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THERAPEUTIC AND ANTIOXIDANT EFFECTS OF MEDICINAL HERB "CURCUMIN" ON FORMALDEHYDE- INDUCED NEUROTOXICITY IN RATS

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ABSTRACT

Our problem is to evaluate the behavioral effects of formaldehyde on the anxiety and cognitive abilities of Wistar rats on the one hand, on the other hand, we have proven the protective effect of an antioxidant, "curcumin".
The positive antidepressant and anti-anxiety effects of curcumin are most likely due to its ability to normalize specific physiological mechanisms, in addition to being a potent antioxidant and anti-inflammatory agent. Curcumin also protects the brain and simultaneously acts on several mechanisms related to depression. It is considered to be the most promising therapeutic target for treating depressive behavior.
25 male rats weighing approximately 240 g were divided into equal five groups, toxicity was induced by a single intraperitoneal injection of formaldehyde at a dose of 10 mg/kg. Behavioral test in "light/dark box test" revealed that animals exhibited an anxious behavior when compared to control. The curcumin, was administered orally (gastric gavages) at a dose of 60 mg / kg.
The effects of formaldehyde gas on the variation in body weight and an alteration in locomotive and exploratory activities when compared to control. Our results show the therapeutic benefits of curcumin against the deficits caused by formaldehyde reflected in a disturbance in rat behavior.

Keywords **:** Formaldehyde, toxicity, curcumin, behavior, antioxidant

Introduction

The Formaldehyde is an atmospheric pollutant with the chemical form of CH_2O (Fiche Demeter, 2010). It has long been the subject of environmental policy discussions; it is a polluting substance that enters the body primarily through breathing. It is not only a powerful trigger for inflammation in the lower respiratory tract, but also harms other organs (Lino-dos-Santos-Franco et *al.,* 2011). It has many routes of entry to the body like the dermis, inhalation, and ingestion (Pidoux, 2015). Epidemiological studies showed that long-term exposure of people to formaldehyde in the air might contribute to a series of neuropsychiatric symptoms, such as; depression, anxiety, sleep disturbances, malaise, balance dysfunctions, headaches, indigestion, lethargy, decreased motor activity, and loss of appetite (Wang and He, 2017).

Certain groups of polyphenols differ in number and arrangement of the hydroxyl groups, as well as by the nature and extent of alkylation. Flavanones, such as naringenin and its glycoside naringin, are highly reactive compounds and are present in citrus fruits and the medicinal herbs of Rutaceae, Rosaceae, and Leguminosae. Curcumin, on the other hand, has diarylheptanoid structure. It is the main polyphenol in turmeric (curry powder), and responsible for many health-related properties of the plant and food that contains it (Damir *et al*., 2015) Curcumin as spice is important to prevent amyloid beta aggregation but not the HSP70 and amyloid beta interaction that is relevant to endoplasmic reticulum stress with relevance to drug toxicity (Martin, 2017 and Martin, 2017). Curcumin has been used for centuries in medicines to treat a variety of inflammatory symptoms. It is a commonly used spice as it is increasingly studied for its antidepressant effect. (Lopresti and Drummond, 2017). Curcumin has also shown anxiolytic-like effects on the biochemistry and behavioral symptoms associated with anxiety (Lee and Lee, 2018). Curcumin or diferuloylmethane is the main pigment in *Curcuma longa*. It is a polyphenolic pigment (curcuminoid) which possesses a yellow color. The *Curcuma longa* is a perennial herbal plant native to southern Asia (Dafri and Lehadi, 2017), perhaps more specifically from India (Rezkallah, 2018). It has been the subject of therapeutic preparation for centuries in different parts of the world. In Ayurvedic medicine, *Curcuma longa* is an effective treatment for various respiratory ailments like asthma, allergy, liver disorders, anorexia, rheumatism, colds, and sinusitis (Tang and Taghibiglou, 2017).

Anxiety is a common and potentially serious condition that can significantly affect individuals' quality of life and predispose them to psychiatric comorbidities. Depression is a consequence of anxiety, affecting 21% of populations (Esmaily et *al.,* 2015).

In this context, we have developed an experimental approach that aims to study the antioxidant power of curcumin and its impact on neurobehavioral alterations and complications on the emotional state and reports about Adrenocorticotropic Hormone (ACTH).

Material and Methods

Animals

The biological material base that we have chosen is the rat *Rattus rattus* of the Wistar strain from Pasteur Institute in Algiers. The rats are nocturnal mammals of the order of rodents. Upon their arrival, the rats weighed an average of 180 grams, and at the time of the experiment, they weighed on average 250 ± 20 grams.

The rats were acclimated under standardized conditions of natural photoperiod, an average temperature of 22 ± 4ºC and humidity of 50-70%. After an adaptation period of three weeks, we have selected 25 males based on weight which we separated into five experimental groups each include five rats (n=5); control lot T, vehicle control lot CV , lot control treated curcumin CC, Lot Formaldehyde vehicle FV, lot treated with formaldehyde and FC .

Treatment of Animals

(i) Administration of Formaldehyde

Toxicity was induced in rats by intraperitoneal injection of Formaldehyde (Sigma Lowis ST, Mo) at a dose of 10 mg/kg body weight according to Mahmoud and Fenghour 2016 after dilution with distilled water.

(ii) Administration of curcumin

Administration is by gastric gavages of rats to a high dose of 60 mg / kg body weight. Treatment with vehicle or the antioxidant olive oil. The quantified doses were added in Eppendorf tubes to be dissolved in olive oil. Before administration, the tubes were shaken well until a homogeneous solution was obtained. The treatment started on the 8th day after the injection of formaldehyde and its administration was by gastric tube for 7 days.

(iii) The light/dark box test

The light/dark box test is based on Crawley and Goodwin's original model (1980). This test encountered the conflict between rodents' natural urge to explore their fear of light. They naturally prefer dark places while avoiding bright places (Ben Ahmed, 2016). The test was carried out in a box divided into two compartments, one compartment painted in black and the other in white illuminated by daylight. There is an opening that serves as a door that has been created between the two zones to facilitate the easy movement of the animal from one region to another. First, the rat was placed in the lighted compartment at this time and start filming the test for 5 minutes in two sessions, on day 7 and day 14, using a high-performance camera.

(iv) Determination of ACTH levels in plasma

This test is realized in plasma on immunometrique sequentiel chimiluminescent phase solid (Menarini, 2010).

The solid phase is a covered ball of murinemonoclonal antibody anti ACTH. The liquid phaseis the alkaline phospha tase (an enzyme whichamplifies the chimiluminescence for t he antigendetection) combined with an antibody polyclonal o fdoe anti ACTH in reagent ACTH.

(v) Data analysis

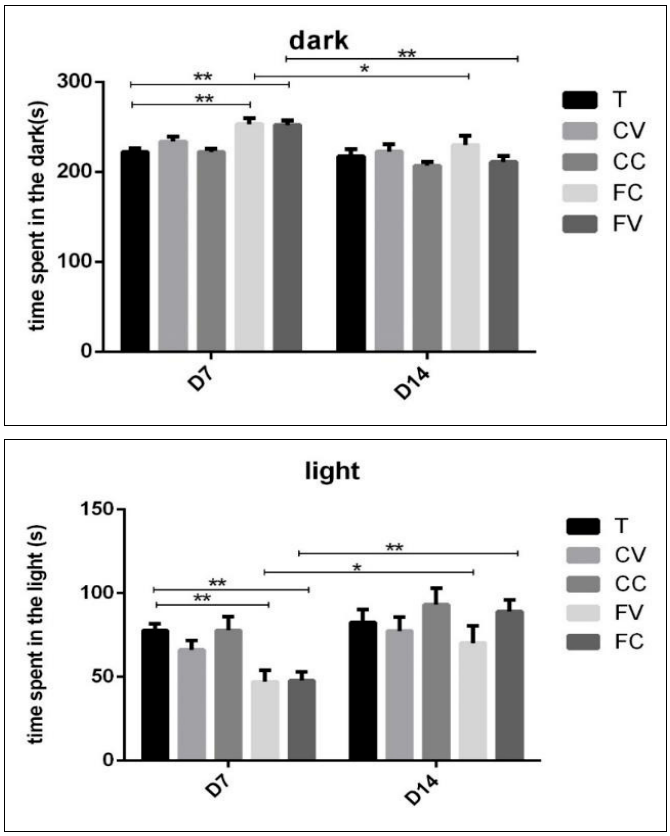
The results were obtained using the XLSTAT 2014 software in the form of histograms and were treated by Student's t-test, which allowed us to compare the results of the formaldehyde groups versus the Controls groups.

Results

Variation of The light/dark box Test parameters

Figure 1 shows the rats' time in each box compartment, light and dark, in the two sessions on day 7 and day 14.

On day 7, the groups FV and FC spend more time in the dark compartments with a very significant increase (**$P < 0.01$) compared to group T. On day 14, a non-significance ($P > 0.05$) at group FV and FC was observed. On the other hand, a significant difference (*$P < 0.05$) was noticed between FV day 7 and FV day 14. Another, a very significant difference (**$P < 0.01$) at group FC day 7 and FC day 14. On day 7, a very significant decrease in the time spent in the clear compartment of the FV and FC compared to T. On day 14, a non-significance difference at the groups FV and FC compared to T, was observed. There is a significant difference at the group FV day 7 and FV day 14. Also, a very significant difference between FC day 7 and FC day 14 was verified.



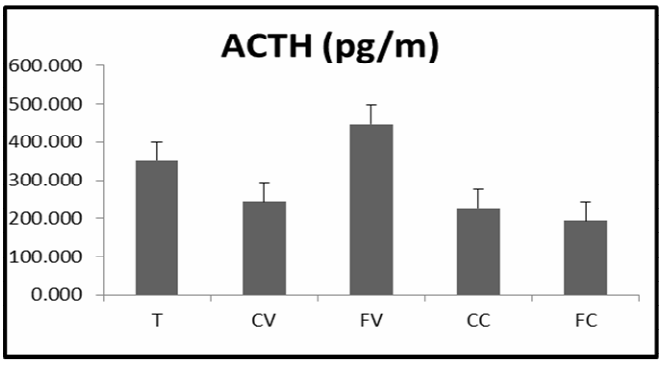
Non-significant difference = $P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Fig. 1 : Time spent in the light/dark box: controls (T), vehicle control (CV), curcumin control (CC), vehicle formaldehyde (FV) and curcumin formaldehyde (FC).

Variation of ACTH levels

The results obtained in this study shows that the level of ACTH plasmatic in diabetic rats was decrease contribution to the controls rats treated with curcumin.

The results showed a increase in level of ACTH plasmatic in controls rats treated with curcumin compared to the group controls vehicle.



Ns. (insignificantdifference p> 0.05; * p <0.05;
** p <0.01; *** p <0.001

Fig. 2 : Variation of ACTH levels in pg /ml The results are expressed on ± SEM (n=6).

Discussion

Our experimental study focused on properties that potentiate curcumin fight against neurobehavioral alterations in rats of Wistar treated with formaldehyde.

Our research has based on two parameters of the light/dark box test: the time spent in the light compartment and the time spent in the dark chamber. We recorded on the 7th day of the rats which were injected with formaldehyde (FV) and (FC) spend more time in the dark compartment than the clear chamber, with a very significant difference compared to the control (T). It is known that mice naturally prefer dark places and avoid lighted ones. This natural behavior has been used to estimate the degree of anxiety in animals (Arrant, 2013). Our results explain that formaldehyde acted on rats' behavior by inducing an increase in anxiety level. This is in agreement with work that demonstrated behavioral sensitization produced after injection of formaldehyde in mice for 7 days, suggesting anxiety caused by formaldehyde (Li, 2016); nevertheless, it had no batch significance (FV) and (FC) of day14.

On the other hand, when the identical batches from the two sessions were compared, the rats treated with the vehicle (FV) J7 and (FV) J14 also which were treated with curcumin (FC) day 7 with (FC) day 14.

The results were consistent with the very significant increase in time spent in the clear zone. Behavioral tests were performed in epileptic rats with epilepsy induced by an intraperitoneal injection of a single dose of kainic acid and subsequently treated with curcumin. The epileptic rats treated with curcumin exhibited anxiolytic behaviors in the light/dark box test, which is less observed in rats treated with the vehicle (Yow et *al.,* 2017). Other research has measured certain behaviors related to anxiety—responses to examine the effects of curcumin on rats' anxiety symptoms (Lee and Lee 2018). Besides, turmeric also significantly reverses the cognitive and behavioral change in rats (Huang *et al.*, 2011; Morrone *et al.,* 2016; Choi *et al.,* 2017).

The results of our work mention a hierarchical efficiency of curcumin against different levels of disorders caused by the disease, glucocorticoïdes are hormones produced and secreted by the cortical region of the adrenal glands and are involved in various physiological functions and adaptation to stress, (Berner, 2014) 15. Cortisol or hydrocortisone is the main circulating glucocorticoides produced by humans, and its synthesis is regulated by the pituitary hormone adrenocorticotropic hormone (ACTH), which is released in response to stimulation by a neuropeptide called corticotrophin-releasing factor produced in the hypothalamus. Our results have showed a decrease level of ACTH plasmatic at groups treated with formaldehyde vehicle contribution to the controls vehicle.

Conclusion

The crucial problem is summarized in the fact that the induction of experimental toxicity causes complications and neurobehavioral, disruption plasma biochemical metabolism and causes of anxiety. The administration of curcumin with a protective effect against anxiety and depressive disorders in rats Wistar. Treatment with curcumin seems store the levels of ACTH; this suggests that it also has an antioxidant effect.

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