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RESEARCH ARTICLE

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Protective Effect of *Ficus carica* against the Insecticide Deltamethrin Toxicity in *Wistar* Rats

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ABSTRACT

Background: Over time, people have created customs related to the use of medicinal plants as a means to safeguard health against harmful agents like pesticides. This study seeks to assess how effective *Ficus carica* is in safeguarding *Wistar rats* against the toxic effects of the insecticide Deltamethrin.

Methods: Six groups of 42 rats are used, G1 (control), G2 and G3 (treated with *Ficus carica* leaves extract at two doses of 200 and 400 mg/kg/d), G4 (treated by Deltamethrin 15 mg/kg/d), G5 and G6 (treated with the combination Deltamethrin-plant). After 30 days of treatment, blood and organs are collected for the biochemical analyses (glucose, triglyceride, cholesterol, total protein, transaminases, creatinine and urea) and histological samples (liver and kidneys).

Result: The study revealed a notable increase ($P \leq 0.001$) in the biochemical parameters of the group treated with Deltamethrin, as compared to the control group, accompanied by several histological changes. However, the results demonstrated that the extract of *Ficus carica* leaves can mitigate the toxicity induced by Deltamethrin, resulting in a substantial improvement in both the biochemical parameters and histological structure of the liver and kidneys in the groups treated with the combined Deltamethrin and *Ficus carica* extract.

Key words: Deltamethrin, *Ficus carica*, Medicinal plants, Toxicity, *Wistar* rats.

INTRODUCTION

Pesticides are chemicals used in agriculture to protect crops from insects; also are commonly used to manage tropical disease vectors in order to preserve public health (Nagarjuna and Doss, 2009). Deltamethrin, a Pyrethroid insecticide like all pesticides, Pyrethroids have high toxicity due to their lipophilic nature often accumulating in adipose tissue (Ambolet-Camoit *et al*., 2012).

Various scientific studies have shown that residues of Deltamethrin have an effect on human health including reproductive, developmental and nervous system disorders as well as the appearance of cancer of certain organs (liver, breast, thyroid, stomach) (Margariti *et al*., 2007)**.** Medicinal plants have been used for centuries because they contain components of therapeutic interest; they were used as a treatment for diseases (Nostro *et al*., 2000). Throughout the centuries, human traditions have developed the knowledge and use of medicinal plants in order to overcome suffering and protect human health from the harm of toxic products. Recent studies have shown that herbal supplements are beneficial for the prevention and mitigation of toxicity of toxins. These supplements are cost-effective, can easily be added to the daily diet and have very few side effects compared to chemical therapy (Zhang *et al*., 2015).

Ficus carica is a plant used in traditional medicine. The fruits, all parts of the plant have been used for the treatment of several ailments such as inflammatory and cardiovascular disorders, ulcerative diseases and cancers (Kabir *et al*., 2012). The current study intends to explore the harmful impacts of Deltamethrin and the potential detoxifying effects of *F.carica*, a medicinal plant, on *Wistar albino* rats.

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MATERIALS AND METHODS

Biological materials

In the year 2022, the study took place during the months of April and May.

The experiment involved using male *Wistar* rats, aged between 7 to 8 weeks and weighing from 160 to 250 grams. These rats were obtained from the Institute Pasteur of Algiers and were given time to adapt to their new environment before the experiment began.

During the experimentation period, the rats were kept in natural environmental conditions and were provided with regular food, which was in the form of pellets made from maize, barley, soybeans, wheat and enriched with vitamins, minerals and cellulose. They were also given fresh water every day.

The plant used in the study, which was *F.carica*, was harvested from the region of Skikda (36°50′12.6″N 6°58′ 11.3″E) Algeria in November 2021 and was identified by Dr. Sakhraoui Nora, a botanist.

Chemical materials

The production of a powdered Pyrethroid insecticide known as Deltamethrin (DLM) is undertaken by Averstar Industrial Co, Ltd, a China-based company.

Methodology

Quantitative study

After maceration, the extraction was performed using solid-liquid maceration in 70% Methanol. The Folin-Ciocalteu technique was used to determine the total amount of polyphenols (Wong *et al*., 2006) and the Aluminum Trichloride ($AlCl_3$) method was used to calculate the quantity of flavonoids (Djeridane *et al*., 2006).

Antioxidant activity study

The free radical scavenging activity of *F.carica* leaves was evaluated using the DPPH method. This method involves the use of antioxidants that donate an electron or hydrogen to reduce the radical state of DPPH.

The experimental protocol

From the 42 animals, six groups consisting of seven rats each were created. The first group was used as the control group, while groups 2 and 3 received doses of 200 mg/kg and 400 mg/kg, respectively, of an extract from the *F.carica* plant. The fourth group was given 15 mg/kg of Deltamethrin, which is one-tenth of the LD50. Groups 5 and 6 received a combination of Deltamethrin and *F.carica* extract at dosages of 200 mg/kg and 400 mg/kg, respectively. The treatment was administered by gavage, using a gastric tube, once a day for 30 days. The animals were weighed daily and after the treatment period, they were euthanized and their blood was collected into Heparin test tubes for the determination of biochemical parameters. Additionally, their liver and kidneys were sampled and weighed. This protocol has been authorized by an internal committee to oversee the treatment and usage of laboratory animals.

Analyses of biochemical markers

At Skikda Hospital, Algeria, the levels of various biochemical markers including glucose, triglycerides, cholesterol, total proteins, urea, creatinine, uric acid, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were measured using commercial kits from Spinreact, Spain and an automatic machine, BECKMAN COULTER AU480.

Histopathological study

Following blood collection, the organs (liver and kidneys) were immediately sampled and washed by a 9% physiological solution to avoid any damage. Each organ was fixed in 10% neutral buffered formalin for 24 h, at 4°C and transferred to a succession of 70-100% ethanol. Later, for kerosene embedding, they were placed in kerosene baths at 58°C., finally, using a rotary microtome, sections of 4-6 mm were cut from the kerosene blocks. Hematoxylin-eosin (H-E) staining was used on these sections and they were examined under a light microscope. (Martoja, 1967).

Statistical analysis

Results are expressed as mean± SEM. The difference between groups is expressed by one-way test of variance (ANOVA). Then groups are classified by Tukey's test Statistical analysis. Data was performed by Minitab version 17 software. The difference is significant when $p \leq 0.05$.

RESULTS AND DISCUSSION

Quantitative analysis and antioxidant activity

The yield obtained after extraction is 5.03%, this result is lower than recorded by Mahmoudi *et al*., (2016) who obtain 9.8%. This difference in yields can be influenced by several factors such as chemical composition, physical characteristics of the plant material, extraction method and other conditions (Dai and Mumper, 2010).

The results of the total polyphenols of the Ethanolic extract show that the *F.carica* extract has a polyphenol content of 42.14±0.14 µg E AG/mgE. This result is close to those obtained by (El-Shobaki *et al*., 2010) while Mahmoudi *et al*., (2016) found that the total polyphenol contents of leaves extracts of ten varieties of *F.carica* in Algeria ranged from 52.296±5.232 - 48.973± 2.015 (µg E.AG /mg E). The content of flavonoids are quantified 30.85±2.85 µg E.Q/mg E. This result is similar to other data obtained by Lahmadi *et al*., (2019) who found 33.52±1.34 and higher than those obtained by Mahmoudi *et al*., (2016) who found 11.29; µg E.Q/mg E and 14.388 µg E.Q/mg E respectively. These observed differences in polyphenol and flavonoid contents can be attributed to several factors such as the used extraction method, the degree of maturity of the plant.

The antioxidant capacity of the crude extract determined from IC50 is estimated to be 420 µg/ml, this result is less than that obtained by Lahouel *et al*., (2016) who found a value of 275.23 µg/ml. Fig leaves contain a Considerable number of beneficial compounds namely Polyphenols and Flavonoids, which act as antioxidants (El-Shobaki *et al*., 2010). This antioxidant capacity of fig leaves is significantly correlated with Phenolic content (Mahmoudi *et al*., 2016).

The weight gain and relative weight growth

The results of the weight gain evaluation show a significant decrease ($P \leq 0.001$) between the control group (G1) and the Deltamethrin-treated group (G4) with a non-significant increase ($p>0.05$) between G4 and groups 5 and 6. (Fig 1).

Fig 2 and 3 show the results of the relative weight examination of the liver and kidneys., the findings indicate a significant decrease ($p \leq 0.001$) in the relative weight of the liver between G4 and G1 and a slight increase in the relative weight is recorded in the groups G5 and G6. On the other hand, data show a non-significant decrease in the relative weight of kidneys in G4 compared to the control and a non-significant increase in the group G5, G6 compared with G4. The weight loss is most likely due to a reduction in food intake and the harmful effects of Deltamethrin. Our results are similar to those found by Saoudi *et al*., (2011) who worked on different pyrethroid compounds (Deltamethrin, Fenvalerate and Diazinon), indicates a non-significant drop in relative weight in the DLM treated group as compared to the control group. This decline might be attributed to the impact of toxins on key organs including as the liver, kidney and rat (Kara *et al*., 2005).

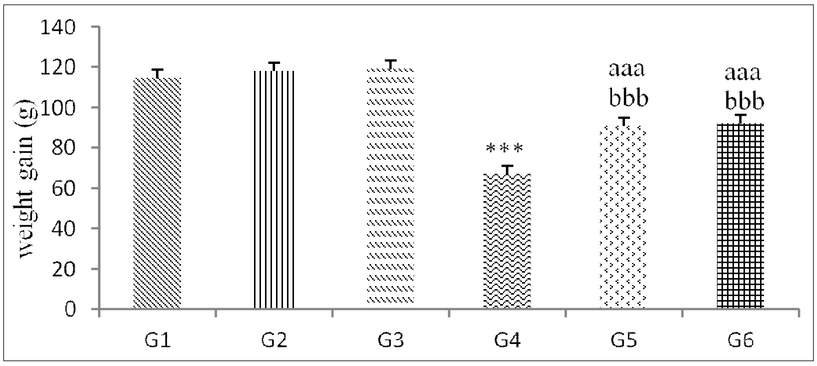

Fig 1: Assessment of weight gain during the treatment period.

Between the Deltamethrin group (G4) and the control group (G1): *p≤0.05, **p≤0.01, ***p≤0.01.

Between the groups Deltamethrin+plant (G5, G6) the group Deltamethrin(G4): ^{a}p≤0.05, ^{aa}p≤0.01, ^{aaa}p≤0.01.

Between the groups Deltamethrin+pante (G5, G6) the group and minus (G1): ^{b}p≤0.05, ^{bb}p≤0.01, ^{bbb}p≤0.01.

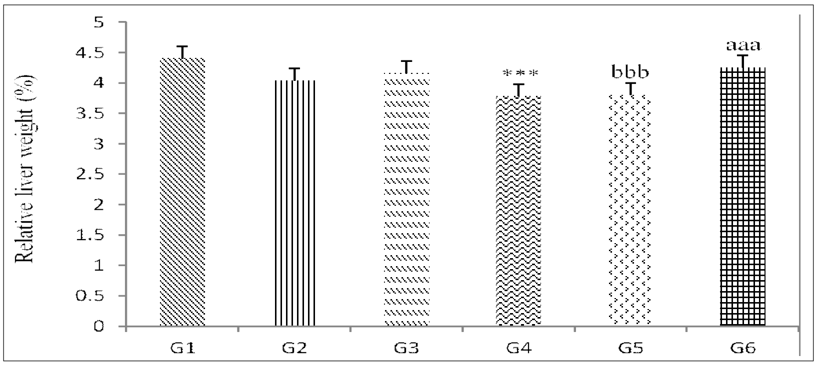

Fig 2: The variation in relative liver weight.

Between the Deltamethrin group (G4) and the control group (G1): *p≤0.05, **p≤0.01, ***p≤0.01.

Between the groups Deltamethrin+plant (G5, G6) the group Deltamethrin(G4): ^{a}p≤0.05, ^{aa}p≤0.01, ^{aaa}p≤0.01.

Between the groups Deltamethrin+pante (G5, G6) the group and minus (G1): ^{b}p≤0.05, ^{bb}p≤0.01, ^{bbb}p≤0.01.

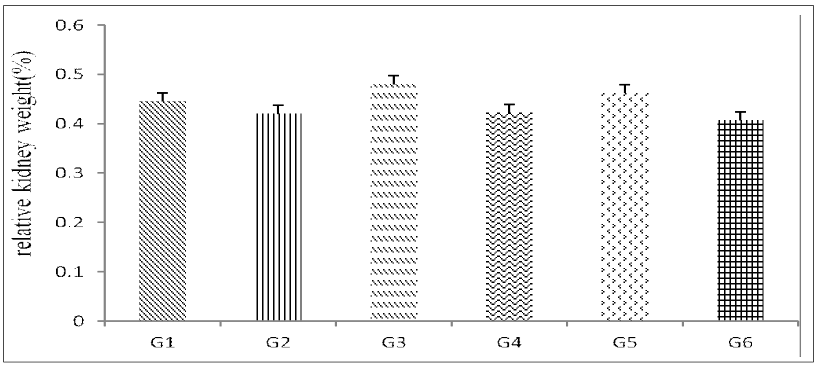

Fig 3: The variation in relative kidney weight.

The values are mean±S.E.M, the difference is significant.

The slowing of body growth in treated rats can be explained by the disruption of cellular metabolism under the effect of oxidative stress generated by "reactive oxygen species" (ROS) witch The most significant endogenous sources of DNA damage are capable of inducing numerous modifications, including lesions to nucleotide bases, as well as effects on lipid oxidation, which represents the utilization of energy substrate. Lipid peroxidation, the degradation of membrane fatty acids and protein damage are also among the notable consequences and other chemical mediators such as a few pro-inflammatory cytokines which the body may discharge upon contact with toxicants like pesticides (Lohiya *et al*., 2017).

Biochemical parameters

The obtained results of Table 1 show that the group treated with deltamethrin presents a significant increase ($P \leq 0.001$) in the biochemical parameters (Glucose, Triglyceride, Cholesterol) as well as a significant increase of the activity of TGO and no significant change of the TGP, the same results are recorded for the indicators of renal activity (creatinine, urea) compared to the control group. In addition, no significant change was observed in total protein, only a slight increase. Data show that the extract of the leaves of *F.carica* is able to decrease the toxicity induced by the DLM, where we recorded a significant decrease in the rate of the biochemical parameters of G5 and G6 compared with G4.

The comparison by the Tuky test showed a no-significant difference between the groups treated by the combination and the control group except for the cholesterol (a significant difference and the decrease is very slight). According to our findings, rats treated with Deltamethrin has significantly higher glucose levels than rats of the control group, these findings are consistent with the study of Manna *et al*., (2005)., this increase of glucose level is due to the entrainment of toxic substances of emotional reactions in the limbic system, which induce an rise in glucagon secretion while also causing an insulin decline. As a result, glucose is produced from hepatic glycogen and enters the bloodstream (Eraslan *et al*., 2007).

A normal level of plasma glucose is observed in rats treated with *F.carica,* These findings are consistent with the work of Stephen Irudayaraj *et al*., (2017), possibly as a result of extract's potentiation of pancreatic insulin production from regenerated β-cells (Sunil 2012).

The group receiving treatment with *F.carica* and Deltamethirin exhibited improved blood glucose levels., this improvement can be explained by *F.carica* extract stimulates glucose absorption in rat peripheral tissues in a dose-dependent manner (Stephen Irudayaraj *et al*., 2017). *F.carica* improve the insulin sensitivity (El Hilaly and Lyoussi, 2002).

Triglycerides in treated rats are higher than in controls, indicating that Deltamethirin causes hepatic hypertri glyceridemia. These results align with previous researchers' findings and which can be explained by the excess of hepatic triglyceride synthesis or by the reduction of triglyceride hydrolysis caused by inhibition of the lipolytic enzyme (Eraslan *et al*., 2007). Rats given the plant exhibit a significant reduction in TG levels compared to controls. This can be explained by production of triglyceride precursors such as acetyl-CoA and glycerol phosphate (Eddouks *et al*., 2005). Our results are similar to the results of Joerin *et al*., (2014), who confirmed the anti-hyperlipidemic effect of *F.carica* leaf extract.

Cholesterol level in MLD-treated rats are significantly higher than in control. Our results are consistent with the study of Golli-Bennour *et al*., (2019), This increase can be attributed to the effect of pesticides on hepatic cell membrane permeability and liver dysfunction (Yousef *et al*., 2006), which is confirmed by the increase of TGO, TGP and glucose.

The same results are recorded in the groups treated with the plant compared to the control, so the plant doesn't show an improvement and this may be due to the short duration of co-treatment with the extract, these results corroborate with the study of Joerin *et al*., (2014). The increase in GOT and GPT levels in the MLD treated group compared to the control groups is similar to that recorded by (Manna *et al*., 2005)**.**

Although Pyrethroids have a selective mechanism of action, their harmful side effects also include severe liver

Table 1: Variations of biochemical parameters.

Parameters	G1	G2	G3	G4	G5	G6
Glucose (g/l)	0.86±0.02	6±0.023	0.97±0.06	1.41±0.01***	1.27±0.059^{abbb}	1.01±0.098^{aaab}
Triglycéride (g/l)	0.63±0.01	0.66± 0.01	0.38± 0.02	0.87±0.03***	0.73±0.026^{a}	0.67±0.026^{a}
Cholestérol (g/l)	0.40±0.02	0.327±0.02	0.282±0.01	0.87±0.03***	0.75±0.07^{aabb}	0.75±0.03^{aabbb}
Protéines T (g/l)	53.25±2.50	58.00±1.4	62.09±1.23	55.50±1.91	59.80±0.74^{aabb}	62.14±0.57^{aabb}
TGO (g/l)	110.18±6.54	16.50±3.32	102.80±4.68	124.70±2.90***	115.65±2.45^{a}	114.85±2.14^{a}
TGP (g/l)	81.50±3,70	78.13±1.44	42.35±5.76	88.78±5.16	74.30±2.58^{aaabbb}	52.47±2.06 ^{aaabbb}
Créatinine (g/l)	5.81±0.08	3.21±0.06	4.72±0.15	6.47±0.20***	5.93±0.20^{aa}	4.91±0.31^{aabbb}
Urée (g/l)	0.195±0.006	0.27±0.022	0.258±0.015	0.323±0.017***	0.298±0.017^{bbb}	0.288±0.022 ^{bbb}

The values are mean±S.E.M, the difference is significant:

Between the Deltamethrin group (G4) and the control group (G1): *p≤0.05, **p≤0.01, ***p≤0.01.

Between the groups Deltamethrin+plant (G5, G6) the group Deltamethrin (G4): ^{a}p≤0.05, ^{aa}p≤0.01, ^{aaa}p≤0.01.

Between the groups Deltamethrin+pante (G5, G6) the group and minus (G1): ^{b}p≤0.05, ^{bb}p≤0.01, ^{bbb}p≤0.01.

dysfunction, interruption of the production of these enzymes and altered liver membrane permeability (Saoudi *et al*., 2011). The co-treatment with *F.carica* show a decrease of GOT and GPT of G2 and G3 compared to the control group, our results are similar to those of Fouad *et al*., (2019) who reported that flavonoid extract of *F.carica* has marked scavenging activities against hydroxyl and super oxide anion free radicals. A possible mechanism of *F.carica* extract as a hepatoprotector may be due to its antioxidant effect or inhibition of cytochrome P450s.

Preliminary phytochemical studies indicate that the Methanolic extract of *F.carica* leaves contains steroids, triterpenoids and their glycosides and coumarins. According to Oh *et al*., (2002), coumarins (phenolic compounds) exhibit hepatoprotective action, hence it is possible that the contents of *F.carica* are responsible for its demonstrated protective effect.

Our study shows a slight increase in total protein levels after exposure of rats to MLD compared to control rats. These results are confirmed by the study of Saoudi *et al*., (2011). Indeed, when environmental stresses (water stress, temperature, oxidative stress, exposure to pollution and infection by pathogens...) are severe, most proteins are denatured (Mohammad and Heidari, 2008).

The study demonstrated a significant increase in protein levels after using *F. carica* extract, indicating the presence of cytoprotective molecules such as phenolic compounds that improve the homeostasis of the biochemical parameters. This is attributed to the antioxidant properties of polyphenols containing the catechol group, as reported by Brglez Mojzer *et al*. (2016). The study also observed an increase in urea and creatinine levels in DLM-treated groups compared to the control group, indicating the harmful effects of DLM on nephron excretory function. This is consistent with previous research that showed similar results with other pesticides. However, the group treated with *F. carica* extract showed a significant decrease in creatinine and urea levels, indicating its antioxidant properties mainly due to flavonoids and phenolic compounds. These findings are consistent with the findings of Kore *et al*., (2011) who showed that *F.carica* extracts significantly reduce creatinine and nephrotoxicity caused by gentamicin. The results indicate the beneficial role of F. carica on renal function and its ability to reduce the harmful effects of DLM.

Histopathological results

The observation of the histological sections of G1 show a normal cellular architecture of the liver with normal hepatocytes. On the other hand, the sections obtained of G4 show an inflammatory infiltrate; hepatocyte cells take a ballooning aspect, acute hepatitis, loss of trabecular architecture (intra lobular necrosis) and clarification of hepatocytes cytoplasm. Group 5 show the presence of an inflammatory infiltrate with little vascularity, clarification of the hepatocytes and vascular congestion (dilation of the vessels). On the other hand, group 6 show a clear improvement with a small vascular congestion (Fig 4). Our findings are consistent with previous research on DLM. By Chargui *et al*., (2012). Deltamethrin exposure induced apoptosis; by increasing mRNA expression of apoptotic markers Bax and caspase-3 as well as decreasing bcl-2 in liver tissues (Maalej *et al*., 2017).

On the other hand, liver tissue apoptosis is clearly reversed by co-treatment with *F. carica*. In particular, it is shown that the extract dose of 400 mg/kg is more efficient to reduce apoptosis. This improvement is a result of the flavonoid present in *F.carica* leaves (Ammar *et al*., 2015).

Furthermore, the DLM exposure increase the expression of inflammatory markers in primary rat hepatocytes. Hepatic slices with mild vasoconstriction can be explained by the reduction response of the liver (pressure is elevated). As a result of its toxic action, DLM caused acute hepatitis and liver damage. However, the recombination of DLM with *F.carica* extract indicates normal hepatocytes due to the plant's hepatoprotective function. A proposed mechanism of Ficus extract. Ethanolic extracts of *F.carica*. leaves at 600 mg/Kg exert a high anti-inflammatory effect of 75.90% in acute

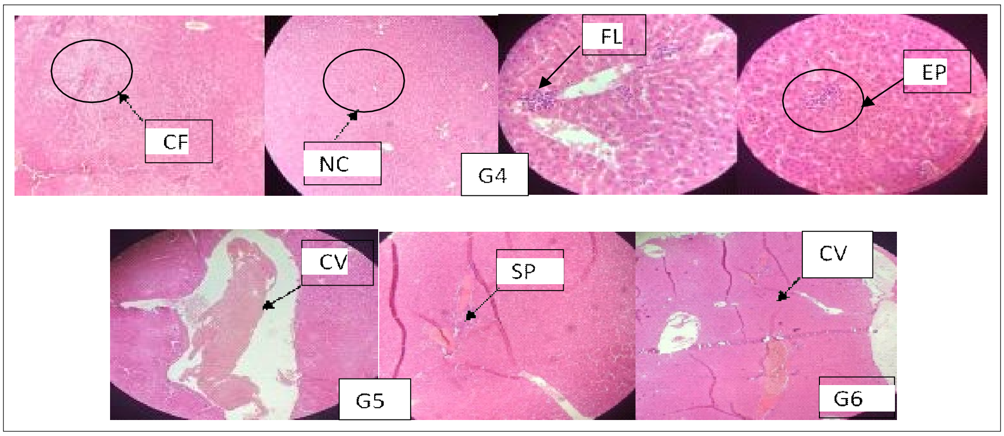

Fig 4: Histological sections of rat livers. EP: Espace porte. H: Hépatocyte. CLV: Centro lobular vein. NC: Nécrose. VC: Vascular congestion. CH: Clarification of the hepatocytes. PF: Peri-vascular filtrate. SP: Signs of portitis. LF: Lymphoplasmacytic filtrate.

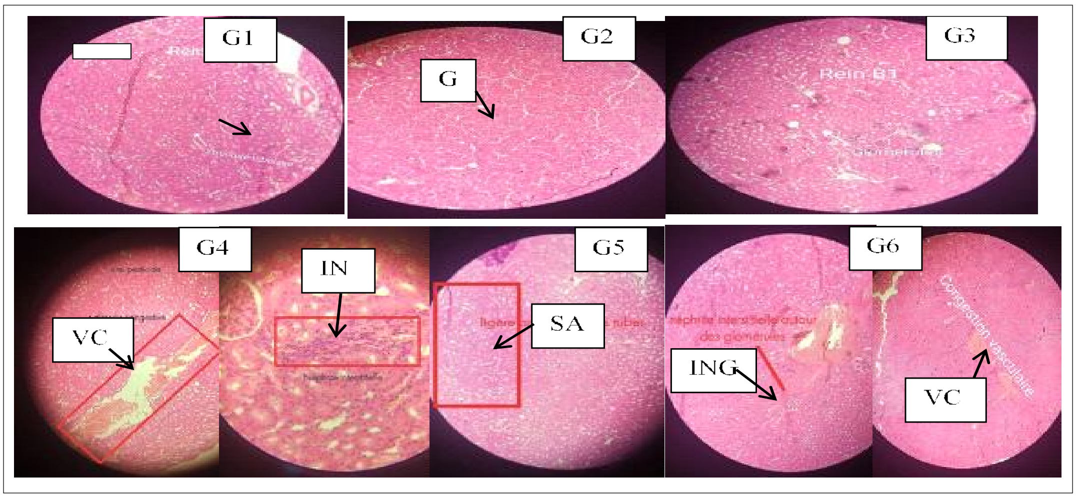

Fig 5: Histological sections of rat kidneys. TS: Tubular structure; G: Glomeruli. VC: Vascular congestion. IN: Interstitial nephritis. SA: Slight atrophy of the kidney tubes; ING: Interstitial nephritis around the glomerules.

inflammation and 71.66% in chronic inflammation by reducing granuloma weight (Patil and Patil, 2011).

Histological sections (Fig 5) show that the kidneys in the control group have a normal architecture (nephrons have glomeruli, glomerular capsules, Bouman capsules and renal tubules in the cortical and medullary areas), without any inflammatory changes. On the other hand, several histological changes can be seen in G4, including an inflammatory filtrum of a lymphoplasmacytic (interstitial nephritis between the nephrons), slight vascular congestion and vessel enlargement (due to increased pressure in the kidneys). However, the group 5 figure shows a slight atrophy of the fibrillation renal tubules and group 6 figure show, a small improvement with vascular congestion, a sign of interstitial nephritis around the glomeruli (lymphoplasmacytic infiltrate). These results support the biochemical data. Our findings are consistent with those of Poonam *et al*., (2014), which can be explained by the short-term toxic effects of Deltamethirine on the kidneys, however, in the groups that received *F. carica* extract, a slight atrophy of the fibrillated renal tubules is observed, a sign of interstitial nephritis around the glomeruli. These findings support those of Kore *et al*., (2011)**,** which demonstrate that the plant reduces the impact of pesticide, due to the brief course of therapy, the kidneys are not entirely healthy. However, treatment of *F. carica* extract significantly reduced the inflammation., this can be explained by the *in vivo* analysis that detected a notable anti-inflammatory regulatory effect of *F. carica* (Patil and Patil, 2011).

CONCLUSION

In conclusion, we can surmise that the treatment of Deltamethrin produces toxicity in rats, as evidenced by the rise in biochemical markers and histological abnormalities in both the liver and kidney, indicating that the application of *Ficus carica* reduces the toxic impact, as we observe a return of biochemical parameters and an improvement in histological structures. To identify the most successful component in removing toxicity, more research is required on the extraction of active chemicals from the extract and their biological activity.

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Conflict of interest

The authors declare that there is not any conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission and redundancy has been completely observed by the authors.

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