PREVENTIVE EFFECTS OF CITRULLUS COLOCYNTHIS. L PLANT EXTRACT ON DELTAMETHRIN PESTICIDE INDUCED PNEUMOTOXICITY IN WISTER RATS

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ABSTRACT

Pesticides are chemicals used to fight agricultural pests. They use causes extensive damage to both humans and animals, resulting in diseases mainly affecting the respiratory and digestive systems. Through this study, we evaluated the pneumotoxicity caused by a deltamethrin (DM) insecticide at a dose of 0.64mg.kg-1.day-1. We also evaluated the preventive and curative effect of the medicinal plant “citrullus colocynthis, L” antagonist of this toxicity at a dose of 150mg.kg-1.day-1. We carried out the experimental application on Wister rats as an animal model of exhalation. Several experiments were carried out on the activity of enzymes and vital indicators. This study revealed a decrease in the concentration of the protein accompanied by a decrease in the means of development of the body [25±0.23]. Then, our study showed that DM has an oxidative effect, resulting in a decrease in the level of GSH [0.05 ±0.00] and the enzymatic activity of GPx [0.34±0.05]. In addition to an increase in the level of MDA [4.90±0.72] and the enzymatic activity of GST [0.84±0.11]. In addition, the histological study carried out on a fragment of lung of rats treated with this pesticide showed changes in the histological structure of the lungs resulting in vascular congestion, infiltration of inflammatory cells, thickening of the walls of blood vessels, as we do. Observed intra-alveolar hemorrhages and hyperplasia of the alveolar lining. On the other hand, we have confirmed the preventive effect of the citrullus colocynthis, L after treatment with this pesticide, which has an anti-oxidant activity, which can reduce the intensity of the oxidative stress resulting from deltamethrin and its effectiveness. In the treatment of lung, tissue effected by this pesticide and it is stored in its natural state.

Keywords: Deltamethrin; Pneumotoxicity; Pyrethroids; Citrullus colocynthis, L; Oxidative stress

INTRODUCTION

Man is one of the living beings making up the multitude of organisms in the biosphere. It remains permanently exposed to numerous attacks of various kinds, in particular toxic substances in its environment such as pesticides. The latter are the most dangerous pollutants in the environment because of their mobility and their ability to accumulate in the environment and their resulting harmful long-term effects on living organisms in general and human health in particular (Marek et al., 2013).

Their widespread use in agriculture, public health, commerce and households around the world is an indication of the importance of these compounds (Alavanza et al., 2004). In addition to their primary purpose, pesticides can also affect humans and animals in the vicinity of the insecticide sprayed area (Gasmi et al., 2017). They are designed to interfere with living species and are necessarily characterized by varying levels of toxicity (Corsini et al., 2007). In fact, the severity of intoxication depends on the toxicity of the product in question, the mode of penetration, the dose absorbed, the physiology and the age of the subject (Miguel-Bouzas et al., 2012).

The use of toxic substances with insecticidal power is very old. 2000 years ago, the Chinese were already using the powder of dried flowers, the pyrethrums (Kumar et al., 2017). In 1690, La Quintinie discovered the antiparasitic qualities of tobacco (Al-Khaldi et al., 2018). Then at the end of the 18th century and the beginning of the 19th century, arsenicals, fluorides and sulfur were in turn used. It was then, with the development of organic chemistry, that synthetic insecticides were developed, the best-known example being that of the discovery of DDT. From that moment on, many other insecticidal compounds have been discovered which are grouped together in the categories of organochlorines, organophosphorus compounds, carbamates, etc (Miguel-Bouzas et al., 2012).

Kumar et al. (2017) note that in recent years, the appearance of strains resistant to these products, in particular to organo-phosphorus compounds, as well as the increasingly in-depth knowledge of the toxic action of the natural components of pyrethrums will then determine the development of the large family of synthetic pyrethroids. One of these pyrethroids is deltamethrin (DM), a non-systemic insecticide belonging to the family of synthetic pyrethroids which acts rapidly by contact and ingestion (Fetoui et al., 2010). This molecule is considered an esterase inhibitor, as well as an inhibitor of the sodium channel in the membranes of neurons in insects. The active dose of deltamethrin (DM) in agricultural treatment is only 5 to 15 g/ha-1 (Gasmi, 2020). DM is considered the most toxic of the other pyrethroids because it is neither completely degraded nor rapidly metabolized and therefore accumulates in lipids (Gasmi et al., 2017).

The general objective of this work is to evaluate the pneumotoxicity of DM and the corrective effect of the extract of the C. Colocynthis, L medicinal plant.

MATERIAL AND METHODS

Plant material

Citrullus colocynthis, L. Schrad, Handhahl. or colocynth is a perennial plant belonging to the Cucurbitaceae family; C. Colocynthis has a rich history as a medicinal plant and as a source of valuable oil. The different parts of this species are used in traditional medicine according to their method of preparation (decoction, spraying, maceration of the seeds), against hemorrhoids in local application of the pulverized seeds, jaundice, ascites, rheumatism, amenorrhea, and gastrointestinal disorders (dysentery, constipation). Several ethnobotanical and pharmacological studies have reported the use of this herb for the treatment of diabetes (Hameed et al., 2020).

Chemical material

In this work, we used on the one hand the pesticides of DM for the treatment of rats in solution form at a dose of 0.64 mg.kg-1.day-1, and on the other hand, the plant extract Citrullus colocynthis, L in aqueous solution. At a dose of 150 mg.kg-1.day-1 for 30 days. Deltamethrin [C9H9BrNO] the active ingredient in Décis® is an insecticide from the pyrethroid family which acts mainly on the sodium channels of nerve fibers which it blocks in the open position (Gasmi et al., 2017 ; Haddadi & Shirani, 2014).
Laboratory animals

The present study was carried out on male Rattus rattus rats of the Wistar strain of 32 rats, from the Pasteur Institute in Algiers, aged 06 to 08 weeks, weighing approximately 150-290g. They are mammals of the rodent order. Widely used in various fields of experimental research. Animal care. The rats were divided into 04 groups at the rate of 08 rats per group. They were subjected to a 30 days adaptation period in the animal facility of the Department of Biology, Faculty of Sciences, Larbi Tebessi University. The ambient temperature is 23±2°C and a natural 12/12h photoperiod with a humidity of 60%. The rats are reared in polyethylene cages which are lined with litter made from wood chips. The cages are cleaned and the litter is changed once every two days until the end of the experiment. The animals were fed a concentrate of bread and corn.

Distribution and treatment of rats

In this experiment, the rats are divided into 4 lots as follows:
- Lots (T): Contains 08 control rats received drinking water by gavage.
- Lots (E): Contains 08 rats treated with Citrillus extract receiving 150mg.kg-1.day-1 for 30 days orally.
- Lots (D): Contains 08 rats treated with DM at a dose of 0.64mg.kg-1.day-1 for 30 days orally.
- Lots (ED): contains 08 rats treated with the combination of DM at a dose of 0.64mg.kg-1.day-1 and with the extract of Citrillus receiving dose of 150mg.kg-1.day-1 for 30 days orally.

Weight measurement

The weight measurement is carried out on the rats every day on a regular basis during the rearing period, during either adaptation or treatment with the aid of electronic scales.

Evaluation of oxidative stress parameters

At the end of the 30-day citrullus and deltamethrin administration period, the animals are sacrificed; the lungs were quickly removed and rinsed in distilled water then weighed and kept in the freezer for the assays of the various parameters, and the other fixed in formalin in order to make histological sections

GSH, MDA and Proteins levels

Glutathione (GSH) concentration was measured utilizing the method described by weckberker and Cory (1988). The protein contents of various samples were determined according to the method of Bradford, 1976; using bovine serum albumin as a standard.

GPx and GST activities

Glutathione peroxidase (GPx) activity was measured by the procedure of Flohe and Gunzler (1984). The activity of Glutathione-S-transferase (GST) was measured according to the method of Habig et al (1974). The P-nitro benzylic chloride was used as substrate. The absorbance was measured at 340 nm at 30s intervals for 3min.

Histopathological examination

For histopathological examination, pancreas was dissected and immediately fixed in boun solution for 24h, processed by using a graded ethanol series, and then embedded in paraffin. The paraffin sections were cut into 5µm thick slices and stained with hema et al. (1974). The P-nitro benzylic chloride was used as substrate. The absorbance was measured at 340 nm at 30s intervals for 3min.

Statistical analysis

Statistical analysis was performed using ANOVA test and p<0.05 was considered the limit for the statistical significance; Data were expressed as means ± SEM.

RESULTS

Effects of citrullus colocynthis. L. on deltamethrin on growth parameters

The results of the evaluation of the growth parameters in terms of body weight, weight gain and relative weight during the 10 days of treatment of the different groups of animals with plant extract (E) and the pesticide (DM) are shown in Fig. 01. By measuring this parameter, we wanted to know the variation in the evolution of body weight in the group that is treated with E and DM. The results of the evaluation of body weight show a very highly significant decrease (p<0.001) in body weight in the rats treated with DM compared to the control rats; While for the lots: E and E + DM no decrease was recorded (figure.

Weight gain (WG)

The results of the weight gain evaluation show a significant decrease (p≤0.001) in weight gain in the batches treated with DM compared to the control batch. These results do not show a significant variation in the rats which are treated with E and E + D (Fig. 2).

Relative lung weight (RLw)

The results obtained following the evaluation of RLw show a very highly significant increase (p≤0.01) in the relative lung weight in the group treated with DM in comparison with the control group, on the other hand in the animals treated with plant E alone or associated with pesticides, they did not show any significant variation (fig. 3).

Effects of Citrillus on the pneumotoxicity of DM on biochemical parameters and redox status

GSH

The results represented in Fig. 04 show a very highly significant decrease (p≤ 0.001) in the level of cytosolic GSH in the total lung respectively in the batches treated with DM when compared to the control. In addition, a very highly significant increase in the ED batch rats (Fig. 4).
Weight Gain

Figure 02 Evolution of body weight gain (GP) in control and treated rats after 30 days of treatment with pesticides and Citrillus. T: Control; E: Extract of Citrillus; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

Relative lung weight

Figure 03 Evolution of the relative lung weight (RLw) in rats treated for 30 days with pesticides and Citrillus colocynthis. L: T; Control; E: Extract of Citrillus colocynthis; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

GST

Figure 05 Change in the level of GST in the lungs of rats after 30 days of treatment with the pesticide and the plant extract. T: Control; E: Extract of Citrillus colocynthis; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

GSH

Figure 04 Change in the level of GSH in the lungs of rats after 30 days of treatment with the pesticide and the plant extract. T: Control; E: Extract of Citrillus colocynthis; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

GPx

Figure 06 Change in the level of GPx in the lungs of rats after 30 days of treatment with the pesticide and the plant extract. T: Control; E: Extract of Citrillus colocynthis; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

MDA

Figure 07 Change in the level of MDA in the lungs after 30 days of treatment with the pesticide and the extract. T: Control; E: Extract of Citrillus colocynthis; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

Proteins

The results obtained show a significant decrease (p≤0.05) in the total protein level of the lung in the DM batches compared to the control and a highly significant
increase (p≤0.01) is observed in the batches treated with the ED mixture compared to the batches. Control; but the latter do not show a significant variation in the groups treated with extract E (Fig. 8).

**Effects of Citrullus colocynthis on Deltamethrin-Induced Pneumotoxicity in Lung Tissues**

To confirm the results of biochemical parameters of oxidative stress we performed a histological testing procedure on the lungs of different groups of experimental animals (Fig. 9).

**Controls (T):** The results obtained show that the pulmonary parenchyma has alveoli of normal morphology and branches with vascular structure (fig. 9-A).

**Extract (E):** This figure shows that the pulmonary parenchyma is made up of alveoli and branches with the presence of vascular structure; there is a discreet dilation of the branches with conjunction of the alveoli and signs of vascular conjunction and nani inflammatory lymphocytic infiltration were found; in comparison to the control (fig. 9-B).

**Deltamethrin (D):** the results show that the pulmonary parenchyma is made up of alveoli and branches with the presence of vascular structure; there is a presence of hemorrhage alveolitis (inflammatory cells) whose alveoli are edematous and pruned by hemorrhage and also inflammatory lymphocytic infiltration of low to moderate intensity harsh in places denounces mononuclear grouped in aggregate and presence of vascular conjunction by report to the Control (Figure 9-C).

**Figure 8**: Variation of the Protein level in the lungs of rats after 30 days of treatment with the pesticide and the plant extract. T: Control; E: Extract of Citrullus colocynthis; D: Deltamethrin; ED: Mixture Extract of Citrillus colocynthis and Deltamethrine; P: level of significance; * Significant difference: p≤0.05; ** Highly significant difference: p≤0.01; *** Very highly significant difference: p≤0.001.

**Protein**

| Group    | Level of protein (mg/mg) |
|----------|--------------------------|
| T        | 0.76                     |
| E        | 0.77                     |
| D        | 0.78                     |
| ED       | 0.82                     |

**Figure 9**: Histological sections (+40) in the striatum of control rats treated with citrullus colocynthis (E), deltamethrin (D), and their combinations after 30 days of treatment. Histological sections (+40) in the striatum of mice treated with citrus colocynthis (E), deltamethrin (D), and their combinations after 30 days of treatment. The arrows show the areas affected by tissue or cellular damage, as this damage could be the result of an apoptosis (organized) or sudden cellular death of the cells of these tissues.

**Pesticide Mixture and Extract (ED):** Figure 9-D show that the pulmonary parenchyma makes alveoli and branches with the presence of vascular structure; there is a slight haemorrhage and vascular conjunction; in comparison with the control group (Figure 9-D).

**DISCUSSION**

Oxidative stress is not a disease, but it creates or accelerates the conditions for the disease. Diagnosis and monitoring are therefore of fundamental importance in the context of preventive medicine, health, monitoring of treatments and pathologies (Bobali, 1991). The involvement of oxidative stress in the development of many pathologies and in aging process is widely documented in the scientific literature. A certain craze has led to believe that antioxidants could be the solution to treat and prevent the most serious diseases, and to age well. The empirical intake of certain antioxidants over the long term appears increasingly questionable. Hence the growing interest in the search for markers of oxidative stress (Gasmi, 2020).

This study treated the toxic effects of deltamethrin on the pulmonary system dear to rats after exposure to a dose of 0.64mg.kg⁻¹.day⁻¹, as well as the protective effect of citrullus colocynthis against the toxicity of this pesticide were put in view evidence by investigation of metabolic parameters, enzymatic parameters, non-enzymatic parameters and growth parameters. In this study allowed us to illustrate the relationship between exposure to this pesticide deltamethrin and the toxic effects they induce, and the preventive and curative effect of an extract of a medicinal plant.

**Effects of deltamethrin and citrullus colocynthis on growth parameters**

Monitoring of body mass in mice treated with the pesticide deltamethrin (DM) and Plant Extract citrullus colocynthis L shows a decrease in body weight and weight gain in the batches treated with Deltamethrin compared to the control batches. Agrees with several studies where the same effect has been noted in laboratory animals (Emara and Draz, 2007; Zhang et al., 2008). The reduction in the rate of body weight gain is used as an indicator of toxicity and deterioration in the general health of rats. This decrease may be due to the effect of pesticides on the gastrointestinal tract through loss of appetite and / or poor food absorption thus causing a reduction in food and water consumption in treated rats by the pesticide (Mairif, 2015). The decrease in body weight gain may also be the result of the disruption of cell metabolism under the effect of the oxidative stress generated by ROS observed in this study, as well as by other chemical mediators such as certain pro-inflammatory cytokines. The organism can after the toxic effects of pesticides (Carole and Harve, 2011; Viviana, 2015). Regarding the effect on the relative weight of the lung, we noticed a very highly significant increase. This can be explained, on the one hand, by the tissue hypertrophy of this organ caused by deltamethrin and on the other hand by the intense accumulation of the pesticide itself in this target organ (Kehili, 2017) obtained the same results by studying the toxicity of cadmium on several organs. In addition, the capacity of the extract of citrullus colocynthis to preserve these weight parameters of the animals. This could be the consequence of its antioxidant power (This plant contains many antioxidants) according to research of Hamed et al., (2020).

**Effects of deltamethrin and citrullus colocynthis on redox status**

**GSH**

Reduced Glutathione (GSH) is a tri peptide (Glu-Cys-Gly) contains a nucleophilic thiol group that readily reacts with alkaline xenobiotics (Tremblay, 2018). It plays a role in detoxifying endogenous or xenobiotic substances and protects cells against oxidative stress. Our results show a decrease in the level of pulmonary GSH after exposure to deltamethrin. This decrease is a response to oxidative stress caused by deltamethrin (Kumar et al., 2017). Reduced glutathione (GSH), reduces hydrogen peroxide and/or organic peroxides thanks to the reaction catalyzed by glutathione peroxidase (GPx) (Garaït, 2006). The decrease in GSH levels indicates that the rat body is building the antioxidant defense system (Grara et al., 2012; Kehili et al., 2017).

**GST**

GST is an enzyme with an important role in the detoxification of xenobiotics and the protection against harmful metabolites generated after the degradation of macromolecules (Aouacheri et al., 2009). According to our results, we observe a highly significant increase in GST in the tissues studied (lung) in the DM batch compared to the other treatment batches. Our results are consistent with the study (Kehili et al., 2017). The increase in the activity of this enzyme is a physiological response to compensate for the damage that is due to free radicals (Aouabhi et al., 2015).

**GPx**

GPx is one of the very powerful antioxidant defense systems; it reduces H₂O₂ to H₂O and protects the body against the cancreros effect of this substance (Zhu et al., 2010). The results obtained revealed that the rats treated with deltamethrin underwent a significant decrease in GPX’s activity, these results in agreement with the work of (Gasmi et al., 2017). The observed decrease in GPX activity in lung tissue following treatment with deltamethrin could be due to their indirect action in reducing the levels of reactive oxygen species, which may reduce oxidative stress work on toxicity caused by a xenobiotic (Kehili et al., 2017).
The results of this study show a highly significant decrease in metabolic parameters in rats treated with DM compared to the control batch. Another explanation would be the excessive use of protein molecules involved in the antioxidant defense against ROS released following the overproduction of MDA in rats treated with DM. This results in a loss of membrane functionality, which affects the functionality of organs.

MDA

The DM toxicity studied was a very highly significant cause of MDA levels, which is the main active aldehyde in the peroxidation of polyunsaturated fatty acid in membranes according to this study (Maiza et al., 2011). ROS can oxidize lipids (Ercal et al., 2001). Lipid peroxidation is followed by the disintegration of biological cell membranes (Fetoui et al., 2009; Bebiano et al., 2005) or other elements containing lipids (Al-Mutairi, 2007). This results in a loss of membrane permeability and potential, mowation of receptors and membrane enzymes (Pampanin, 2005). These functional disturbances can lead to cell death. Thus, lipid peroxidation is an endogenous source of DNA damage (Marnett, 2002). On the other hand, studies by (Harris, 1992) show an overproduction of MDA in earthworms treated with zinc oxide and titanium oxide (0.1, 0.5, 1 and 5 μg/g).

For the majority of the parameters studied a supply of citrullus colocynthis. L bark extract to the rats treated with the studied pesticide improved the Redox status of the animals by restoring a certain balance of primary metabolites (MDA) but also of enzymatic biomarkers (GPx, GST) and non-enzymatic explored (GSH). This can be explained by the richness of citrullus colocynthis in polyphenols (Gasmii et al., 2017), molecules endowed with an immense antioxidant power (Macheix et al., 2005), mainly due to the presence of hydroxyl functions on the benzene nucleus of these phenolic compounds. Polyphenols, which are molecules of exclusively plant origin, are the basis for the design of most drug preparations, due to their various biological activities (Macheix et al., 2005). In this study, they demonstrated a strong therapeutic power against poisoning with the phytosanitary product, namely deltamethrin.

Protein

These results indicate a significant increase of total protein with the treatment of oral deltamethrin (LCT) and captan and its impact on the metabolic parameters (Michielsen et al., 2010). In addition, protein is initially involved in the defense mechanisms of the body and plays an important role in the protection of lung tissue, as well as in the metabolism of free radicals. In this context, studies by (Harris, 1992) show an overproduction of MDA in rats treated with DM compared to the control batch. This results in a loss of membrane functionality, which affects the functionality of organs.

CONCLUSION

The administration of citrullus colocynthis. L. at a dose of 150 mg/kg/day for 30 days to rats treated with deltamethrin at a dose of 0.64 mg/kg/day restored all values to normal, which reflects the protective effect of citrullus colocynthis. L on lung function.

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