

THE EFFECTS OF HYDROGEN CYANAMIDE (DORMEX) ON THE BRAIN AND LUNGS OF ALBINO RATS AND THE POTENTIAL PROTECTIVE IMPACT OF VITAMIN E

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ABSTRACT

Objectives: Hydrogen cyanamide is the active gradient of dormex, which is sprayed on grapes for early bud break. The **aim of the work:** This study aims to detect the toxic effect of dormex on the brain and lungs of albino rats and the protective role of vitamin E. **Methodology:** This experimental study was conducted on forty-eight albino rats. They were divided randomly into four groups, with 12 rats in each group. Group I (control group) received saline. Group II received tocopherol (2 mg/kg). Group III received dormex (4 ml/kg). Group IV was given 4 mL/kg dormex and 2 mg/kg tocopherol. After 12 hours, venous blood samples were drawn for total antioxidant capacity (TAC), and then all rats were sacrificed for histopathological studies, malondialdehyde (MDA) and catalase. Dormex caused a significant increase in brain and lung MDA (0.001**), a significant decrease in brain and lung catalase (0.001**), and a significant decrease in serum total antioxidant capacity (0.001**). Vitamin E + dormex significantly reduced MDA in the brain and lungs (0.001**), significantly increased catalase in the brain and lungs (0.001**), and significantly increased serum total antioxidant capacity (0.001**). Histopathological examination of the brain and lungs in the dormex group showed marked inflammatory changes, but in the group of dormex + vitamin E, mild inflammatory changes were detected. **Conclusion:** The present study concluded that dormex has highly toxic effects on the brain and lungs of rats, and vitamin E could prevent these dangerous effects.

Keywords: Hydrogen Cyanamid, dormex, Malondialdehyde, catalase, total antioxidant capacity, vitamin E.

INTRODUCTION

Some countries use hydrogen cyanamide (CH₂N₂), the active gradient of

dormex, as a fertiliser in agriculture. Farmers sprayed dormex on fruits to stimulate buds' opening and hasten flowering (Oreby et al., 2015).

Dormex poisoning may occur by dermal contact, inhalation, or oral ingestion. Dermal exposure results in severe inflammation and burns in the eyes and skin. Many experimental studies reported that dormex had toxic systemic effects on the kidney, blood, liver, and thyroid gland (El Mahdy & Kharoub, 2020).

Dormex was a highly toxic substance as it had corrosive effects and systemic effects on multiple organs California Environmental Protection Agency, (1993).

The mechanism of action of dormex on humans or animals is not yet known. Animal studies revealed that, at the cellular level, dormex resulted in uncoupling oxidative phosphorylation by catalase inhibition and the formation of free radicals as malondialdehyde (MDA), a lipid oxidation product (El Masry et al., 2000).

Malondialdehyde (MDA) $C_3H_4O_2$ is a three-carbon diadehyde that is generated as a by-product of lipid peroxidation. It is initially liberated in the extracellular space and then emerges in the blood, so its serum level reflects the magnitude of lipid peroxidation and also the severity of oxidative stress (Lorente et al., 2018).

Enzymatic and non-enzymatic antioxidant systems are essential for cellular responses to handle oxidative stress. They include antioxidant enzymes such as catalase enzyme (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SODs). Non-enzymatic antioxidants such as glutathione, vitamin E, and vitamin C (Canayakin et al., 2016).

Vitamin E (C₂₉H₅₀O₂) exists in several chemical forms, the only one suitable for human consumption being alpha-(α) tocopherol (Traber et al., 2006).

Most patients presented at the hospital with disturbed consciousness level and respiratory distress, so this experimental study aimed to detect the toxic effects of dormex on the brain and lungs. So, in this study, we will use α -tocopherol (vitamin E) to see if it can help treat dormex poisoning or not.

MATERIALS AND METHODS

This experimental study was carried out in the laboratory of the Departments of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Minia University during the period from 1st of April to 8th of April 2022.

Animals

Forty-eight albino rats with an average weight of 200-250 grammes were included in this research. Animals came from the National Research Centre in Giza, Egypt. Rats were kept in hygienic plastic cages (5 rats per cage). The name of the drug and the number of the group were written outside each cage to avoid mixing. They are kept in a clean, well-ventilated environment at room humidity and temperature with 12-hour light-dark cycles. Animals fed on rat pallets and water, which were provided ad libitum. Animals were acclimatized to the laboratory conditions for a week before the onset of the experiment to exclude any possible stress. The study was conducted in accordance with the recommendations and guidelines for the care and usage of laboratory animals authorized by the ethical committee, Faculty of Medicine, Minia University, with approval number 325-4-2022.

Chemicals

Dormex is a blue liquid substance containing 50 % hydrogen cyanamide, obtained from Endoconsult Chemical Company. Vitamin E (in the form of α -tocopherol) was a powder that was soluble in corn oil. It was obtained from the Egypt Company. One gramme of α -tocopherol was dissolved in 350 ml of corn oil (inert vehicle) (Omara & Blakely, 1993).

Study design

Rats were separated into four groups, with 12 rats per each group. The control group (Group I) received saline to exclude stressful conditions by oral route through an orogastric tube. Group II was given α -tocopherol orally at a dose of 2 mg/kg (Reynold et al., 1993). Group III received dormex at a dose of 4 ml/kg (Engel, 1973). Group IV was given 4 mL/kg dormex and 2 mg/kg α -tocopherol. After twelve hours, venous blood samples were taken from the plexus of the retroorbital region of all rats by capillary pipette for total antioxidant capacity (TAC), and then all rats were sacrificed by cervical decapitation for histopathological studies.

After scarification of rats by cervical decapitation, the brain and lung of each rat were carefully dissected under complete aseptic conditions into two parts: the first part was homogenized with a potter-Elvehjem tissue homogenizer in phosphate buffer saline (PBS) 10 mM pH 7.4 and centrifuged. The supernatant was used for the determination of malondialdehyde (MDA) levels and catalase activities (Bancroft & Gamble, 2008).

The second part was prepared for histological examination. The

dehydration was done after the tissues were fixed in a 10% neutral buffered formalin solution in increasing or ascending alcohol grades, infiltrated with paraffin wax to make the block sufficiently rigid for a uniformly thin section of about 5 μ m thickness and ready for cutting, trimming, and finally staining with (H&E) stain, preparing for light microscopic examination (John et al., 2002).

The examination of the brain and lung sections was carried out using a light microscope with an attached camera to photograph these sections (Olympus BX51, Tokyo, Japan), in the Pathology department, Faculty of Medicine, Minia University.

Methods

The catalase enzyme was measured spectrophotometrically by (Claiborne's, 1985) method.

malondialdehyde was measured by using the colorimetric method. Malondialdehyde (MDA) reacts with thiobarbituric acid (TBA) in an acidic medium at a temperature of 95°C for 30 minutes to form a thiobarbituric acid reactive product. The absorbance of the resulting pink product can be measured at 534 nm (Ohkawa et al., 1979).

The Total Antioxidant Capacity Assay Kit was used to measure total antioxidant capacity. Sigma Co MAK187 (Huang et al., 2005).

Statistical analysis

To collect and analyse the data, the Statistical Package for Social Sciences (SPSS) software version 26 was used. The quantitative data was expressed as mean \pm SD with a minimum and maximum range. Analysis of quantitative data was done using

a One-Way ANOVA Test between the four groups, followed by a post hoc test between each two groups. A difference was considered to be significant if the P value was ≤ 0.05 .

RESULTS

The present study included 48 albino rats that were separated into four groups, with 12 rats per each group. The control group (Group I) received saline. Group II received α -tocopherol in a dose of 2 mg/kg orally. Group III received dormex at a dose of 4 ml/kg. Group IV was given 4 mL/kg dormex and 2 mg/kg α -tocopherol. Analysis of quantitative data was done using the One-Way ANOVA Test between the four groups, followed by a post hoc test between each two groups.

The ANOVA test in table (1) revealed a significant increase in the level of MDA in the brain in the dormex group compared with the control and vitamin E treated groups ($P < 0.001$). Vitamin E administration induced a significant decrease in MDA compared with the dormex group ($P < 0.001$).

As regards catalase of the brain in table (2), dormex led to a significant reduction in catalase enzyme level compared with the control and vitamin E treated groups (P

< 0.001). The vitamin E group resulted in a significant increase in catalase level compared with the dormex group ($P < 0.001$).

In this study, Dormex resulted in a significant increase in the MDA level of the lungs in comparison with the control and vitamin E treated groups ($P < 0.001$). Meanwhile, treatment with vitamin E led to a significant reduction of MDA in comparison with the dormex group ($P < 0.001$) (table 3).

Table 4 showed that dormex decreased the level of catalase in the lung significantly in comparison with all other groups ($P < 0.001$). Administration of vitamin E resulted in a significant increase of catalase in the lungs compared with the dormex group ($P < 0.001$).

Total antioxidant capacity (TAC) was significantly lower in the dormex group than in the control and vitamin E treated groups ($P < 0.001$). In the vitamin E protected group, TAC was significantly increased compared with that of the dormex group (Table 5).

Table (1): Comparison between MDA brain in all groups by One way ANOVA with post hoc tuckeys.

	Group I (control)	Group II (α tocopherol)	Group III (dormex)	Group IV (dormex + α tocopherol)
MDA (nmol/mg) <i>Mean \pm SD</i>	3.89 \pm 0.36	3.88 \pm 0.38	17.26 \pm 1.10	4.62 \pm 0.92
Group I (control)			0.001**	
Group II (α tocopherol)			0.001**	
Group III (dormex)	0.001**	0.001**		0.001**
Group IV (dormex + α tocopherol)	0.108	0.103	0.001*	

Table (2): Comparison between catalase brain in all groups by One way ANOVA with post hoc tuckeys.

	Group I (control)	Group II (α tocopherol)	Group III (dormex)	Group IV (dormex + α tocopherol)
CAT (u/mg) <i>Mean \pm SD</i>	12.98 \pm 0.76	13.13 \pm 0.68	3.78 \pm 0.43	12.38 \pm 0.86
Group I (control)			0.001**	
Group II (α tocopherol)			0.001**	
Group III (dormex)	0.001**	0.001**		0.001**
Group IV (dormex + α tocopherol)	0.179	0.060	0.001**	

Table (3): Comparison between MDA lung in all groups by One way ANOVA with post hoc tuckeys.

	Group I (control)	Group II (α tocopherol)	Group III (dormex)	Group IV (dormex + α tocopherol)
MDA (nmol/mg) <i>Mean \pm SD</i>	1.15 \pm 0.10	1.14 \pm 0.10	4.50 \pm 0.35	1.26 \pm 0.74
Group I (control)			0.001**	
Group II (α tocopherol)			0.001**	
Group III (dormex)	0.001**	0.001**		0.001**
Group IV (dormex + α tocopherol)	0.539	0.438	0.001**	

Table (4): Comparison between catalase lung in all groups by One way ANOVA with post hoc tuckeys.

	Group I (control)	Group II (α tocopherol)	Group III (dormex)	Group IV (dormex + α tocopherol)
CAT (u/mg) <i>Mean \pm SD</i>	216.27 \pm 7.45	215.43 \pm 6.77	56.97 \pm 5.82	210.28 \pm 6.45
Group I (control)			0.001**	
Group II (α tocopherol)			0.001**	
Group III (dormex)	0.001**	0.001**		0.001**
Group IV (dormex + α tocopherol)	0.137	0.244	0.001**	

Table (5): Comparison between total antioxidant capacity in all groups by One way ANOVA with post hoc tuckeys.

	Group I (control)	Group II (α tocopherol)	Group III (dormex)	Group IV (dormex + α tocopherol)
TAC <i>Mean \pm SD</i>	1197.5 \pm 58.22	1190.04 \pm 58.49	738.15 \pm 55.78	1143.33 \pm 57.40
Group I (control)			0.001**	
Group II (α tocopherol)			0.001**	
Group III (dormex)	0.001**	0.001**		0.001**
Group IV (dormex + α tocopherol)	0.112	0.207	0.001**	

Histopathological results

All rats in each group were sacrificed by cervical decapitation. After scarification, the brain and lungs were carefully dissected from each rat and were prepared for histopathological examination.

Histopathological examination of the brain in the control group I showed molecular, perkinje, and granular cell layers (**Fig 1**). Group II was similar to the control group as vitamin E has no effect on brain tissue (**Fig 2**). Histopathological examination of group III (**Fig 3**) revealed necrotic changes in the form of pyknotic nucleus and neuropil vacuolization due to the toxic effect of dormex. Group IV revealed

mild perineuronal edema with some neuronal degeneration (**Fig 4**).

Histopathological examination of lung in control group I showed normal oligodendroglia cells (**Fig 5**), and group II (**Fig 6**) showed intact alveolar spaces lined by flattened cells which were also normal because vitamin E has no toxic effect on lung. But histopathological examination of group III revealed marked peribronchiolar inflammation and congestion formed of lymphocytes, plasma cells, and hemosiderin-laden macrophages and RBCS due to the toxic effect of dormex (**Fig 7**). Group IV showed a mild peribronchiolar inflammatory infiltrate, mainly plasma cells and lymphocytes (**Fig 8**).

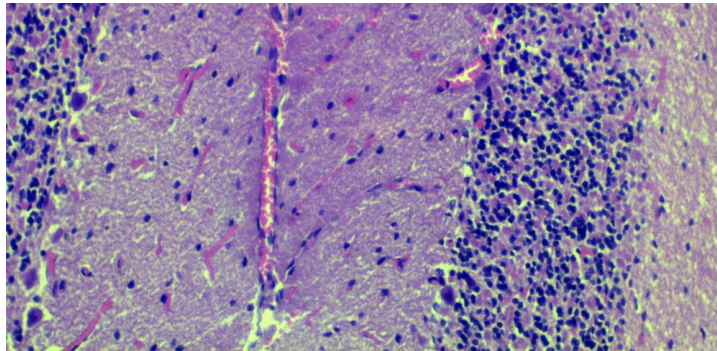


Figure (1): Section in normal brain showing molecular, perkinje and granular cell layer with H & E stain ($\times 4$) (group I)

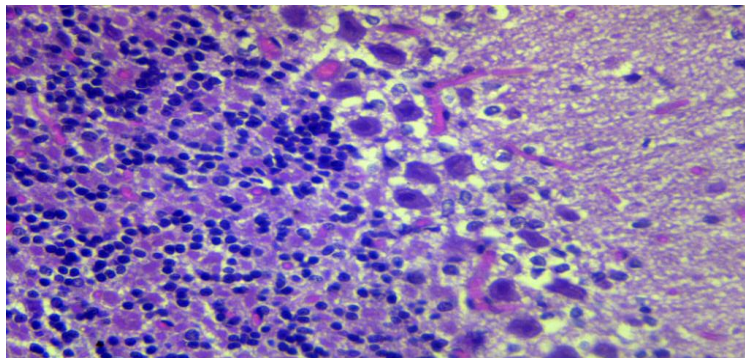


Figure (2): Section in normal brain showing molecular, perkinje and granular cell layer with H & E stain ($\times 40$) (group II).

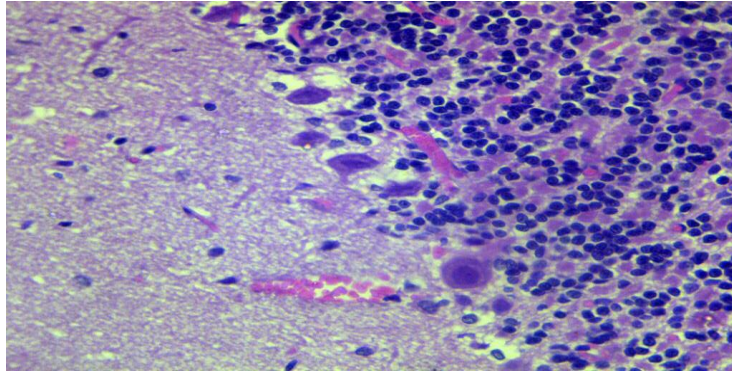


Figure (3): Section examined in the brain revealed necrotic changes in the form of pyknotic nucleus and neuropil vacuolization with H & E stain ($\times 40$) (group III)

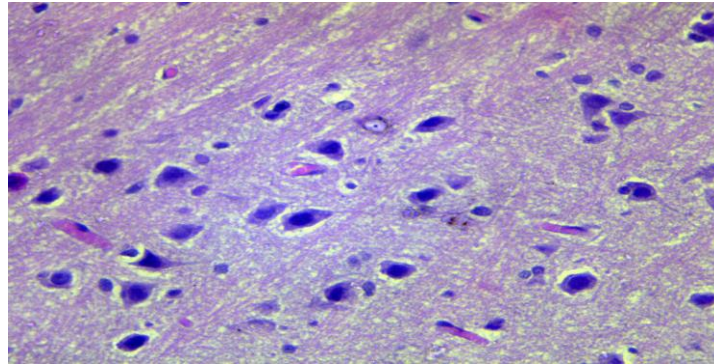


Figure (4): Section in the brain showing mild perineuronal edema with some neuronal degeneration with H & E stain ($\times 40$) (group IV)

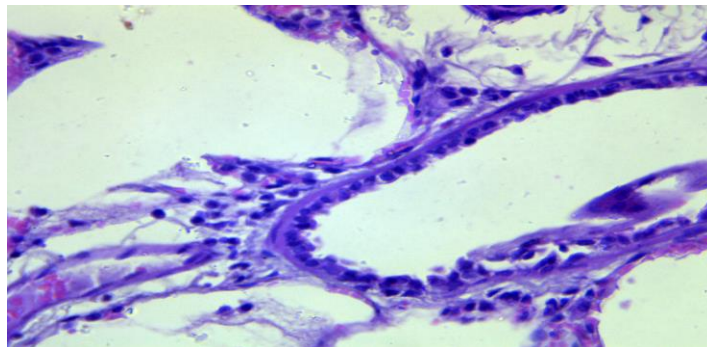


Figure (5): Section in normal lung showing normal bronchiole lined by simple columnar epithelium with H & E stain ($\times 20$) (group I)

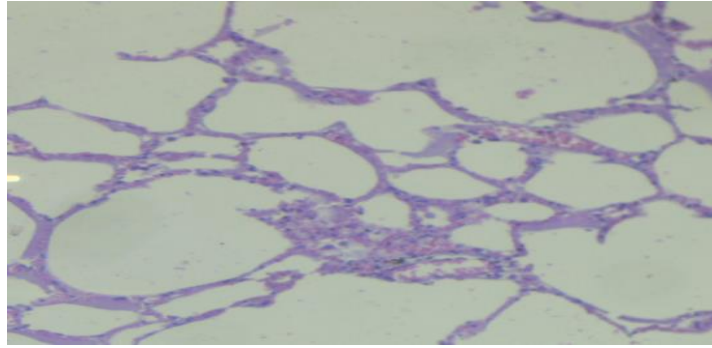


Figure (6): Section in normal lung showing intact alveolar spaces lined by flattened cells with H & E stain ($\times 4$) (group II).

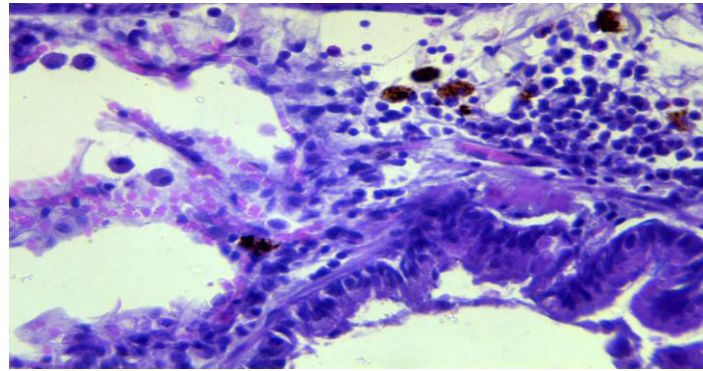


Figure (7): Section in lung revealed marked peribronchiolar inflammation and congestion formed of lymphocytes, plasma cells, and hemosiderin laden macrophages and RBCS with H & E stain ($\times 20$) (group III)

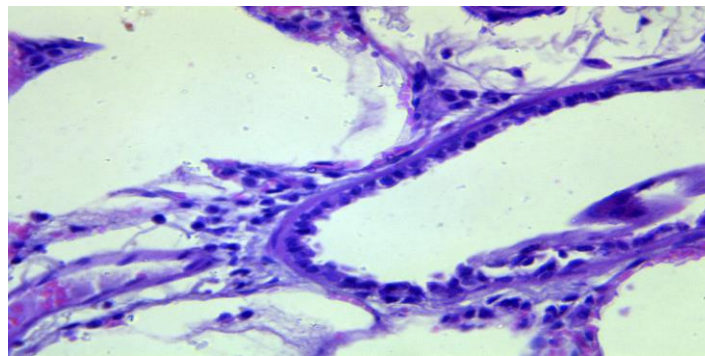


Figure (8): Section in lung showed peribronchiolar inflammatory infiltrate mainly plasma cells and lymphocytes with H & E stain ($\times 10$) (group IV)

DISCUSSION

Hydrogen cyanamide is the active gradient of dormex, which is used as a growth regulator for plants; it is sprayed on grapes for early bud break. Dormex is sold on the market as a blue liquid containing 50 % hydrogen cyanamide (**Catrina et al., 2008**). The current study was designed to investigate the biochemical and histopathological effects of acute dormex toxicity on the brain and lungs, as well as the protective role of α -tocopherol. We used the oral route in our study as it was the most suitable route in acute and chronic toxicity with hydrogen cyanamide (**Cochran et al., 1993**).

In the present study, the selected dose was 4 mg/kg in agreement with **Engel (1973)**, who observed severe convulsions occurred by this dose after 6–24 hours, especially in male albino rats. **Morseth (1989)** reported that an oral dose of 0.2-0.35 ml/Kg led to convulsions and hunched posture. **Daamen (1994)** revealed that cyanamide toxicity at a dose of 5ml/kg orally produced tremors, breathing difficulties, and lethargy in most rats.

The exact mechanism of dormex toxicity was unclear, but **Koppaka et al. (2012)** reported that hydrogen cyanamide inhibited catalase enzyme activity that leads to uncoupling oxidative phosphorylation and inhibited synthesis of adenosine nucleotide. Cyanamide leads to aldehyde dehydrogenase inhibition and may lead to disulfiram-like syndrome (**DeMaster et al., 1998**).

Tocopherol, a fat-soluble antioxidant, is found in the phospholipid bilayer of cell membranes. As a result, it may either prevent the formation of free radicals or reduce their effects. The main roles of tocopherol were the protection of low-density lipoprotein

(LDL), poly unsaturated fatty acids, and all cell membrane components from free radical oxidation (**Jin et al., 2007**). Also, **Tantavisut et al. (2017)** reported that vitamin E is capable of increasing the capacity of cellular antioxidants.

In our study, there was a significant increase in the level of MDA in the brain and lung in the dormex toxicity group, in agreement with **Hafez et al. (2015)**. In agreement with **Tam et al. (2005)**, Vitamin E led to a significant decrease in MDA levels.

In accordance with **Elhosary et al. (2018)**, catalase was significantly decreased in the dormex group as dormex resulted in a decrease in all antioxidants, while **Lúcio et al. (2009)** explain the role of vitamin E as an antioxidant and its ability to suppress oxidative stress in all organs.

In this study, elevation of MDA was associated with a significant reduction in TAC in the dormex group, in agreement with **Srinivasan et al. (2008)**, who reported that reduction of total antioxidant capacity was an attempt to destroy the free radicals. Vitamin E was capable of significantly increasing the TAC in agreement with **Suantawee et al. (2013)**.

Regarding histopathology of the brain and lungs, the rats that received dormex showed severe inflammatory changes in the brain and lungs due to an increase in oxidative stress and the inflammatory effect of dormex on multiple organs, in agreement with **Hafez et al. (2015)** and **Oreby et al. (2015)**. The Vitamin E group showed signs of mild inflammation as vitamin E had anti-inflammatory and antioxidant effects (**Singh et al., 2005**).

CONCLUSION

The present study concluded that domex had toxic effects on the brain and lungs and that vitamin E may be used as a protective agent.

RECOMMENDATION

- Other studies to clarify the toxicity of domex
- Preventing farmers from using domex

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الملخص العربي

تأثيرات سيناميد الهيدروجين على مخ ورنيتين الجرزان البيضاء والتأثير الوقائي المحتمل لفيتامين هـ.

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سيناميد الهيدروجين هو التدرج النشط لدورمكس الذي يرش على العنب لكسر البراعم في وقت مبكر. لذا تهدف هذه الدراسة إلى الكشف عن التأثير السام للدورمكس على المخ والرئة لدى الجرزان البيضاء والدور الوقائي لفيتامين هـ. أجريت هذه الدراسة التجريبية على ثمانية وأربعين جرذاً ألبينو. تم تقسيمهم عشوائياً إلى أربع مجموعات، 12 جرذ في كل مجموعة. المجموعة الأولى (المجموعة الضابطة) تلقت محلول ملحي. تلقت المجموعة الثانية توكوفيرول (2 مجم / كجم). تلقت المجموعة الثالثة دورمكس (4 مل / كجم). تلقت المجموعة الرابعة 4 مل / كجم من دورمكس + 2 ملغم / كجم من توكوفيرول. بعد 12 ساعة، تم سحب عينات الدم الوريدي لقياس القدرة المضادة للأكسدة الكلية ثم تم ذبح جميع الفئران من أجل الفحص الهستولوجي. وأوضحت النتائج أن مادة الدورمكس أدت إلى زيادة معنوية في مادة المالنونديالدهيد للمخ والرئة (0.001 **)، وانخفاض معنوي في إنزيم الكاتالاز في المخ والرئة (0.001 **) وكذلك انخفاض كبير في قدرة مضادات الأكسدة في الدم (0.001 **). أدى فيتامين هـ + دورمكس إلى انخفاض معنوي في مادة المالنونديالدهيد للمخ والرئة (0.001 **)، وزيادة ملحوظة في إنزيم الكاتالاز في المخ ورنيتين (0.001 **) وكذلك زيادة ملحوظة في قدرة مضادات الأكسدة الكلية في الدم (0.001 **). أظهر الفحص الهستولوجي لعينات المخ والرئة في مجموعة الدورمكس تغيرات التهابية ملحوظة، ولكن في مجموعة دورمكس + فيتامين هـ تم اكتشاف تغيرات التهابية خفيفة. نستخلص من هذه الدراسة أن مادة الدورمكس لها تأثيرات شديدة السمية على مخ ورنيتين الفئران وأن فيتامين هـ يمكن أن يمنع هذه الآثار الخطيرة.