEUROTUS OSTREATUS)* ON NEUROTOXICITY INDUCED BY CIPROFLOXACIN IN RATS

Nageeb MM[1], Abd elgaffar S Kh[2], Gaadee, HIM[3], Omar HM[4]

[1]Chemist at Animal Research Institute, Sohag

[2]Department of Pathology, Faculty of Veterinary Medicine, Assiut University

[3]First Researcher. Biochemistry Unit, Agriculture Research Center,Research Institute.

[4]Department of Zoology, Faculty of Science, Assiut University

Received: 17/2/2021 **Accepted:** 10/3/2021 **Available Online:** 1/6/2021

Ciprofloxacin (CPX) is a broad-spectrum antibiotic widely used in both human and veterinary medicine, however, it is misuse causes neurological disorders. In the current study, the protective effects of Mushroom *P. ostreatus* aqueous extract (MAE) against CPX-induced neurotoxicity have been investigated. Twenty -four adult rats were allocated into four groups, control group, CPX group that received a daily dose of 50 mg/kg for two weeks, MAE group that was supplemented with a daily dose of 200 mg/kg for two weeks and CPX plus MAE group which received CPX (50 mg/kg) for two weeks then supplemented with MAE (200mg/kg) for another two weeks. The results showed that CPX caused alterations in the levels of acetylcholinesterase (AChE), glutathione (GSH) and lipid peroxidation in the brain tissue accompanied with neurodegenertion in the cerebral cortex and hippocampus in comparison with the control. However, MAE caused alterations in the levels of AChE, total antioxidant capacity and LPO in comparison with CPX group. Brain of rats treated with CPX and supplemented with MAE showed improvement in the parameters of oxidative stress and the histological structure with less neurodegenerative cells in the cerebral cortex and hippocampus. In conclusion, CPX caused neurotoxicity mediated by oxidative stress and MAE can ameliorate brain tissue against CPX- induced brain toxicity due to its content of antioxidant compound.

Key words: Ciprofloxacin, brain, rats, oxidative stress, Mushroom aqueous extract.

INTRODUCTION

Ciprofloxacin (CPX) is the most potent second-generation fluoroquinolone drug and is on the World Health Organization (WHO) model list of essential medicines for human **(WHO, 2017; Rusch *et al.*, 2019).** CPX is the main metabolite of enrofloxacin; a fluoroquinolone antibacterial agent which is commonly used for the treatment of farm animals from various infections, including pneumonia, skin, and soft tissue infections **(Ananda Chitra *et al.*, 2018; Rusch *et al.*, 2019).** However, CPX has toxicological effects on humans and animals as it causes significant increase of lipid peroxidation (LPO) and alteration of glutathione (GSH) redox status in hepatic tissues of rats (**Hincal and Taskin, 1995**). Also, it caused severe congestion with perivascular edema in the blood vessels and capillaries of cerebral cortex and hippocampus associated with alterations of the neurotransmitter levels (**Rawi et al., 2011**). Moreover, a different dose CPX alters whole brain and selected brain regions, excitatory and inhibitory amino acids, brain monoamines, AChE, and glutathione levels (**Rawi et al., 2014**). Administration of CPX to rats increased MDA as well as decreased GSH and catalase activity with respect to their controls, indicated enhanced oxidative stress in the brain (**Ilgin et al., 2015**)

Recently, people are shifting towards available natural and herbal medicines (**Ibitoye et al., 2019; Dubey et al., 2019**). Many researchers found that most edible mushrooms are therapeutic foods that have biological potentials such as antibacterial, anticancer, and antioxidant (**Garcia-Lafiente et al., 2011; Schillaci et al., 2013**). Also, they are rich sources of natraceuticals (**Ribiro et al., 2007; Ghate and Sridhar, 2017)**. Edible

mushrooms are increasingly being recognized as important food products and therapeutic properties (**Majesty et al., 2019**). *P. ostreatus* is one of the most cultivated edible mushrooms worldwide as it is rich in bioactive components as phenolic compounds that possess antioxidant properties (**Dicks and Ellinger, 2020)**. Therefore, the present study aims to assess the main active component of *P. ostreatus* aqueous extract and to evaluate the efficacy of the extract in ameliorated the neurotoxicity induced by CPX in rats.

MATERIALS AND METHODS

A. Materials

1. Chemicals:

Ciprofar (500 mg) tablets, PHARCO PHARMACEUTICALS, Alexandria, Egypt. Total antioxidant capacity, (CAT. NO. TA 25 13), Bio-Diagnostic, Giza, Egypt. Sodium dodecyl sulfate (SDS), 1, 1, 3, 3-tertramethoxypropane (TMP), thiobarbituric acid (TBA), sulfanilamide, naphthylethylene diamine dihydrochloride, glacial meta-phosphoric acid, epinephrine, and triton-X 100 were purchased from Sigma Aldrich Company, USA.

2. Animals:

A total of 24 adult male rats with average initial body weight 180±20 gm. were purchased from the Animal House of Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt. Experimental rats were housed in cages at room temperature (25±5ºC) with normal 12 hrs. light/12 hrs. dark cycle with *ad libitum* access to pelleted diet containing 80% carbohydrates, 18% proteins, 2% fat and water for one week of adaptation. All experimental protocols that held on animals were done according to regulations set by the Institutional Animal Care and approved by Assiut University. And all efforts were done to minimize the pain of experimental rats.

Experimental design:

Rats were randomly allocated into four groups consisting of 6 rats each, as follows:

1) **Control group:** Rats were maintained at comfort conditions and fed the basal diet without any supplementation.
2) **CPX group:** Rats fed the basal diet and were orally adjuvant dose of CPX (50 mg/Kg) once daily for two weeks.
3) **MAE group:** Rats fed the basal diet and were orally supplemented with 200mg/kg of MAE once daily for two weeks.
4) **CPX plus MAE group:** Rats fed the basal diet and were orally received CPX (50 mg/Kg) for two weeks, then supplemented with MAE (200 mg) for two weeks.

Collection of samples:

On the day scheduled, rats were euthanized by cervical dislocation. Brain from each rat were quickly removed, washed in a saline solution, then, one half of the brain was fixed immediately in 10 % neutral buffered formalin for histopathological study **(Drury and Wallington, 1980)** and the other half was immersed in liquid nitrogen and then kept at -20^0C for biochemical study.

B. Methods:

Preparation of mushroom aqueous extract:

Twenty-five gram of fruiting bodies dried at 50°C and then grounded in a blender, after which the crude powder used for the extraction. The powder was extracted in 500 ml water by heating in the water at 90°C for three hrs. After cooling to room temperature, the extract was filtered **(Lee *et al.*, 2009).**

Gas chromatography–mass spectrometry (GC–MS) analysis:

The analysis was carried out by gas chromatography-mass spectrometry (GC-MS) using ethanol as solvent at Chromatographic Analysis Unit (GC-MS/DIP), Rigorous Analysis Unit of the Central Lab., Faculty of Science, Assiut University, Assiut, Egypt. The extracts analyzed by (GC/MS (7890A/5975B)).

Preparation of brain homogenate:

10% w/v homogenate of the brain tissue was prepared in 0.1 M phosphate buffer PH 7.4 using a homogenizer (IKA Yellow line DI 18 Disperser, Germany). The homogenates were centrifuged at 8,000 rpm for 20 mins at 4ºC and the supernatants were kept frozen at -20ºC for the subsequent biochemical assays.

Biochemical assays:

Lipid peroxidation as thiobarbituric reactive substance measured by the method of **Ohkawa *et al.* (1979)**. Reduced glutathione form (GSH) measured according the method of **Beutler *et al.* (1963)**. Total antioxidant capacity measured by the method of **Koracevic *et al.* (2001).** Total protein and acetylcholinesterase activity estimated according to the methods described by **Lowry *et al.* (1951)** and **Ellman *et al.* (1961),** respectively.

Histopathological investigation:

The morphological analysis was done by Research Microscope type Axiostar Plus made by Zeiss transmitted light bright field examinations upgradeable to professional digital image analysis system (Carl Zeiss Axiovision Product Suit DVD 30).

Statistical Analysis:

The normal distribution of sample data and the homogeneity of the variances were firstly assessed by Shapiro-Wilk's test and Leven's test, respectively. One-way ANOVA was conducted followed by a post-hoc test (Duncan's test) for multiple comparisons among experimental groups. The results were expressed as the mean±standard error (SE). Statistical analysis was performed with IBM® SPSS® for Windows (IBM Corp., Armonk, NY, USA) statistics version 21 for Windows.

RESULTS

GC–MS analysis:

Aqueous extract of mushroom was analyzed and identified by GC-MS which showed ten peaks as Fig (1). The active principles with their retention time (RT), molecular formula, molecular weight (MW), peak % and nature are presented in Table (1). GC-MS analysis showed the revealed that existence of many compounds known by their biological activities such as phenols, steroids, alcohols and fatty acids.

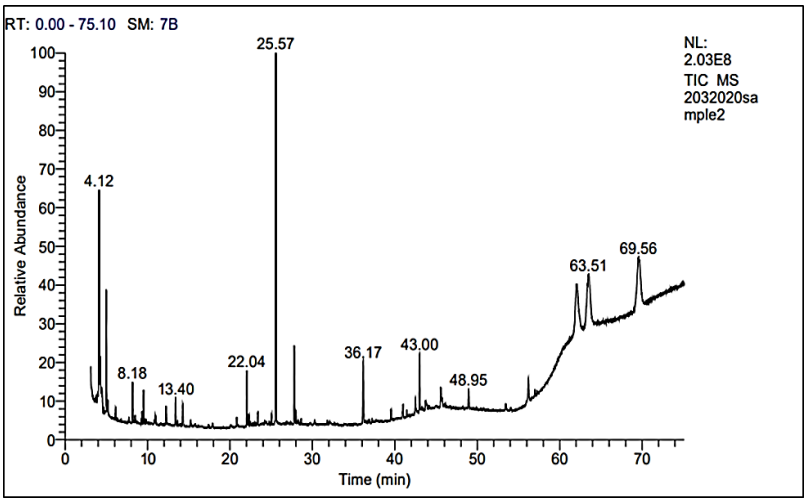


Fig.(1): GC-MS chromatogram of aqueous extract of mushroom *P. ostreatus*

Table (1): GC-MS analysis of aqueous extract of mushroom *P. ostreatus*

R.T. (min)	Name of the compond	M.F.	M.W.	Peak area (%)	Nature of the compound
4.12	2-Pyridinecarboxylic acid	$C_6H_5NO_2$	123	9.38	Pyridine derivative
	2,4-Pentadienenitrile	C_5H_5N	79		Nitrile compound
	Pyridine	C_5H_5N	79		N-heteroaromatic
5.0	Butanoic acid, 3-methyl-	$C_5H_{10}O_2$	102	4.98	short-chain fatty acid
	Pentanoic acid, 3-methyl-	$C_6H_{12}O_2$	116		Medium-chain fatty acid
8.18	Benzene, 1-chloro-3-methyl	C_7H_7Cl	126	1.79	Toluene
	Benzene, 1-chloro-4-methyl-	C_7H_7Cl	126		Toluene
	Benzyl chloride	C_7H_7Cl	126		Hydrocarbon halides
13.40	2-Heptafluorobutyroxydodecane	$C_{16}H_{25}F_7O_2$	382	1.35	halogenated alkane Organofluorine
	4-Trifluoroacetoxytetradecane	$C_{16}H_{29}F_3O_2$	310		
	3-Trifluoroacetoxytetradecane	$C_{16}H_{29}F_3O_2$	310		
	3-Trifluoroacetoxypentadecane	$C_{17}H_{31}F_3O_2$	324		
	2-Trifluoroacetoxypentadecane	$C_{17}H_{31}F_3O_2$	324		

22.05	1-Hexadecanol " Cetyl alcohol"	$C_{16}H_{34}O$	242	2.50	alcohol
	3-Trifluoroacetoxytetradecane	$C_{16}H_{29}F_3O_2$	310		halogenated alkane Organofluorine
	Hexadecen-1-ol, trans-9-	$C_{16}H_{32}O$	240		alcohol
	n-Heptadecanol-1	$C_{17}H_{36}O$	256		alcohol
25.57	Phenol, 2,4-bis(1,1-dimethylethyl)-	$C_{14}H_{22}O$	206	17.32	Phenols
	Phenol, 3,5-bis(1,1-dimethylethyl)-	$C_{14}H_{22}O$	206		Phenols
36.17	10-Heneicosene (c,t)	$C_{21}H_{42}$	294	3.80	Unbranched alkene
	1-Docosene	$C_{22}H_{44}$	308		Alkene
	n-Heptadecanol-1	$C_{17}H_{36}O$	256		Alcohol
	1-Eicosanol	$C_{20}H_{42}O$	298		alcohol
43.00	1-Hexadecanol, 2-methyl-	$C_{17}H_{36}O$	256	3.85	alcohol
	17-Pentatriacontene	$C_{35}H_{70}$	490		unsaturated aliphatic hydrocarbons
	Octatriacontyl pentafluoropropionate	$C_{41}H_{77}F_5O_2$	969		alpha-halo carboxylic acid derivatives
	Behenic alcohol	$C_{22}H_{46}O$	326		saturated fatty alcohol
	Hexadecane, 1,1-bis(dodecyloxy)-	$C_{40}H_{82}O_2$	594		hydrocarbon
48.95	Ethyl iso-allocholate	$C_{26}H_{44}O_5$	436		steroids
	Oleic acid, eicosyl ester	$C_{38}H_{74}O_2$	562		oleates

	9-Octadecenoic acid (Z)-, tetradecyl ester	**$C_{32}H_{62}O_2$**	**478**	**1.18**	**Fatty acid Ester**
	7,8-Epoxylanostan-11-ol, 3-acetoxy-	**$C_{32}H_{54}O_4$**	**502**		**Steroid**
	Oleic acid, 3-(octadecyloxy)propyl ester	**$C_{39}H_{76}O_3$**	**592**		**oleates**
63.50	**1-Monolinoleoylglycerol trimethylsilyl ether**	**$C_{27}H_{54}O_4Si_2$**	**498**	**9.39**	**monoglyceride**
	Benzo[b]triphenylene	**$C_{22}H_{14}$**	**278**		**PAH**
	1,4-Bis(phenylethynyl)-2,5-cyclohexad iene-1,4-diol	**$C_{22}H_{16}O_2$**	**312**		**Diol compound**
	Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-h exadecamethyl	**$C_{16}H_{50}O_7Si_8$**	**578**		**Polysiloxane**
	Dibenzo-1,2,7,8-anthracene	**$C_{22}H_{14}$**	**278**		**PAH**

Biochemical analysis:

In the present study, CPX at a dose of 50 mg/kg BW for two weeks caused a non-significant increase in the AChE activity; however, there were a significant increase in the LPO with significant decrease in GSH level in the brain tissue. While, MAE caused a significant reduction in the AChE activity compared with the control and CPX groups. In addition, it significantly reduced the LPO compared with CPX group. Besides, MAE significantly improved the total antioxidant capacity compared with the control and CPX groups. As for the CPX and MAE group, this treatment made a remarkable recovery over the CPX group, since there were significant reductions in the AChE compared with the control and CPX

groups. Also, it significantly reduced the LPO level compared with the CPX group. In addition, it significantly elevated the total antioxidant capacity in comparison to the CPX group, and even the control. However, it caused a marked decrease in the GSH content if compared with the control group (**Table,2).**

Table (2): Oxidative stress parameters and acetylcholinesterase activity in the brain of control and treated rats

Parameter	Groups				
	Control	CPX	Mush	CPX + Mush	P-Value
AChE activity (moles/l./min x 10^{-8}/g of tissue)	2.04±0.18	2.26 ±0.44	1.08±0.20^{BD}	0.97±0.16^{CE}	0.003**
LPO (nmol/mg)	0.21±0.01	0.41±0.04^{A}	0.25±0.03^{D}	0.20±0.02^{E}	0.001**
GSH (µg/mg)	14.13±0.50	11.18±0.96^{A}	12.84±0.53	11.53±0.49^{C}	0.034*
Total antioxidants (mM/mg)	0.10±0.01	0.12±0.01	0.14±0.01^{BD}	0.14±0.01^{CE}	0.022*

AChE: Acetyl cholinesterase, LPO: Lipid peroxidation, GSH: Glutathione.

- Data are represented as mean±SEM. The P-values reported are for a one-way ANOVA test. The used symbols *, **, and *** to represent significance at $P \leq 0.05$, $P \leq 0.01$, and $P \leq 0.001$ respectively for the ANOVA test.
- The letters A, B, C, D, E, and F were used to denote the significant differences based on the Duncan test at the 0.05 significance level. as follows: A for CPX vs. control, B for Mush vs. control, C for CPX + Mush vs. control, D for Mush vs. CPX, E for CPX+ Mush vs. CPX, and F CPX + Mush vs. Mus

HISTOPATHOLOGY

Plate (1): Photomicrographs from brain section of control rats, (A) normal histology of the cerebral cortex, showing the neurons are evident from their shape and their distinct, basophilic cytoplasm. glial cells nuclei are seen adjacent to neurons. **(B**) normal histology of the hippocampus showed the hippocampal neurons are compactly arranged, with complete cell morphology and normal pyramidal cells. The two-headed black arrow refers to the normal thickness of the pyramidal layer. **Brain section from rats of CPX group, (C)** depicts microgliosis (black arrowhead) besides the presence of damaged cells with satellitosis (black arrow) and neurophagia (black star). Tau protein also demonstrated (dashed arrows). (**D)** showing decreased thickness of pyramidal cell layer (two-headed black arrow), with increased pyknotic cells (black arrow) and degenerated cells (black head arrow) and perivascular oedema (black stars)**. (E)** showing lymphoid hyperplasia in the choroid plexus from the lateral ventricle **(F)** showing perivascular lymphoid cells reaction (black arrowhead) and focal gliosis (oval shape), **H&E (x40).**

Plate (2): Photomicrographs from the brain section of MAE supplemented rats, (G) showing cerebral cortex of more or less normal neurons besides (black arrow) the presence of perivascular edema (black star)**. (H)** showing the hippocampus region with normal thickness of the pyramidal cell layer (two-headed arrow), and more or less normal neuron (small black arrows) In addition, there was perivascular edema (stars) and apoptotic cells (black arrowheads). **Brain section from rats received CPX and supplemented with MAE, (I)** showing apoptotic neurons (black arrow) and perivascular edema (star), besides pyknotic cells (black arrowheads). **(J)** showing shrinkage in the thickness of pyramidal cell layer and few numbers of degenerated cells (black arrowheads), with the presence of perivascular edema (star). **H&E (x40)**

Plate: 1

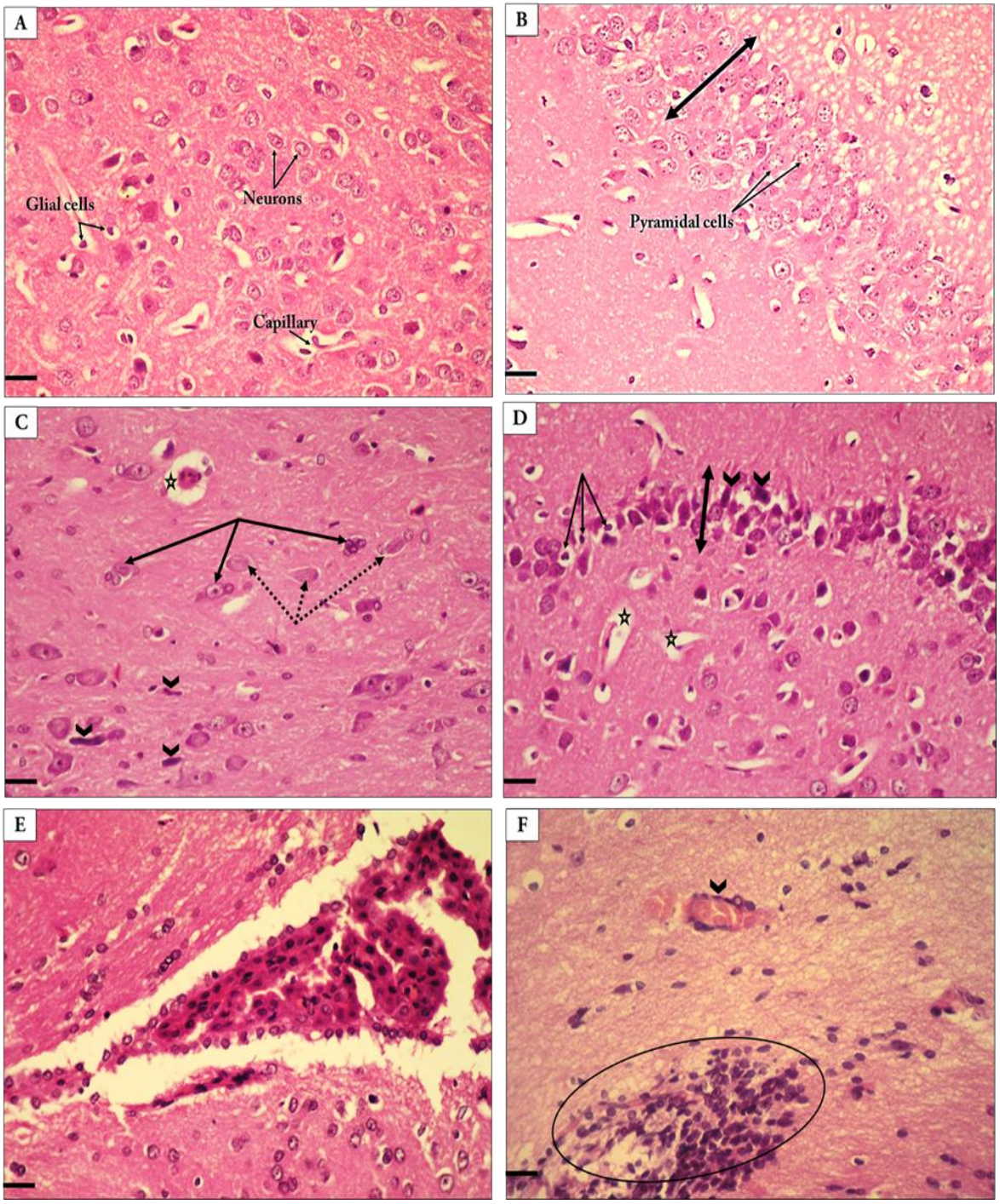
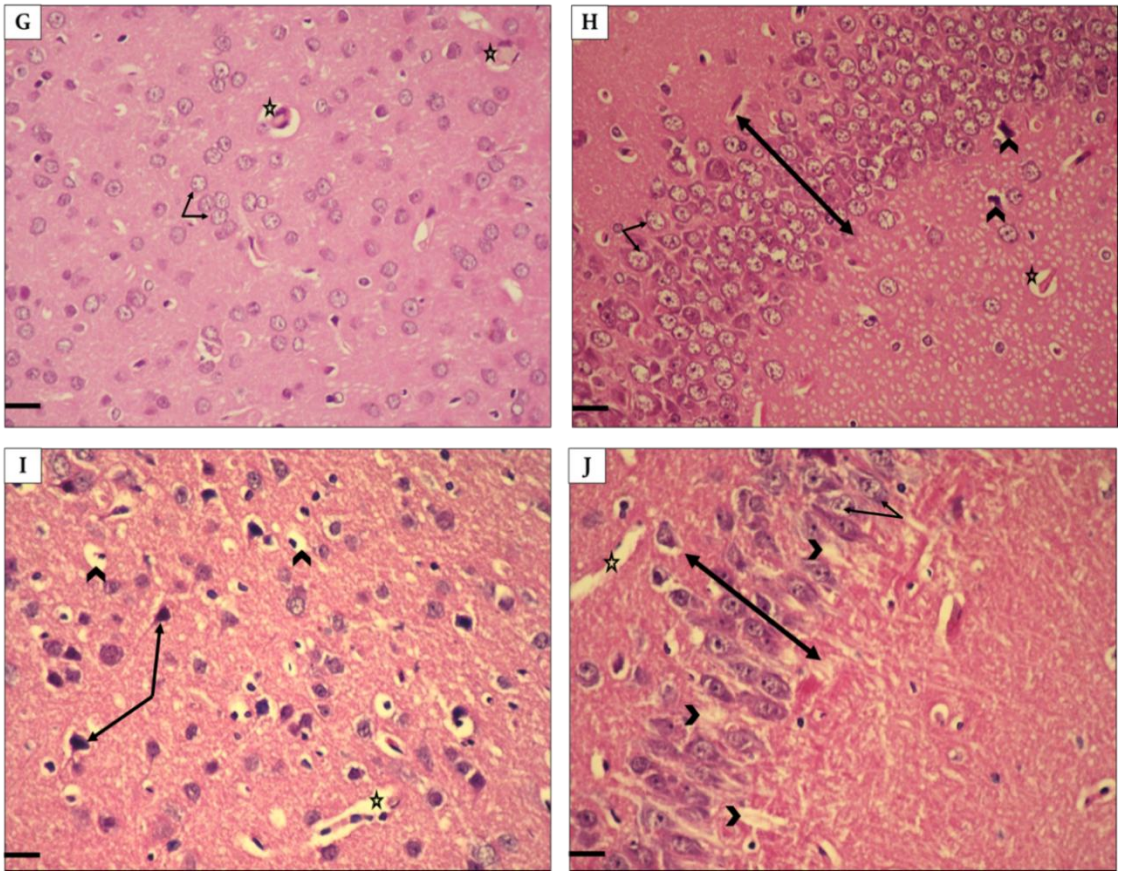


Plate: 2



DISCUSSION

GC-MS is the best technique to identify the bioactive constituents of long chain hydrocarbons, alcohols, acids, ester, alkaloids, steroids, amino and nitrogen compound (**Venkatesh et al., 2014**). In the present study, GC-Ms analysis of MAE showed complex mixture of many constituents including 38 identified compounds which influence their nutritional and medicinal properties **(Zhang et al., 2008).** From these detected compounds; 3-trifluoroacetoxytetradecane, 3-trifluoroacetoxypentadecane (**Hussein *et al.*, 2016),** hexadecen-1-ol, trans-9- (**Huang *et al.*, 2016),** phenol, 2,4-bis(1,1-dimethylethyl)- (**Wang *et al.*, 2016),** and phenol, 3,5-bis(1,1-dimethylethyl)- (**Manorenjitha *et al.*, 2013)** which have antioxidant activities (Table 1)**.**

CPX is one of the most commonly used antibacterial antibiotic easily cross blood brain barrier and may cause brain tissue injury **(Hamdi *et al.*, 2018).** However**,** repeated pharmacological doses of CPX were found to induce neurological toxicity as evident by increased LPO as well as decreased GSH and catalase activity with respect to their controls (**Ilgin et al., 2015**). Current results found that CPX altered brain AChE activity and oxidative stress markers were thought to be the possible underlying mechanisms of CPX-induced neurotoxicity. This result is in agreement with **Ilgin *et al.* (2015)** who showed that oxidative stress is critical in the pathogenesis and development of neurodegenerative disorders. Likewise, **Gürbay *et al.* (2019)** and **Ibitoye *et al.* (2019)** who found that CPX produces free radicals leads to LPO induction with a concomitant decrease in thiol levels and increased in the AChE activity. Histopathologically, CPX caused neurons damage and hemorrhagic defects in the brain **(Dogan *et al.*, 2019).** Generally, **Hangas *et al.* (2018)** suggested that CPX toxicity have broad range of mechanisms including topoisomerase inhibition, generating double-strand breaks, oxidative stress and altered calcium homeostasis**.**

GC-MS analysis of the extract showed the presence of picolinic acid (2-pyridinecarboxylic acid) and pyridine which explains the significant reduction in the AChE activity compared with the control and CPX groups. Since it was found that the replacement of the benzene ring moiety with the *N*-heterocyclic ring and the introduction of the nitrogen atom cause inhibition in AChE activity, probably due to the additional affinity with the active pocket of AChE **(Wu *et al.*, 2018).** The presence of antioxidants mentioned before may explain the ability mushroom extract to significantly reduce LPO compared to CPX group, while significantly reduce total antioxidants content

relative to both CPX and control groups. This also may be able to explain the observed enhancement in the brain tissue histopathological results in this group compared to the CPX group. It worth mentioning that although the GC-MS analysis showed that MAE contains compounds that possess antioxidants, anti-inflammatory, anti-tumor and other activities, it also revealed the presence of other toxic compounds such as PAHs as indicated in **(Table 1),** and that may be due to the contamination with PAHs from environmental sources like mushroom soil, and substrate because PAHs are readily absorbed by organic matter in soil and difficult to degrade. The accumulation of PAHs in soil may lead to contamination of food chains, which could cause a potential risk to human health **(Igbiri *et al.*, 2017).**

Regarding to the rats received CPX and supplemented with MAE, the significant reduction in the AChE activity, LPO and total antioxidants compared to the control and CPX groups may be returned to the competitive antagonistic effect of mushroom on CPX effect against AChE activity in the brain tissue. Moreover, the pathological investigations showed that MAE was able to alleviate the neurotoxic effect of CPX on the brain tissue due to its contents of compounds with antioxidants, anti-inflammatory such as oleic acid and eicosyl ester **(Gurunathan *et al.*, 2016),** 17-Pentatriacontene **(Dinesh Kumar G *et al.*, 2018),** as well as 7,8-Epoxylanostan-11-ol, 3-acetoxy- **(Zekeya *et al.*, 2014),** as shown in **(Table 1).**

In conclusion, it is evident that aqueous extract of mushroom *P. ostreatus* ameliorated CPX-neurotoxicity in brain rat's due to its contents of phenolic and steroids compounds and consumers must be carefully when eating edible mushrooms because may contain toxic compounds due to environmental pollution of soil.

REFERENCES

AnandaChitra M, Jayanthy C and Nagarajan B (2018): Virulence Genes Detection and Antimicrobial Susceptibility of Staphylococcus *pseudintermedius Isolates* from Canine Skin Infection in Chennai, India. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, *88*(1), 355-361.

Beutler, E., Duron, O., & Kelly, B. m. (1963): Improved method for the determination of blood glutathione. *J. lab. clin. Med.*, 61, 882-888.

Dicks, L., & Ellinger, S. (2020): Effect of the Intake of Oyster Mushrooms (Pleurotus ostreatus) on Cardiometabolic Parameters-A Systematic Review of Clinical Trials. *Nutrients*, 12(4), 1134.

Dinesh Kumar G, Karthik M and Rajakumar R (2018): GC-MS analysis of bioactive compounds from ethanolic leaves extract of Eichhornia crassipes (Mart) Solms and their pharmacological activities**.** *The Pharma Innovation Journal***; 7(8): 459-462.**

Dogan, Z., Cetin, A., Elibol, E., Vardi, N., & Turkoz, Y. (2019): Effects of ciprofloxacin and quercetin on fetal brain development: a biochemical and histopathological study. *The Journal of Maternal-Fetal & Neonatal Medicine*, 32(11), 1783-1791.

Drury, R. A., & Wallington, E. A. (1980): Carleton's Histological Technique. 5th Edition, Oxford University Press, New York.

Dubey, S. K., Chaturvedi, V. K., Mishra, D., Bajpeyee, A., Tiwari, A., & Singh, M. P. (2019): Role of edible mushroom as potent therapeutics for the diabetes and obesity. *3 Biotech*, *9*(12), 450.

Ellman, G. L., Courtney, K. D., Andres Jr, V., & Featherstone, R. M. (1961): A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochemical pharmacology*, 7(2), 88-95.

García-Lafuente A, Moro C, Villares A, Guillamón E, Rostagno MA, D'Arrigo M, Martínez JA. (2011): Mushrooms as a source of anti-inflammatory agents. *Am J Comm Psychol.*48: 125–141.

Ghate, S. D., & Sridhar, K. R. (2017): Bioactive potential of Lentinus squarrosulus and Termitomyces clypeatus from the Southwestern region of India. *Indian Journal of Natural Products and Resources (IJNPR) [Formerly Natural Product Radiance (NPR)]*, *8*(2), 120-131.

Gürbay, A., Gonthier, B., Daveloose, D., Barret, L., Favier, A., & Hıncal, F. (2019): Ciprofloxacin-induces free radical production in rat cerebral microsomes. *Free radical research*, 53(4), 397-404.

Gurunathan, A., Senguttuvan, J., & Paulsamy, S. (2016): Evaluation of Mosquito Repellent Activity of Isolated Oleic Acid, Eicosyl Ester from Thalictrum javanicum. *Indian journal of pharmaceutical sciences*, 78(1), 103–110.

Hamdi, H., El-Ghareeb, A. E. W., & Sharawy, E. (2018): Fetal exposure to the antibiotic drug (Ciprofloxacin) in Albino rats. *J Pharm Chem Pharmacol*, *2*(1), 39-42.

Hangas, A., Aasumets, K., Kekäläinen, N. J., Paloheinä, M., Pohjoismäki, J. L., Gerhold, J. M., & Goffart, S. (2018): Ciprofloxacin impairs mitochondrial DNA replication initiation through inhibition of Topoisomerase 2. *Nucleic acids research*, 46(18), 9625-9636.

Hincal F and Taskin T (1995): The mechanism induced by ciprofloxacin may involve the generation of free radicals and the activation of excitatory amino acid receptors. *Abstracts of the International Congress of Toxicology, W. A. Abstr* 99, VII Seattle, p. 27.

Huang, F. C., Horváth, G., Molnár, P., Turcsi, E., Deli, J., Schrader, J., Sandmann, G., Schmidt, H., & Schwab, W. (2009): Substrate promiscuity

of RdCCD1, a carotenoid cleavage oxygenase from Rosa damascena. *Phytochemistry*, 70(4), 457-464.

Hussein, H. M., Hameed, I. H., & Ibraheem, O. A. (2016): Antimicrobial Activity and spectral chemical analysis of methanolic leaves extract of Adiantum Capillus-Veneris using GC-MS and FT-IR spectroscopy. *International Journal of Pharmacognosy and Phytochemical Research*, 8(3), 369-385.

Ibitoye, O. B., Aliyu, N. O., & Ajiboye, T.O. (2019): Protective Influence of Phyllanthus Muellarianus on Ciprofloxacin-Induced Neurotoxicity in Male Rats. *Journal of dietary supplements*, 1-15.

Igbiri, S., Udowelle, N. A., Ekhator, O. C., Asomugha, R. N., Igweze, Z. N., & Orisakwe, O. E. (2017): Polycyclic Aromatic Hydrocarbons in Edible Mushrooms from Niger Delta, Nigeria: Carcinogenic and Non-Carcinogenic Health Risk Assessment. *Asian Pacific journal of cancer prevention: APJCP*, *18*(2), 437–447.

Ilgin, S., Can, O.D., Atli, O., Ucel, U.I., Sener, E., & Guven, I. (2015): Ciprofloxacin-induced neurotoxicity: evaluation of possible underlying mechanisms. *Toxicology mechanisms and methods*, 25(5), 374-381.

Koracevic, D., Koracevic, G., Djordjevic, V., Andrejevic, S., & Cosic, V. (2001): Method for the measurement of antioxidant activity in human fluids. *Journal of clinical pathology*, 54(5), 356-361.

Lee, S. H., Hwang, H. S., & Yun, J. W. (2009): Antitumor activity of water extract of a mushroom, Inonotus obliquus, against HT-29 human colon cancer cells. *Phytotherapy Research*, 23(12), 1784-1789.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., & Randall, R. J. (1951): Protein measurement with the Folin phenol reagent. *Journal of biological chemistry*, 193(1), 265-275.

Majesty, D., Ijeoma, E., Winner, K., & Prince, O. (2019): Nutritional, anti-nutritional and biochemical studies on the oyster mushroom, *Pleurotus ostreatus. EC Nutrition*, 14(1), 36-59.

Manorenjitha, M. S., Norita, A. K., Norhisham, S., & Asmawi, M. Z. (2013): GC-MS analysis of bioactive components of Ficus religiosa (Linn.) stem. *Int J Pharm Bio Sci*, 4(2), 99-103.

Ohkawa, H., Ohishi, N., & Yagi, K. (1979): Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical biochemistry*, 95(2), 351-358.

Rawi SM, Alshibly NM, Seif El-Nasr F (2014): Neurotoxic effect of ciprofloxacin on albino rat. J App Pharm., 6(1): 121-132.

Rawi SM, Arafa NMS, El-Hazmi MM (2011): Evaluation of the effects of ciprofloxcin or gatifloxacin on neurotransmitters levels in rat cortex and hippocampus. *African Journal of Pharmacy and Pharmacology*,5(8),993-1005.

Ribeiro, B., Valentão, P., Baptista, P., Seabra, R. M., & Andrade, P. B. (2007): Phenolic compounds, organic acids profiles and antioxidative properties of beefsteak fungus (Fistulina hepatica). *Food and Chemical Toxicology*, *45*(10), 1805-1813.

Rusch, M., Spielmeyer, A., Zorn, H., & Hamscher, G. (2019): Degradation and transformation of fluoroquinolones by microorganisms with special emphasis on ciprofloxacin. *Applied microbiology and biotechnology*, 103(17), 6933-6948.

Schillaci, D., Arizza, V., Gargano, M. L., & Venturella, G. (2013): Antibacterial activity of Mediterranean Oyster mushrooms, species of genus Pleurotus (higher Basidiomycetes). *International journal of medicinal mushrooms*, *15*(6).

Venkatesh R, Vidya R and Kalaivani K (2014): Gas chromatography and mass spectroscopy analysis of Solanum villosum (Mill) (Solanceae). IJPSR,. 5(12): 5283-5287.

Wang, X., Hou, X., Hu, Y., Zhou, Q., Liao, C., & Jiang, G. (2018): Synthetic phenolic antioxidants and their metabolites in mollusks from the Chinese Bohai Sea: Occurrence, temporal trend, and human exposure. *Environmental science & technology*, 52(17), 10124-10133.

WHO, (2017): WHO model list of essential medicines, 20th list (March 2017, amended August 2017). World Health Organization.

Wu, W., Liang, X., Xie, G., Chen, L., Liu, W., Luo, G., Zhang, P., Yu, L., Zheng, X., Ji, H. & Zhang, C. (2018): Synthesis and evaluation of novel ligustrazine derivatives as multi-targeted inhibitors for the treatment of Alzheimer's disease. *Molecules*, *23*(10), 2540.

Zekeya, N., Chacha, M., Shahada, F., & Kidukuli, A. (2014): Analysis of phytochemical composition of Bersama abyssinica by gas chromatography–mass spectrometry. *J. Pharmacogn. Phytochem*., 3(4), 246–252.

Zhang ZM, Wu WW, Li GK (2008): A GC-MS study of the volatile organic composition of straw and oyster mushrooms during maturity and its relation to antioxidant activity. Journal of chromatographic science; 46(8): 690-696.

التأثير المخفف للمستخلص المائي للفطر (P. ostreatus) علي السمية العصبية المستحثة بالمضاد الحيويciprofloxacin في الجرذان

سيبروفلوكساسين (CPX) هو مضاد حيوي واسع الطيف يستخدم على نطاق واسع في كل من الطب البشري والطب البيطري. ومع ذلك ، غالبًا ما يُساء استخدامه ، مما يؤدي إلى العديد من الآثار الضارة مثل الاضطراب العصبي. في الوقت الحاضر ، هناك اتجاه عالمي متزايد لتوظيف المنتجات الطبيعية في إدارة العديد من مشاكل صحة الإنسان. الفطريات القابلة للأكل مثل (P. ostreatus) تستخدم في العديد من الثقافات

القديمة كمصدر للغذاء وممارسات الطب التقليدي. في الدراسة الحالية تم تحليل مكونات المستخلص المائي لهذا الفطر باستخدام كروماتوجرافي الغاز كما تم دراسة تأثيره العلاجي علي سمية الدماع نتيجة تعاطي الجراذن للمضاد الحيوي CPX، تم تفسيم عدد ٢٤ من الجرذان البالغة بشكل عشوائي إلى أربع مجموعات (٦ لكل منها) على النحو التالي: المجموعة الضَّابطة ، المجموعة المُعالجة بـ CPX التي تلقت جرعة يومية من CPX ٥٠ مجم / كجم لمدة أسبوعين ، المجموعة المُعالجة بالمُستخلص الماء للفطر بجرعة يومية ٢٠٠ مجم / كجم لمدة أسبوعين ، والمجموعة التي عولجت بـ ٥٠ مجم / كجم من CPX لمدة أسبوعين ثم تم تجريعها بالفطر بجرعة ٢٠٠ مجم / كجم لمدة أسبوعين آخرين. تم تقدير الدلالات البيوكيميائية مثل نشاط إنزيم أستيل كولينستريز (AChE) والكفاءة الكلية لمضادات الأكسدة، الجلوتاثيون والأكسدة الفوقية للدهون في نسيج الدماغ وعمل قطاعات هستولوجية في الدماغ في كل المجموعات.

أظهرت النتائج أن CPX أدى إلى زيادة غير معنوية إحصائياً في نشاط AChE، ومع ذلك ، كان هناك انخفاض كبير في مستوى الجلوتاثيون (GSH) مع زيادة كبيرة في معدل أكسدة الدهون (LPO) في أنسجة المخ. بينما تسبب المُستخلص المائي للفطر في انخفاض معنوي في نشاط إنزيم AChE مقارنة بالمجموعة الضَّابطة ومجموعة CPX. كما أنها زادات بشكل كبير من الكفاءة الكلية لمضادات الأكسدة ولكنها قللت بشكل كبير من LPO مقارنة بمجموعةCPX . إلى جانب ذلك ، تسببت تناول CPX في حدوث تدهور في القشرة الدماغية والحُصين ، وارتشاح للخلايا الالتهابية، بينما كانت القطاعات في الجرذان المعالجة بالفطر أكثر قرابة للمجموعة الضَّابطة. أخيرًا ، في المجموعة المعالجة بـ CPX والفطر معاً، كان هناك تحسن ملحوظ حيث وجد عدد أقل من الخلايا العصبية المتضررة، ولم يكن هناك ارتشاح التهابي، وكان سُمك الطبقة الهرمية طبيعياً مثل ذلك الموجود في المجموعة الضَّابطة. وخلصت الدراسة إلي أن المستخلص المائي للفطر نتيجة إحتوائه علي مركبات ذات

نشاط مضاد للأكسدة ومسكن للالتهابات مثل الفينولات والأستورودات يخفف من السمية العصبية المستحثة ب المضاد الحيويز مع الأخذ في الإعتبار الأثار السلبية للفطر نتيجة إختوائه علي مركبات ضارة تحدث نتيجة التلوث البيئي.