

Antiapoptotic effect of apigenin and vitamin E against deltamethrin induced toxicity in rats

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Abstract:

Deltamethrin was thought to be one of the safest pyrethroid insecticides and is being used in agriculture and home appliances. Apigenin has several beneficial and pharmacological effects. It is a natural flavonoid that is found in many plants. Vitamin E, fat soluble vitamin, is a well known antioxidant and anti-inflammatory effect. The present study was performed to investigate the hepatoprotective effect of both apigenin and vitamin E against deltamethrin toxicity in rats.

Administration of deltamethrin (5 mg/kg) orally for 30 days in rats revealed a significant increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels while significantly decreased albumin level as compared to control rats. Furthermore, deltamethrin induced apoptotic markers including caspase-3 and first apoptosis signal receptor ligand (FAS-L). Concomitant administration of apigenin (10 or 20 mg/kg), vitamin E (100 mg/kg) or combination of both apigenin (20 mg/kg) in combination with vitamin E (100 mg/kg) for the same period normalized most of the altered biochemical parameters. These results suggest that apigenin and vitamin E administration can protect the liver from deltamethrin intoxication.

Key words:

Apigenin, Apoptosis, Deltamethrin, Vitamin E, Liver damage, liver function test.

Introduction

Synthetic pyrethroid have comprised approximately 25% of the worldwide insecticide market that is widely used in urban settings and to upgrade the productivity of crops in the agrofields (Casida *et al.*, 1998; Ogaly *et al.*, 2015). World Health Organization (WHO) recommended the use of deltamethrin, a type II synthetic pyrethroid insecticide for indoor utilization (Nájera *et al.*, 2001). Deltamethrin has become an insecticide of choice in most countries for killing various insects by paralyzing their nervous system and was believed to be one of the safest classes of pesticides for mammals (Chargui *et al.*, 2012; Sakamoto *et al.*, 2012).

Sodium channels of the central nervous system in insects and humans are the primary targets of deltamethrin toxicity (Narahashi, 2002; Ray *et al.*, 2006). The

toxic effects of deltamethrin on several tissues were found in brain, thyroid gland, liver and kidney (Abdul-Hamid *et al.*, 2013; Chargui *et al.*, 2012; Mani *et al.*, 2014; Martinez-Larranaga *et al.*, 2003; Nieradko-Iwanicka *et al.*, 2015). Further, Deltamethrin was reported to induce oxidative stress (Nieradko-Iwanicka *et al.*, 2015) and increase the formation of reactive oxygen species (ROS) inside the body.

Pyrethroids are rapidly metabolized in mammals and their metabolites were accumulated in liver tissues at high concentrations that in turns increase ROS production (Abdel-Daim *et al.*, 2015; Abdel-Daim *et al.*, 2013).

Dietary supplementation rich in certain vegetables and plant products significantly reduced the toxicity induced by various toxicants and environmental

contaminants. This protective effect is exerted through free radicals scavenging activity and modulating antioxidant defense system (Zhang *et al.*, 2016).

Apigenin, a polyphenolic flavonoid, present in ordinary human diet especially in edible flowering plants. Apigenin has many pharmacological effects by affecting different pathways inside the body (Houghton *et al.*, 1996). Apigenin has been proved to have antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, neuroprotective, antidepressant and anticancer effects (Lee *et al.*, 2007; Liu-Smith *et al.*, 2016; Shukla *et al.*, 2004; Singh *et al.*, 2014; Venigalla *et al.*, 2015; Weng *et al.*, 2016; Zhang *et al.*, 2014)

Vitamin E (α -tocopherol) is found naturally in human diet. It acts mostly by capturing and inactivating free radicals found in the body. The antioxidant function of Vitamin E could, at least in part, enhance immunity by maintaining the functional and structural integrity of important immune cells (Chew, 1995). Vitamin E also possesses many other functions including anti-inflammatory, neuroprotective and hepatoprotective effects (Ambrogini *et al.*, 2014; Ji *et al.*, 2014; Schwab *et al.*, 2015).

The present study aimed at examining the protective effect of apigenin and Vitamin E on liver damage induced by deltamethrin intoxication.

Material and methods

Experimental animals

Adult male albino rats weighing 150-180 gm were used in the present study. Animals were purchased from the national research center, Cairo, Egypt. Rats were acclimatized for two weeks prior to the experiment. The animals were kept at controlled temperature ($23 \pm 2^\circ$ C), humidity ($60\% \pm 10\%$) and light/dark cycle (12/12 h). Rats were supplied with commercially available normal chow diet (El Nasr Company for Pharmaceutical

Chemicals, Zagazig, Egypt) and allowed free access to water.

Ethical statement

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were approved by the local authorities, Ethical Committee for Animal Handling at Zagazig University (ECAHZU), at the Faculty of Pharmacy, Zagazig University, Egypt in accordance with the recommendations of the Weatherall report with approval number P-1-12-2016. Every effort was done to minimize the number of animals used and their suffering during experiments.

Drugs and chemicals

Deltamethrin (Empirical Formula $C_{22}H_{19}Br_2NO_3$) was kindly provided by M.D. Industries, El sharkeya, Egypt.

Apigenin (CAS Number: 85702, Empirical Formula $C_{15}H_{10}O_5$) was purchased from NYLES7 LLC Company (Tucson, Arizona, USA).

Vitamin E (Empirical Formula $C_{29}H_{50}O_2$) was purchased from Pharco Pharmaceutical Company, Egypt.

Experimental design

After 2 weeks of acclimatization, rats were randomly assigned into six groups (10 animals each) as follows:

1. **Group 1:** served as control group and received corn oil orally.
2. **Group 2:** treated orally with deltamethrin 5 mg/kg in corn oil (Ismail *et al.*, 2013).
3. **Group 3:** treated orally with deltamethrin 5 mg/kg + apigenin 10 mg/kg (Chakravarthi *et al.*, 2009; Haleagrahara *et al.*, 2014).
4. **Group 4:** rats treated orally with deltamethrin 5 mg/kg + apigenin 20 mg/kg (Chakravarthi *et al.*, 2009; Haleagrahara *et al.*, 2014).
5. **Group 5:** treated orally with deltamethrin 5 mg/kg + Vitamin E (100 mg/kg) (el-Demerdash *et al.*, 2004; Ozden *et al.*, 2013).

6. **Group 6:** animals treated orally with deltamethrin 5 mg/kg + Vitamin E 100 mg/kg then after 30 minutes apigenin 20 mg/kg.

These chemicals were administered daily for 30 days with at least 30 minutes interval between deltamethrin administration and other chemicals. All administrations were carried out between 10:00 am and 1:00 pm daily.

Methods:

Blood and tissue sampling

After 24 hour from last treatment rats were fasted overnight, blood samples were collected from the retro-orbital sinus of rats using heparinized microcapillary tubes 24 hours from last administration. The collected blood samples were allowed to clot for 30 min at room temperature. Serum was separated by centrifugation at 3000 r.p.m for 15 min and stored at -20°C for further biochemical analysis.

As quickly as, possible liver samples were dissected out. Parts of the liver were quickly frozen in liquid nitrogen and stored at (-20°C) till needed for further biochemical analysis.

Measurement of the liver function

Serum AST and ALT levels were measured by colorimetric methods using diagnostic kits provided by Diamond Diagnostics (Cairo, Egypt), while albumin level was measured using colorimetric method by a kit provided by Vitroscent (Cairo, Egypt).

Estimation of apoptotic markers

Active caspase 3 was measured in liver tissue by colourimetric assay using a kit provided by Sigma- Aldrich (St. Louis, MO, USA).while the content of FAS-L was assayed by sandwich ELISA using Novatein Biosciences rat FAS-L ELISA kit, USA.

Statistical Analysis

All data are expressed as mean \pm standard error of the mean (SEM). Statistical analysis was performed using Graphpad prism software v.6 (GraphPad

Software Inc., La Jolla, CA, USA). The statistical significance of differences between groups was tested using one-way analysis of variance (ANOVA) followed by Tukey's Post-hoc test. A significant difference was assumed for values of $P < 0.05$.

Results:

Effect on the liver function tests

Figure 1 demonstrates that deltamethrin had significantly elevated serum ALT (28.09 ± 0.66 vs. 19.68 ± 1.19 IU/L), AST (46.24 ± 2.98 vs. 29.53 ± 2.24 IU/L) level compared with the control rats. While albumin was significantly reduced in deltamethrin rats (2.53 ± 0.1 vs. 3.3 ± 0.09 g/dL) compared with the control rats. Treatment with apigenin at doses of 10, 20 mg/kg/day provoked a significant reduction of ALT level by 39.01% and 35.95% respectively, and a significant reduction in serum AST level by 30.70% and 28.54%, respectively, as well as a significant increase in the albumin level by 57.06% and 53.52%, respectively compared with deltamethrin group. Likewise, Vitamin E administration caused a significant reduction in AST level by 37.52% and a significant increase in serum albumin level by 49.23% compared with the deltamethrin group. Furthermore, the combined administration of apigenin 20+ Vitamin E significantly reduced serum ALT by 22.35% and significantly increased serum albumin level by 64.11% compared with deltamethrin group while caused a non significant decrease in AST level.

Effect on apoptotic markers

As shown in **figure 2**, the administration of deltamethrin caused significant increases in both caspase 3 (26.53 ± 2.02 vs. 4.46 ± 0.53 ng/mL) and FAS-L content (25.43 ± 1.06 vs. 4.6 ± 0.3 pg/g tissue) compared with the control group. Apigenin at doses 10, 20 mg/kg elicited significant reductions of caspase 3 content by 45.23% and 22.84%, respectively and FAS-L by 58.04% and

64.87%, respectively, compared with deltamethrin group. Additionally, Vitamin E And combination of Vitamin E + Apigenin 20 caused a significant reduction

of caspase 3 content by 71.35% and 59.78%, respectively, and FAS-L by 37.47% and 49.94%, respectively compared with deltamethrin group.

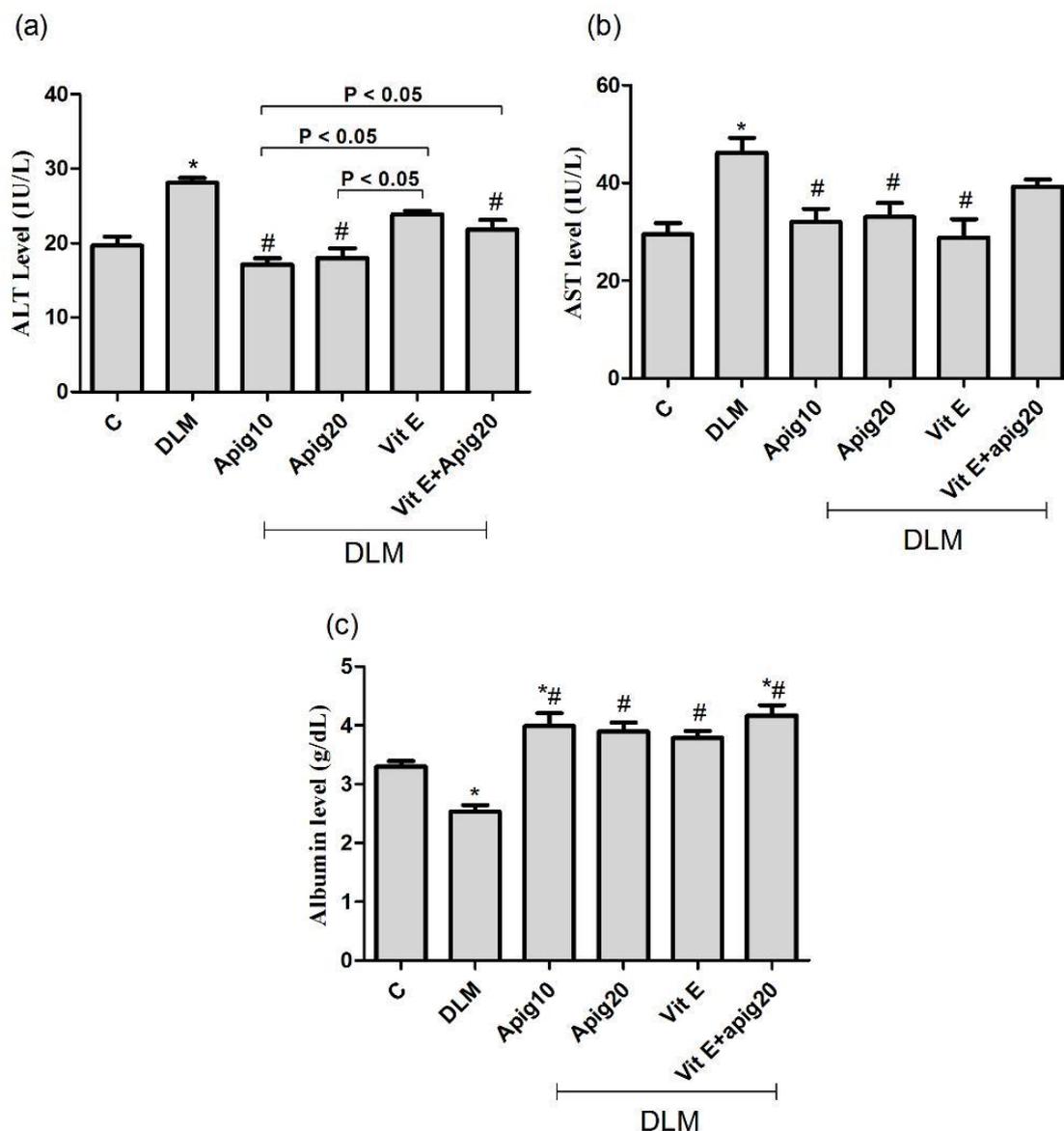


Figure 1: Effect of apigenin (10, 20 mg/kg/day), Vit E (100 mg/kg/day) and the combined administration; Vit E (100 mg/kg) plus Apigenin (20 mg/kg) once daily on (a) serum ALT, (b) serum AST, (c) serum albumin. (*n* = 6). **C**, control rats received corn oil; **DLM**, rats received deltamethrin (5 mg/kg, by oral gavage.); **Apig10** or **Apig20**, rats received deltamethrin (5 mg/kg/day) plus apigenin (10 or 20 mg/kg), respectively once daily by oral gavage; **Vit E**, rats received deltamethrin (5 mg/kg/day) plus vitamin E (100 mg/kg) once daily by oral gavage; **Vit E + apig 20**, rats received deltamethrin (5 mg/kg/day) plus vitamin E (100 mg/kg) plus apigenin (20 mg/kg) once daily by oral gavage. **P*<0.05 vs. C; #*P*<0.05 vs. DLM; *P* values above the columns indicate significance of difference between the corresponding pairs.

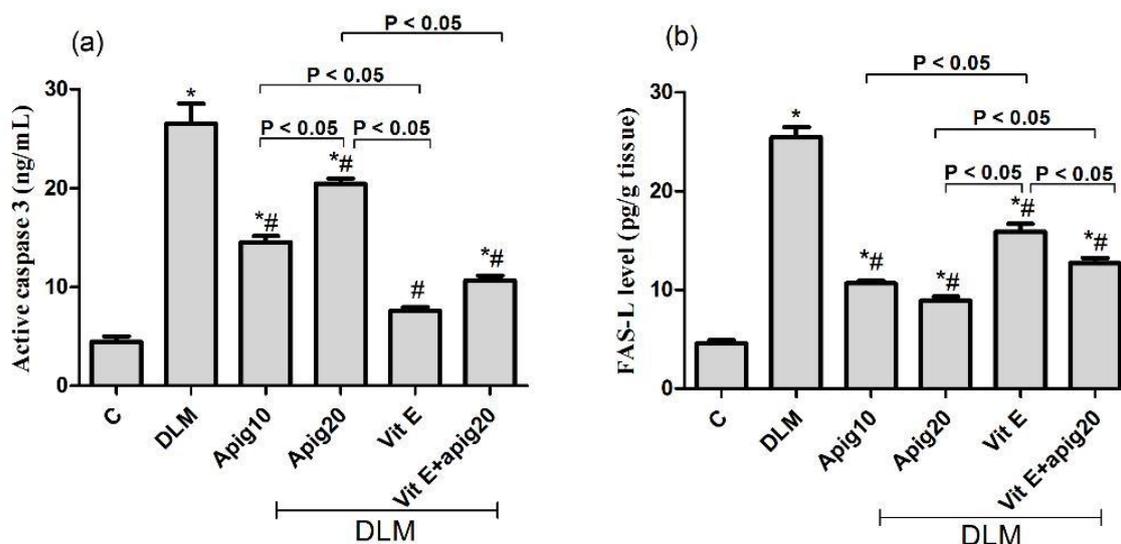


Figure 2: Effect of apigenin (10, 20 mg/kg/day), Vit E (100 mg/kg/day) and the combined administration; Vit E (100 mg/kg) plus Apigenin (20 mg/kg) once daily on (a) liver caspase3 level, (b) liver FAS-L level. ($n = 6$). C, control rats received corn oil; DLM, rats received deltamethrin (5 mg/kg, by oral gavage.); Apig10 or Apig 20, rats received deltamethrin (5 mg/kg/day) plus apigenin (10 or 20 mg/kg), respectively once daily by oral gavage; Vit E, rats received deltamethrin (5 mg/kg/day) plus vitamin E (100 mg/kg) once daily by oral gavage; Vit E + apig 20, rats received deltamethrin (5 mg/kg/day) plus vitamin E (100 mg/kg) plus apigenin (20 mg/kg) once daily by oral gavage. * $P < 0.05$ vs. C; # $P < 0.05$ vs. DLM; P values above the columns indicate significance of difference between the corresponding pairs.

Discussion

Despite hazardous effects of pesticides on non-target organisms, like human, it is not possible to stop their uses to meet the demand of more food production for increased population and to control the domestic pests (Satpute *et al.*, 2017). The liver is the critical target organ for xenobiotic compounds (Abdel-Daim *et al.*, 2013).

The biological effects of repeated exposure at low dose should be considered in animal and human health as deltamethrin affects several body organs. Changes in the cardiac contractility and increased heart rate were recorded in rats received deltamethrin (Yalın *et al.*, 2012). Prenatal exposure to deltamethrin causes persistent changes in learning, motor behavior, muscarinic acetylcholine receptor binding and blood-brain barrier

permeability (Johri *et al.*, 2006; Kung *et al.*, 2015).

Furthermore, deltamethrin induced heavy congestion, marked perivascular edema, foamy macrophage accumulation, emphysema, peribronchial lymphoid tissue hyperplasia and focal hemorrhage (Erdogan *et al.*, 2006).

In a previous study conducted by Rjeibi *et al.* (2016) histopathological variations in hepatic parenchyma of treated rats show hypertrophy of hepatocytes and cytoplasmic vacuolation in these cells, appearance of necrotic cell's foci, dilatation of sinusoids, dislocation of the wall of the central vein and an increase of necrotic cells and Kupffer cells. Elevation of hepatic levels of lipid peroxidation (MDA), reduction of superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and

glutathione peroxidase (GPx) indicating oxidative stress causal relationship.

Our results revealed that deltamethrin induced hepatocellular apoptosis manifested as increased contents of FAS-L that activate procaspase-3 to the active cleaved caspase -3 in the liver tissues of the rats administered deltamethrin, these results were in agreement with Park *et al.*, (2017) findings.

The increase in the activities of AST and ALT in plasma is indicative for liver damage and thus causes alteration in liver function. The increase in plasma AST and ALT activities is in agreement with the findings of Mongi *et al.*, (2011). Cellular damage caused by toxic substances is frequently accompanied by increasing cell membrane permeability (Fan *et al.*, 2009). In the present study, the increase in AST and ALT of plasma may be due to liver dysfunction with alteration in the permeability of liver membrane takes place.

In a previous study Joshi *et al.*, (2017) reported that the reduction in plasma protein, particularly albumin, in animals could be attributed to changes in protein and free amino acid metabolism and their synthesis in the liver. Also, the observed decrease in plasma albumin could be attributed in part to the damaging effect of deltamethrin on liver cells as confirmed by the increase in the activities of plasma AST, ALT and LDH (Mongi *et al.*, 2011).

In this study we compared the effects of apigenin with vitamin E, a well-known antioxidant and anti-inflammatory fat soluble vitamin that has been used by others to protect against deltamethrin toxicity (Cengiz *et al.*, 2016; Galal *et al.*, 2014; Nazrun *et al.*, 2012).

El Maghraby *et al.*, (2012) reported that vitamin E co-administration with deltamethrin restored the levels of hepatic markers enzymes, ALT, AST and alkaline phosphatase (ALP), catalase (CAT) acetylcholinesterase (AChE), and glutathione S-transferase (GST) enzyme,

renal markers such as urea and creatinine to near-normal values. Serum cholesterol, triglycerides, low-density lipoprotein (LDL) and the level of high-density lipoprotein (HDL) were also normalized through vitamin E administration. In this work vitamin E induced a significant difference in serum AST and albumin level and in the liver content of FAS-L and caspase-3 compared to deltamethrin group.

Herbal drugs have played a significant role in maintaining human health and improving the quality of human life for thousands of years owing to their effectiveness and fewer side effects (Agarwal *et al.*, 2004). The administration of apigenin significantly improved the disturbances induced by deltamethrin intoxication. Apigenin in either doses (10,20 mg/kg) triggered significant amelioration in liver function parameters including AST, ALT and albumin as well as the apoptotic markers caspase-3 and FAS-L. These results are similar to many other studies showing the cytoprotective effect of apigenin (Wang *et al.*, 2017a; Wang *et al.*, 2017b; Zhou *et al.*, 2017).

One of the crucial effects of apigenin is keeping the balance of apoptosis. Apigenin possesses the ability to restore the hepatic contents of FAS-L and caspase-3 that were elevated by deltamethrin administration (fig.2). A similar effect was seen by Tsalkidou *et al.*, (2014) after liver ischemia-reperfusion injury in rat.

The results of the present study show the significant hepatoprotective effect of apigenin as seen by the reduction in the serum liver enzyme plus the elevation of serum albumin level (fig.1). Previous studies examined the ability of apigenin to protect the liver (Ali *et al.*, 2014; Tsaroucha *et al.*, 2016). However, this is the first study, to our knowledge, discussing the ability of apigenin to regain the liver function after exposure to deltamethrin toxicity.

Conclusion

In conclusion, the present study provides an evidence of the

hepatoprotective potential of apigenin and vitamin E against deltamethrin intoxication. Such effect is likely mediated through the reduction of serum hepatic enzymes, as well as its ability to restore serum albumin level and apoptotic markers. . Thus, sufficient intake of apigenin by individuals, who are regularly exposed to these insecticides, is beneficial in combating the adverse effects of deltamethrin.

Conflicts of interest

The authors declare no conflicts of interest.

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تأثير الابينجينين و فيتامين هـ المضاد لموت الخلايا المبرمج ضد سمية الدلتامثرين في الجرذان.

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يتمتع مركب الابينجينين بالعديد من التأثيرات الفارماكولوجية التي يمكن الاستفادة منها في الكثير من المجالات. هذا و يعتبر مركب الابينجينين من الفلافونويدات الطبيعية الموجودة في نباتات عدة. يعتقد بأن الدلتامثرين واحد من أمن المبيدات الحشرية البيريثرويدية. يدخل الدلتامثرين في الاستخدامات المنزلية والزراعية. وقد أجريت هذه الدراسة لفحص التأثير الوقائي الكبدي للابينجينين علي سمية الدلتامثرين في الجرذان.

الفئران المسممة بالدلتامثرين أظهرت ارتفاع ذو دلالة احصائية في مستوى الانزيمات الكبدية والتي تشمل أنزيم ألانين أمينو ترانسفيراز و أنزيم الأسبرتيت أمينو ترانسفيراز وعلي النقيض ظهر انخفاض مستوى الزلال بالمقارنة بالمجموعة الضابطة. كما أدي تعاطي الدلتامثرين الي زيادة موت الخلايا المبرمج. علي النقيض من ذلك فإن علاج الفئران بمركب الابينجينين أدي إلي تحسن ملحوظ في تلك النتائج.