Original Article

Fluconazole Toxicity in a Rat Model: Histopathological and Neurobehavioral Effects

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ABSTRACT

Background: The harmful effects of medications on cells can be either direct or indirect. These effects are due to increased free radicals or changes in the gene expression of specific proteins in the cells.

Objectives: This study examined the effects of fluconazole at high dosages on the brain and liver of rats and their neurological behavior and motor activity. It also investigated the mechanisms that caused these changes by testing key enzymes and proteins.

Methods: We used two LD_{50} percentages: 10% and 20%. Three groups of animals were formed. Group I was the control group. Fluconazole was given to groups II and III as a daily oral dose for 14 days at 583 mg/kg and 292 mg/kg, respectively.

Results: Neurobehavioral testing revealed that rats with fluconazole 583 mg/kg experienced hyperactivity, increased movement, and poor cognition. The findings showed a substantial dose-related rise in malondialdehyde and caspase-3 and an increase in liver function enzymes but no significant change in cholinesterase activity. A fluconazole dose of 538 mg/kg also caused severe histological alterations in the brain and liver. Furthermore, enhanced glial fibrillary acidic protein (GFAP) expression has been observed in brain tissue.

Conclusion: These findings led us to conclude that fluconazole is toxic at higher doses because it alters rat neuromotor behavior and negatively affects liver and brain tissues. It results in altered levels of some enzymes, elevated oxidative stress markers and increased apoptosis with a higher expression of GFAP in brain tissues.

Keywords: Fluconazole, Immunohistochemistry, Neurological and hepatic toxicity, Glial fibrillary acidic protein (GFAP)

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Introduction

Animals and humans are both treated with fluconazole. In addition, it is sprayed on the fields of plants infected with fungus. In animals, fluconazole is used as an antifungal medication marketed under the brand name Diflucan® (Lysková et al., 2021).

With a veterinarian's prescription, fluconazole is given to dogs and cats to treat fungus infections, particularly those affecting the brain and spinal cord. Moreover, it treats several other illnesses, including ringworm, onychomycosis, and cryptococcosis (Toda et al., 2021). Giving the animal a higher dose than standard or mistakenly consuming the medication could result in toxicity. In agriculture, the fluconazole belongs to the triazole family. Triazole is a significant class of fungicides frequently used in agriculture to stop fungus growth on many types of fruit, cereals, vegetables, soybeans, and other crops (Singer et al., 2014; Alnuimi & Alabdaly, 2022).

Some animals who graze in those regions become poisoned due to the widespread use of triazole fungicides and probable adverse effects on animals that may result from spray erosion or runoff after rain to nearby farms and consumption by the animal (Alabdaly, 2021). Triazole fungicide properties result from their ability to obstruct steroid production by blocking CYP51 (cytochrome P450 enzyme). This enzyme is crucial for converting the lanosterol to the ergosterol in yeast and fungus (Carmona & Limper, 2017). Fluconazole inhibits the synthesis of ergosterol, an important membrane component significantly affecting fungal cell membrane permeability (Parker et al., 2014; Sant et al., 2016).

This investigation was conducted to study the toxic effects of fluconazole on neurobehavioral motor activity and the association between pathological immunohistochemistry with antioxidant and biochemical alteration in the brain and liver of rats.

Materials and Methods

Study chemicals

Fluconazole in pure form as a powder was purchased from the Pioneer Company, Iraq. Caspase-3 was measured using a kit from the French company BIOLABO. Finally, aspartate transaminase (AST) and alanine transaminase (ALT) liver enzymes were assessed using relevant kits from Elabscience Company, America.

Study animals

The animal model consisted of 4-5 weeks-old rats weighing 150–200 g. The animals were cared for humanely and kept in the animal house at the College of Veterinary Medicine, Mosul University, Mosul, Iraq. The standard laboratory conditions, such as temperature, humidity, light, and darkness, were applied, and the animals received the required amounts of food and water throughout the study (McKeny et al., 2022).

Dose preparation

The 10% and 20% concentrations were prepared by dissolving fluconazole powder in distilled water following the dosage guidelines and the animal weight. The medication administration volume is 2 mL/kg.

Experimental approach

The oral LD_{50} of fluconazole was determined using 5 animals by Dixon's up-and-down method (Dixon, 1980). Subsequently, specific percentages of LD_{50} were calculated: 10% representing 292 mg/kg and 20% representing 583 mg/kg, respectively.

A total of 18 animals were divided into 3 groups. The first group was the control. Fluconazole was given to the second and third groups as a daily oral dose of 583 mg/kg and 292 mg/kg for two weeks. Neurobehavioral tests were performed on the animals following the end of the treatment period.

Neurobehavioral tests

An open-field test assesses the rat's neurobehavioral and motor functions in an open-field box (Moser, 1988). A negative geotaxis test is conducted by timing how long the animal turns around (Al-abdaly et al., 2023). During the tonic immobility test, the animal is held vertically from the skin of the neck fold just below the base of the skull, which gauges the animal's level of fear and stress (Al-abdaly et al., 2023). In the Pocking test, the experiment is carried out by counting the instances in which the animal's head is inserted into the holes (Shahsavari et al., 2009).

Following test completion, the animals underwent ether anesthesia to draw blood from the ocular vein. Blood was placed in clean, sterile plastic tubes, left for 30 minutes, then centrifuged for 15 minutes to separate the serum. Then, the rats' livers and brains were removed and stored in containers containing 10% neutral formalin.

Table 1. Fluconazole median lethal dose (LD_{50})

Variables	Result
LD_{50} (mg/kg)	2916
Range	3000-2000=1000
The 1st dose (mg/kg)	3000
The last dose (mg/kg)	3000
The number of animals	X0X00
The increase or decrease in doses (mg/kg)	1000

X=Dead rat; 0=survives rat.

The biochemical measurements used included malondialdehyde (MDA) (Mmol\L) (Buege & Aust, 1978), glutathione (GSH) (Mmol\L) (James et al., 1982), cholinesterase (Mohammad et al., 1997), caspase-3 kit in brain tissue, (ng/mL), GOT/AST kit and GPT/ALT (IU/L) kit.

Statistical analysis

The parametric data were statistically analyzed using a one-way test in the SPSS software, version 2010, and the results were then examined for the least significant difference (LSD). The Mann-Whitney test was applied to the non-parametric data. The magnitude of the significant difference had a probability of <0.05.

Results

The median LD_{50} for rats was 2916 mg/kg for oral administration (Table 1). Neurobehavioral measurements showed general stimulation in the motor behavioral measurements of rats treated with 583 mg/kg, represented by an increase in the number of squares passed and the times of standing (rearing) compared to the control group and fluconazole 292 mg/kg. In addition, a significant decrease was recorded in the test of immobility response as compared to groups I and III, and a decrease in the number of times of inserting the head into the holes in the Pocking test, while there is no significant difference in negative geotaxis at P<0.05 (Table 2).

The MDA concentrations of 4.86±0.9 and 7.57±0.08 (Mmol\L) revealed an increase in its level in the two groups of fluconazole at 292 and 583 mg/kg, where the higher dose differed from the control and the group treated with the lowest dose of fluconazole. In contrast, GSH levels of 0.71±0.07 in all groups did not significantly differ, and cholinesterase activity (0.28±0.1) had no significant changes. In contrast, the level of the liver enzyme function (ALT, AST) (IU/L) (40.6±1.91, 88.4±2.05) and caspase-3 (95±1.2) were significantly increased in brain tissue as compared to a control group, and dose of 292 mg/kg (Table 3).

A microscopic examination of the normal liver revealed normal hepatocytes and a central vein with sinusoids (Figure 1). There were variable architecture lesions based on the severity according to the concentration of fluconazole.

Figure 1 shows the normal architecture of liver tissue. In the fluconazole 292 mg/kg group, vacuolar degeneration in the hepatocytes and congestion in the central vein. In group III, the lesions are severe and characterized by necrosis, vacuolar degeneration of the hepatocytes, and dilation of the sinusoids. Figure 4 shows the cerebral cortex with normal architecture. In the brains of rats treated with fluconazole (292 mg/kg), the microscopic examination revealed vacuolization, perivascular, and periaxonal edema with steatosis (Figure 5).

The histological examination shows that the cerebral cortex has vacuolization and necrosis of the neuron (Figure 6). In the brain tissue of the rats treated with the fluconazole dose of 538 mg/kg, the histological examination shows the cerebral cortex with severe vacuolization and liquefactive necrosis with cavities (Figure 7), as well as lipofuscin pigment (Figure 8). Immunohistochemical analysis for the study of glial fibrillary acidic protein (GFAP) in brain tissue (glial cells, astrocyte) shows that the brain tissues of control animals recorded a mild expression for GFAP. Moderate expression appeared in the brain tissue of rats treated with fluconazole (292 mg/kg), while a strong expression of GFAP was found in the rats treated with fluconazole (538 mg/kg).

Table 2. Neurobehavioral measurement tests in rats treated with fluconazole

Groups (n=6)	Test				
	No. Pass Squares	Rearing	Negative Geotaxis\Second	TIR Response\s	Pocking
Control	70±0.1	17±2	2±0.1	50±0.1	9±1
Fluconazole, 292 mg/kg	82±1*	20±1.2*	2±0.2	25±0.3*	9±1
Fluconazole, 538 mg/kg	96±2*a	23±1*a	2±0.2	17±1.6*a	4±0.1*a

*Control significant difference, aSignificant difference from fluconazole (292 mg/kg).

Notes: The significance level is<0.05.

Discussion

According to the results of our study, fluconazole has toxic effects in high doses supported by observing the neurobehavioral and motor activity of rats, measuring some pertinent biochemical parameters, and correlating these effects with histopathology and immunohistochemistry to support these conclusions.

Rats' neurobehavioral and motor activities were assessed through neurobehavioral tests. Fluconazole molecules are tiny and can pass through the blood-brain barrier and impact the brain (Matthews, 2015).

Fluconazole is cytotoxic because it disrupts typical metabolic functions by blocking cytochrome P450. Examples of enzymes associated with triazole-induced toxicity include mammalian CYP26 family enzymes (Pais et al., 2020).

One of the reasons for increased motor neuroactivity may be the influence of acetylcholine receptors, causing hyperactivity (Wang et al., 2021).

Fluconazole may affect nerve cells (glial cells) and cause increased motor neuron activity (Liu et al., 2021). Studies have also shown that fluconazole affects the electronic system of nerve cells. The previously mentioned mechanisms affect the increase in motor activity (Liu et al., 2021).

Our findings reveal that the rats' activity increases in the open field test; it may be due to stimulation of the acetylcholine receptor, and the animal's nervous system transitions from a deep slumber to full wakefulness. Moving from being distracted and unfocused to being entirely focused. Acetylcholine has a significant function in cognition, learning, motivation, memory and attentiveness (Ben-Azu et al., 2019; Gupta, 2022).

The injury of nerve cells in the hippocampus causes memory impairment (Lenz, 2017). A high dose of fluconazole causes oxidative stress, which is detected through increased MDA levels. This result is consistent with one of the studies on *Gobiocypris rarus* embryos, showing that higher doses of fluconazole produced more free radicals and low levels of superoxide dismutase (SOD) and GST. This event explains why triazoles can weaken

Table 3. Biochemical parameters in rats treated with fluconazole

Group (n=6)	Parameter					
	MDA (Mmol\L)	GSH (Mmol\L)	Inhibition Ache (Δ PH)	Caspase-3 (ng/mL)	ALT (IU/L)	AST (IU/L)
Control	2.52±0.1	0.71±0.07	0.29±0.1	80.9±1.95	25±0.95	63.5±1.05
Fluconazole, 292 mg/kg	4.86±0.9*	0.71±0.07	0.28±0.1	82±2.13	40.6±1.91*	88.4±2.05*
Fluconazole, 583 mg/kg	7.57±0.08*a	0.7±0.06	0.28±0.1	95±1.2*a	65±1.31*a	98±1.05*a

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase; MDA: Malondialdehyde; GSH: Glutathione; Ache: Cholinesterase.

*A control significant difference, aA significant difference from fluconazole (292 mg/kg).
Notes: The significance level is <0.05.

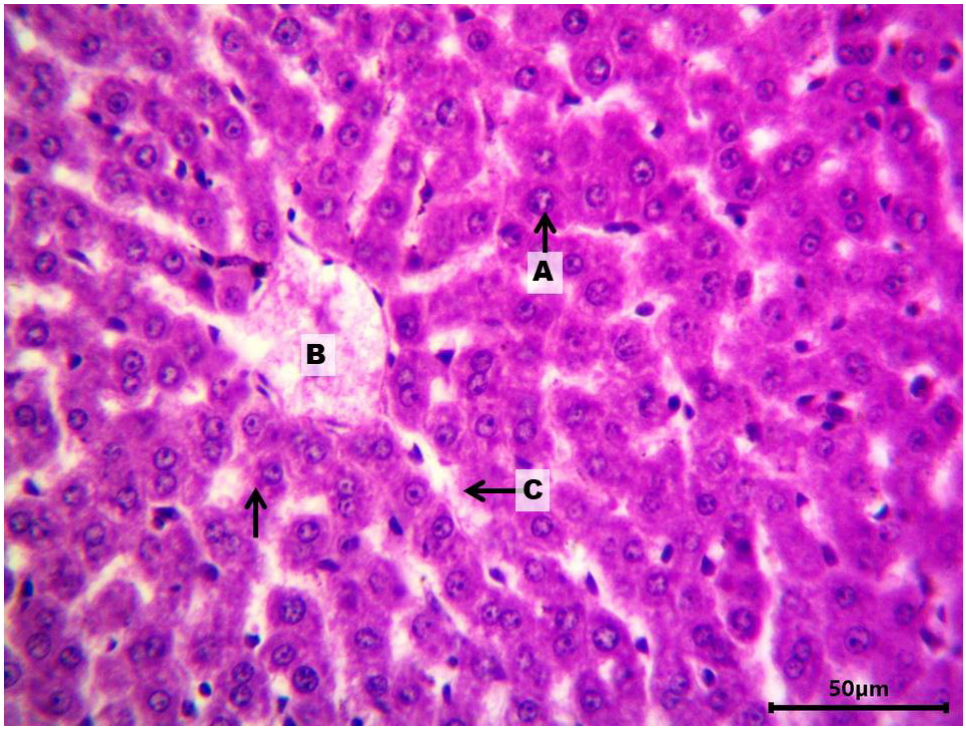

Figure 1. Histopathologic section for the liver of the control animals showing a normal architecture (H & E staining, X400)

Notes: The hepatocytes (A), the central vein (B) and the sinusoids (C)

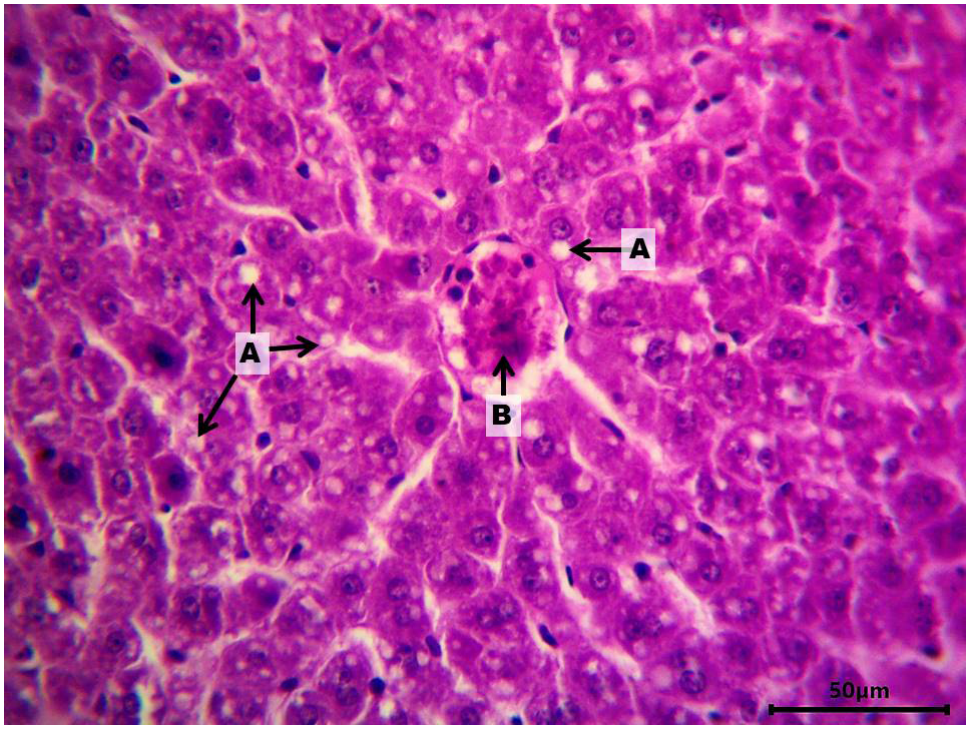

Figure 2. Histopathologic section for the liver of the fluconazole group (292 mg/kg) appearing vacuolar degeneration of the hepatocytes (A) and the congestion of a central vein (B) (H & E staining, X400)

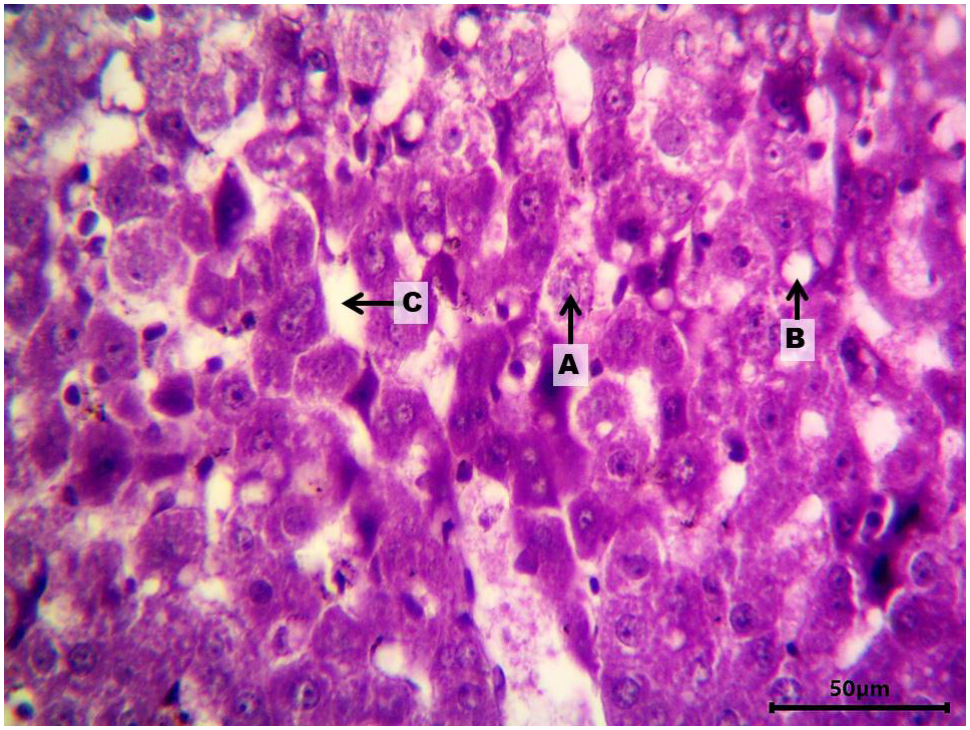

Figure 3. Histopathologic section for the liver of the fluconazole group (538 mg/kg) (H & E staining, X400)

Notes: Showing necrosis (A) vacuolar degeneration of hepatocytes (B), and dilation of sinusoids (C).

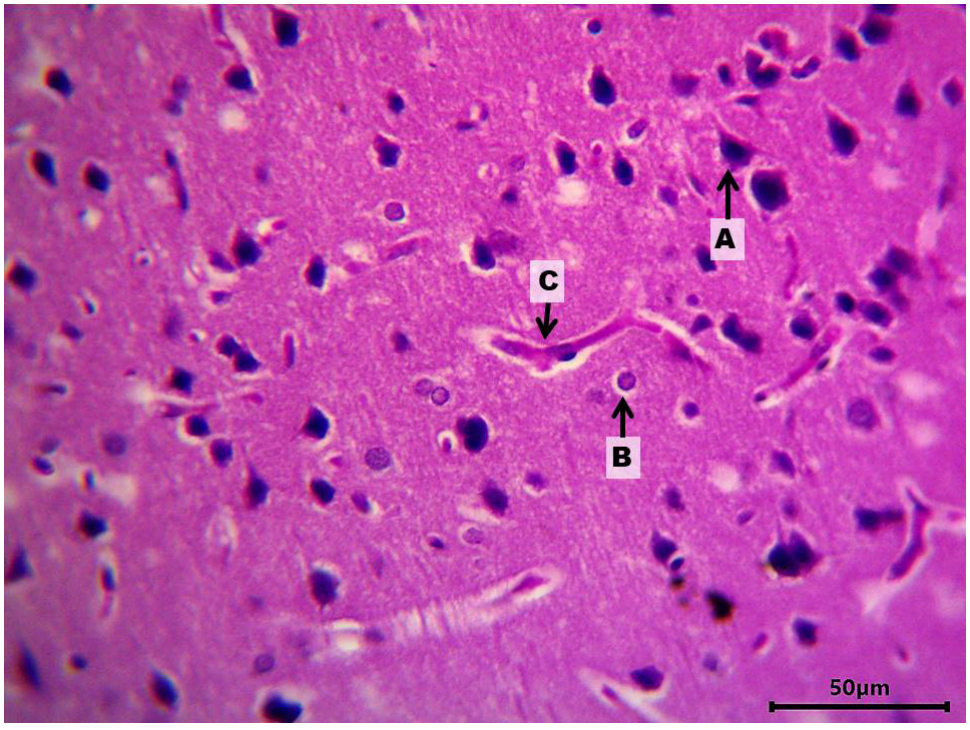

Figure 4. Histopathologic section for the brain of the control animals (H & E staining, X400)

Notes: Showing the cerebral cortex with the normal architecture, showing: A) the neuron, B) Glial cells and C) Blood Vessels.

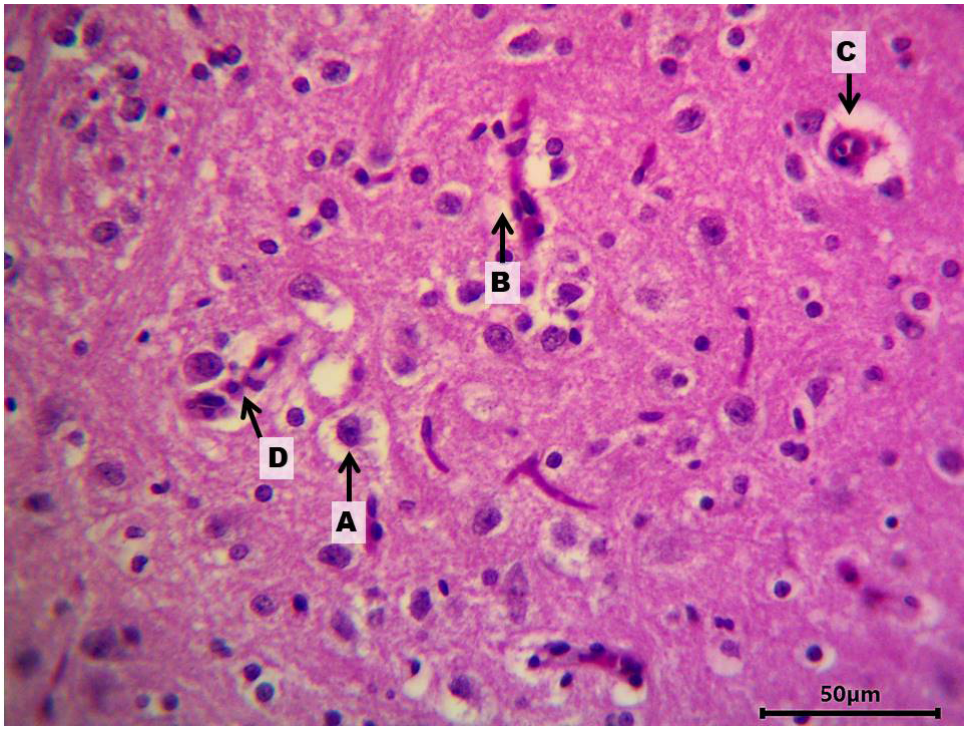

Figure 5. Histopathologic section for the brain of the fluconazole group (292 mg/kg) (H & E staining, X400)

Notes: Showing the cerebral cortex with vacuolization (A) perivascular (B) and periaxonal edema (C) and satellitosis (D).

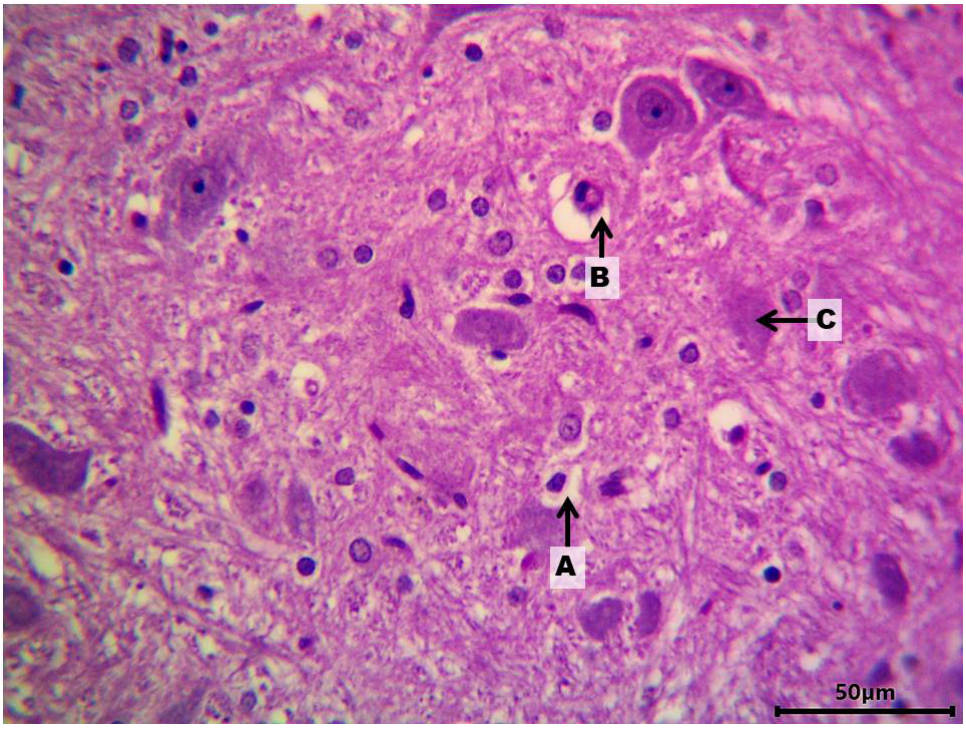

Figure 6. Histopathologic section for the brain of the fluconazole group (292 mg/kg) (H & E staining, X400)

Notes: Showing the cerebral cortex with vacuolization (A) perivascular edema (B) and necrosis of the neuron (C).

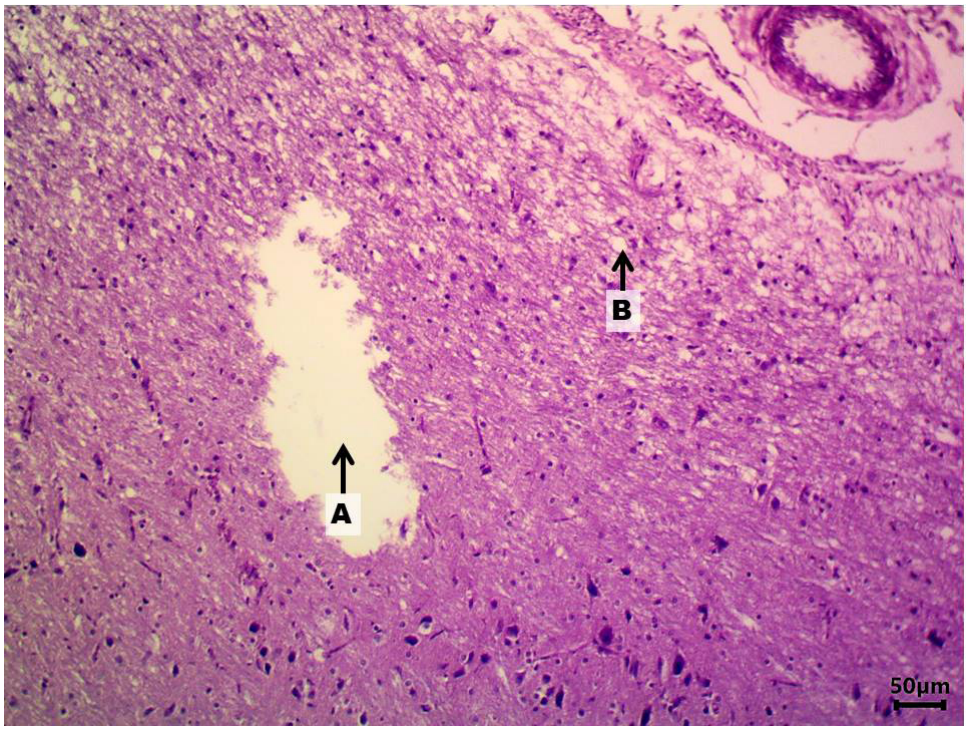

Figure 7. Histopathologic Section for the Brain of the Fluconazole Group (538 mg/kg) (H & E staining, X400)

Notes: Showing the cerebral cortex with severe vacuolization (A) and liquefactive necrosis with a cavity (B).

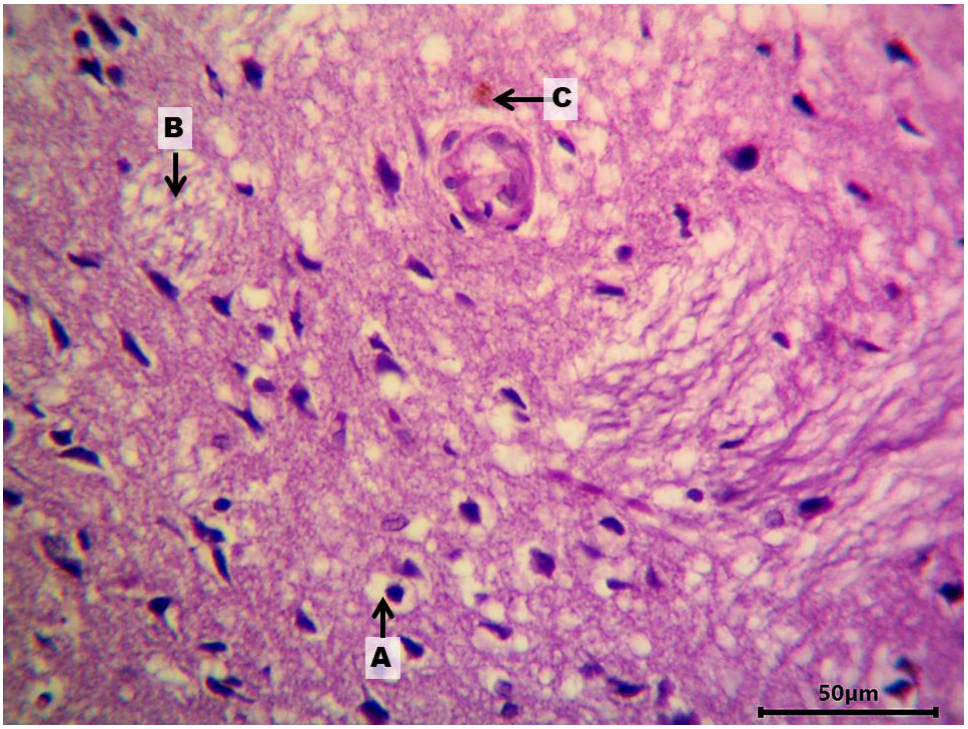

Figure 8. Histopathologic Section for the Brain of the Fluconazole Group (538 mg/kg) (H & E staining, X400)

Notes: Showing the cerebral cortex with severe vacuolization (A), liquefactive necrosis with a cellular membrane (B), and presence of lipofuscin pigment.

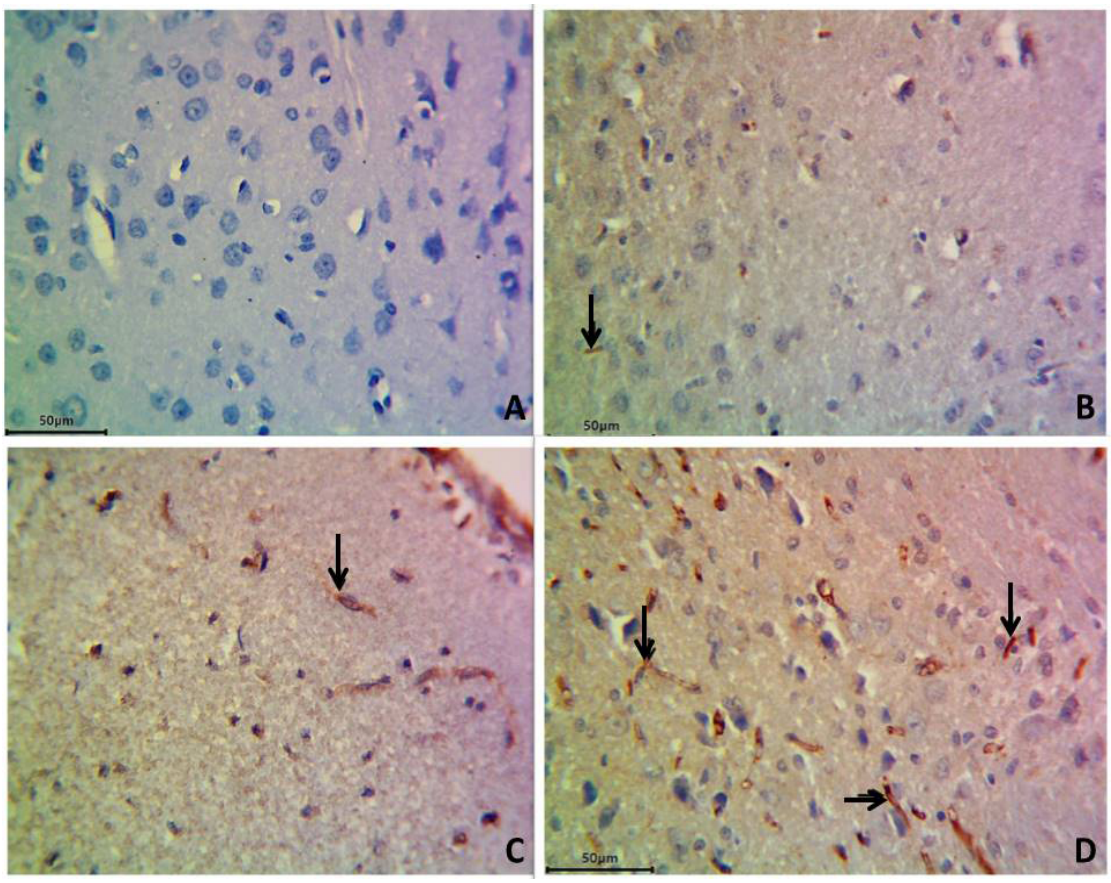

Figure 9. Immunohistochemical staining for the rat brain GFAP expressions in the glial cells (magnification X400)

A) Negative GFAP expression in the negative control, B) Weak GFAP expression in the control group, C) Moderate GFAP expression in the fluconazole group (292 mg/kg), D) Strong GFAP expression in the fluconazole group (538 mg/kg).

the antioxidant defense mechanism (Liu et al., 2021; Al-Jammas et al., 2025). Fluconazole causes programmed cell death in the tissue of the brain when administered in a large dose. Certain chemicals and toxins can explain this result, disrupting the inner mitochondrial membrane, increasing the membrane's permeability, and triggering the release of proteins, activating the programmed death pathway in mitochondria (Eliwi et al., 2020; Saeed et al., 2023).

The increased expression of GFAP, which is dose-dependent, suggests that high doses of fluconazole damaged neurons and glia, and this interpretation is consistent with one study demonstrating that high doses of fluconazole caused damage to neurons and glia (Liu et al., 2020; Alfathi et al., 2023). This finding is consistent with our results, which indicated pathological changes in the brain.

Increased GFAP in the immunohistochemistry is evidence of slow progression of neuronal damage. In addition, the release of GFAP only occurs after neuronal death and damage or as a symptom of ischemia injury (Shahsavari et al., 2023; Al-Taee & Saeed., 2023).

Glial cells can react to injury in a variety of ways. Many neurodegenerative diseases, as well as injuries that harm nerve tissue, can cause glial scarring. The up-regulation of GFAP contributes to the formation of the scar, which is caused by the interaction of astrocytes with fibrotic tissue to restore glial margins surrounding the central damage core (Wang et al., 2010; Kemeir, 2014; Alabdaly & Medhat, 2023).

Fluconazole causes cholestasis and hepatitis and affects liver enzymes (Gayam et al., 2018). It is also toxic to cells and interferes with some metabolic functions by inhibiting cytochrome P450. (Kemeir, 2014; Jeter & Colak Obelik, 2020). It reaches the brain at a high level and

causes cellular damage and pathological tissue changes (Liu et al., 2020; Guglielmo et al., 2022; Soltani et al., 2023).

Fluconazole directly affects nerve cells, such as cell membranes and proteins. It may lead to neuronal death (Liu et al., 2021). It can also affect gene expression (Wang et al., 2021; Saeed et al., 2023).

The increased expression of GFAP, which intensifies with dose, suggests that high doses of fluconazole damage neurons and glial cells, and this finding is consistent with one study showing that high doses of fluconazole damage neurons and glial cells (Eşkut., 2021; Farzaneh et al., 2023). This finding is also consistent with our results, which indicated pathological changes in the brain.

Increased GFAP in tissues indicates nerve cell damage. Moreover, the release of GFAP occurs after neuronal cell death and damage due to ischemia (Farkhakfar et al., 2023; Bahrami et al.,2023). As glial cells react to injury, they appear in neurodegenerative diseases and can cause glial cell scarring. Up-regulation of GFAP contributes to scarring at the interaction of astrocytes and fibroblasts (Hol & Pekny, 2015; Shahsavari et al., 2023).

Conclusion

Fluconazole causes harmful neurobehavioral effects, histopathological changes in the brain and liver, differences in the levels of some biochemical variables, and an increase in the expression of GFAP. The toxicity found in this study supports the need for caution when administering high doses of fluconazole. The study also highlights the risk associated with the environmental release of azole fungicides.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the College of Veterinary Medicine, University of Mosul, Mosul, Iraq (Code: UM.VET. 2022.08, dated 3\2\2022).

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Authors' contributions

Conceptualization and study design: Yamama Alabdaly; Experiments: Thanoon AL-hbiti, and Hana Ismaeil Kaleel; Writing: Yamama Alabdaly, and Hana Ismaeil Kaleel; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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