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The ameliorative effect of N-acetylecysteine on cyclosporine induced testicular toxicity in male albino rats

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Abstract

Introduction: Cyclosporine A (CsA) is considered one of the potent drugs that are used extensively in organ transplant and oncology patients. It is also used in autoimmune diseases. Unfortunately, its use is accompanied with several hazards; one of these is testicular toxicity. N-acetylecysteine (NAC) is an antioxidant found to reduce CsA toxicity. **Aim of the work:** The study aims to determine the toxic effect of exposure to cyclosporine on the testis and to investigate the protective role of NAC. **Methods:** The study conducted on 50 adult male albino rats for 4 weeks divided into 5 groups, group A the negative control group, group B the olive oil group (0.5 ml/d orally), group C the cyclosporine group (25mg/kg/d orally), group D the NAC group (600mg/kg/d orally) and group E the cyclosporine+NAC group. At the end of the study the evaluation was achieved by biochemical analysis and histopathology. **Results:** Cyclosporine significantly affects the testis morphologically and functionally. The morphological changes are in the form of degenerative changes in the tubules with dislocation of germ cells into the lumen and irregular outlines, Congestion of blood capillaries in the interstitial tissue, and functionally the cyclosporine cause significant decrease in serum testosterone level. While co-administration of NAC with cyclosporine attenuate these effects. **Conclusion:** Cyclosporine causes testicular injury through oxidative stress and NAC as an antioxidant attenuates but not fully protect against cyclosporine induced testicular toxicity.

Key words Cyclosporine, N-acetylcysteine, Testicular toxicity

Introduction

Cyclosporine A (CsA) is one of the potent immunosuppressant drugs which is used in transplant medicine. It is obtained from *Cylindrocarpon lucidum* and *Tolypocladium inflatum* fungi. It was firstly used as an antibiotic but it also has some fungicidal and antiparasitic effects *(Fahr, 1993 & Alazouny et al., 2014).*

In addition to its use in transplantation it is also used in the treatment of many autoimmune diseases including rheumatoid arthritis, idiopathic nephritic syndrome, uveitis and psoriasis *(Najafi et al., 2016).*

T lymphocytes are responsible for the immune response to a transplanted organ. Cyclosporine A suppresses the synthesis of many cytokines as interleukin IL-2, IL-4, interferon-g and granulocyte-macrophage colony stimulating factor which are responsible for T cells activation. Cyclosporine A usage has increased the survival rate in transplanted organs *(Bennett and Norman, 1986 & Damaino et al., 2015).*

Unfortunately, CsA treatment is accompanied by many hazards such as hepatotoxicity, cardiotoxicity and testicular toxicity *(Khattab and Mansoury, 2020).*

Cyclosporine A effects on the male reproductive system are by reduction of organs weight, sperm counts, motility, and fertility. In addition, it decreases testosterone and LH levels *(Georgiou et al., 2016).*

Despite the exact mechanism of cyslosporine toxicity on organs is still unclear; the formation of reactive oxygen species (ROS) and membrane lipid peroxidation are considered the causes by which cyclosporine induce toxicities. Additionally, cyclosporine induces testicular toxicity by affection of the hypothalamic-pituitary-gonadal axis and decreases of Sertoli cell phagocytic activity *(*Türk *et al., 2007 & Najafi et al., 2016).*

Recently, attention has been directed to the use of antioxidants to counter the reproductive toxicity induced by cyclosporine. One of the antioxidants is the ellagic acid which has been found to attenuate cyclosporine induced testicular damage and spermatotoxicity *(Najafi et al., 2016).*

N-acetylcysteine (NAC) is one of the powerful antioxidant which is a precursor of L-cysteine and reduced glutathione (GSH) and its use increases GSH availability to detoxify ROS and other reactive substances *(Duru et al., 2008).*

Materials and Methods

Animals

The present work was conducted on 50 sexually mature male albino rats. Their weight ranged from (180:220) gm at the beginning of the experiment. Animals were fed with standard pellet feed and water.

They were acclimatized to the laboratory condition for one week before starting the treatment protocol. The protocol of ethics and husbandry conditions of animal research were considered and the study was approved by the ethical committee of Faculty of Medicine, Sohag University.

Chemicals

Cyclosporine A presents in the form of soft gelatin capsules under traditional name (Sandimmune, Neoral)® obtained from Novartis pharma and freshly dissolved in olive oil. N-acetyl cystein purchased from Pharco Co Egypt in powder form. Olive oil purchased from commercial market. Testosterone kits, testosterone architect plus I 1000 SR kits for measurement of serum testosterone. Hematoxyline and Eosin stains, from ALPHACHEMIKA.

Animals groups and methods

Rats were divided into 5 groups 10 rats each

Group A: Negative control group, where animals received no treatment. Group B: Positive control group where animals received olive oil at a dose of 0.5 ml / day orally by gavage for 4 weeks. Group C: cyclosporine A-treated group with a dose of 25 mg/kg/day (double the therapeutic dose *(feagan et al., 1994)*) orally by gavage for 4 weeks *(Zal et al., 2007).* Group D: NAC-treated group with a dose of 600 mg/kg/day orally by gavage for 4 weeks *(Saleh, 2014).* Group E: Combined CsA and NAC by same doses of group C&D.

Collection of blood samples

Blood samples were collected before scarification from retro-orbital plexus into clean dry tubes. Blood samples then centrifuged. The serum was separated and transferred to sterile screw capped vials for measurement of serum testosterone levels.

Histopathological examination

At the end of experiments rats were sacrificed by cervical decapitation under ether anesthesia. The testis for all animals was fixed in bouin's solution. Then absolute ethyl alcohol used for dehydration. After those specimens were embedded in blocks for sectioning at 5 micro thicknesses then stained with hematoxylin and eosin (H&E). Sections of the testis were examined then photographed.

Statistical analysis

The data are demonstrated as mean ± SD. Differences between groups were determined by one way analysis of variance (ANOVA) and a post-hoc test of least significant difference (LSD) was assessed by Statistical package for social sciences (SPSS) software, version 24 for windows. Probability value for significance (P values) less than 0.05 were considered to be statistically significant.

Results

Biochemical results:

There was no significant differences in the mean value of testosterone hormone level between negative control group (A), positive control (B) and NAC treated group (D) as shown in table (1)

The mean value of testosterone level in cyclosporine treated group (group C) showed very highly significant decrease (P<0.001) as compared to negative control group (group A), positive control group (group B) and NAC treated group (D) as shown in table (2)

Combination of cyclosporine with NAC (group E) showed significant decrease (P<0.05) in the mean value of testosterone level compared to negative control group (group A) and NAC treated group (D). There was very high significant decrease (P<0.001) in the mean value of testosterone level compared to positive control group (group B) as shown in table (3)

As regard cyclosporine plus NAC treated group (group E) when compared to cyclosporine group (C), there was very highly significant increase (P<0.001) in the mean value of testosterone level in cyclosporine plus NAC treated group (group E) as shown in table (4)

Histopathological findings:

Light microscopic examination of H&E stained sections of testis of the negative control group (group A), positive control group (group B) and NAC treated group (group D) revealed normal appearance of the testis is formed of seminefrous tubules separated by interstitial tissue. The seminefrous tubules are lined with many layers of spermatogenic cells and sertoli cells. Spermatogenic cells are organized as the follow: spermatogonia, primary spermatocytes, secondary spermatocytes, rounded spermatide, elongated spermatide and sperms (fig 1, 2 & 4).

Light microscopic examination of the cyclosporine group revealed degenerative changes in the tubules with vaculation and dislocation of germ cells into the lumen and irregular outlines. Congested blood capillaries in the interstitial tissue was observed (fig 3).

Light microscopic examination of the cyclosporine + NAC treated group revealed that histological alterations were reduced as most of tubules appear more or less as control group a part of some tubules show degeneration as compared to cyclosporine treated group. The interstitial tissue, leydig cells and blood capillaries are similar to control group (fig 5).

Table (1): Statistical analysis of the mean value of testosterone in the negative control group (A) compared to positive control group (B) and NAC treated group (D) using ANOVA and a post-hoc test:

Groups / Parameters	Mean ± SD			P-Value	
	Group A (Negative control)	Group B (Positive control)	Group D (NAC)	Negative control Vs Positive control	Negative control Vs (NAC)
Testosterone (ng/ml)	3.15 ± 0.533	3.49 ± 0.617	3.12 ± 0.513	0.224 NS	0.924NS

P values are shown as: P>0.05: Non significant difference, < 0.05: significant difference, NS: Non significant

SD: Standard deviation

Table (2): Statistical analysis of the mean value of testosterone in the cyclosporine group (C) compared to negative control group (A), positive control group (B) and NAC treated group (D) using ANOVA and a post-hoc test:

Group / Parameters	Mean ± SD				P-value		
	Group C (Cyclosporine)	Group A (Negative control)	Group B (Positive control)	Group D (NAC)	Cyclosporine Vs Negative control	Cyclosporine Vs Positive control	Cyclosporine Vs (NAC)
Testosterone (ng/ml)	1.45±0.509	3.15±0.533	3.49±0.617	3.12±0.513	0.000***	0.000***	0.000***

*P values are shown as: P>0.05: Non significant difference, < 0.05: significant difference, ***P < 0.001 (very highly significant), SD: Standard deviation*

Table (3): Statistical analysis of the mean value of testosterone in the cyclosporine + NAC treated group (E) compared to negative control group (A), positive control group (B) and NAC treated group (D) using ANOVA and a post-hoc test:

Group / Parameters	Mean ± SD				P-value		
	Group E (NAC+ Cyclosporine)	Group A (Negative control)	Group B (Positive control)	Group D (NAC)	NAC+ Cyclosporine Vs Negative control	NAC+ Cyclosporine Vs Positive control	NAC+ Cyclosporine Vs (NAC)
Testosterone (ng/ml)	2.50±0.430	3.15±0.533	3.49±0.617	3.12±0.513	0.043 *	0.000***	0.039 *

*P values are shown as: *P < 0.05 (significant), ***P < 0.001 (very highly significant), SD: Standard deviation*

Table (4): Statistical analysis of the mean value of testosterone in the cyclosporine + NAC treated group (E) compared to cyclosporine group (C) using ANOVA and a post-hoc test:

Group / Parameters	Mean ± SD		P-value
	Group E (NAC+ Cyclosporine)	Group C (cyclosporine)	
Testosterone (ng/ml)	2.50 ± 0.430	1.45 ± 0.509	0.000***

*P values are shown as: ***P < 0.001 (very highly significant), SD: Standard deviation*

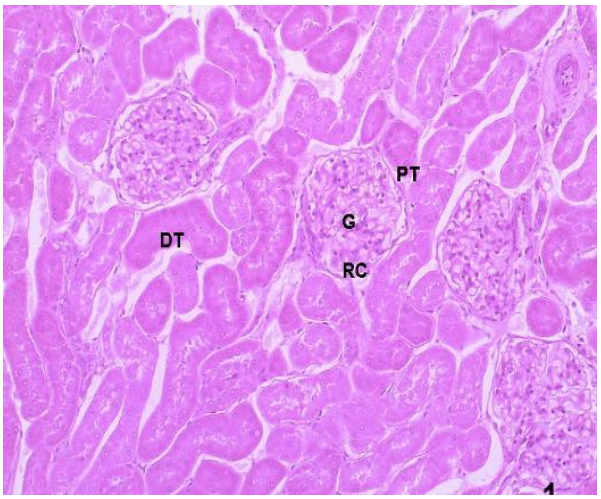

Fig. (1): A photomicrograph of a section in the testis of the negative control group showing normal appearance in the form of seminefrous tubules (T) with regular outlines and the lumen has worely appearance full of sperms(S). Interstitial tissue (I). H&E X 200

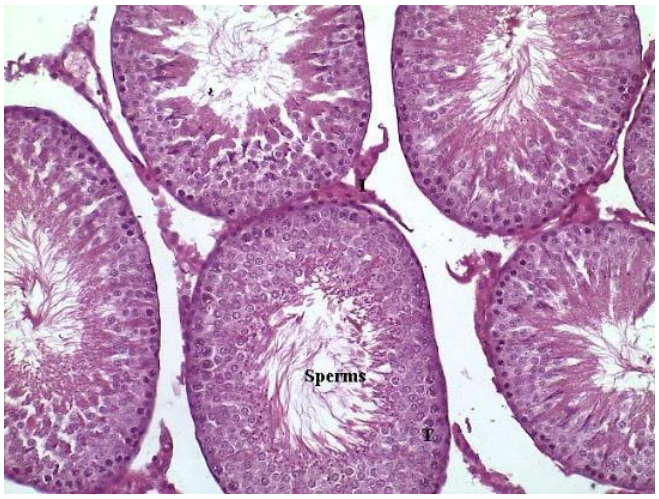

Fig. (2): A photomicrograph of a section in the testis of the positive control group showing seminefrous tubules (T) with regular outlines and the lumen has worely appearance full of sperms. Interstitial tissue (I) similar to the negative control group. H&E X 200

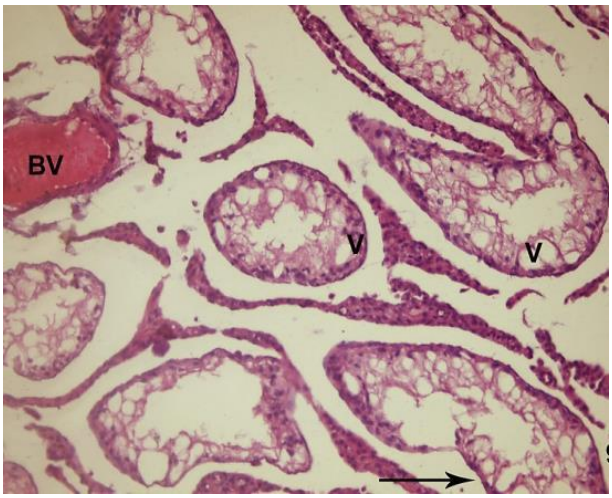

Fig. (3): A photomicrograph of a section in the testis of the cyclosporine group showing seminefrous tubules with irregular outlines with absence of sperms, spermatogenic cells showing degeneration & vaculation (V). Interstitial blood vessels (BV) showing congestion. H&E X 200

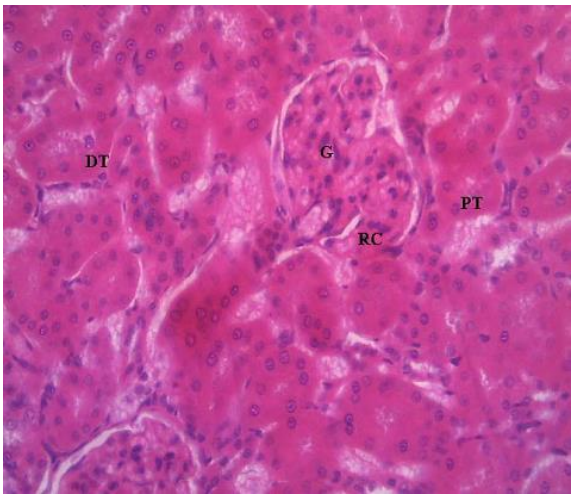

Fig. (4): A photomicrograph of a section in the testis of the NAC treated group showing seminefrous tubules (T) with regular outlines and the lumen has worely appearance full of sperms similar to the negative control group. Interstitial tiss (I). H&E X 200

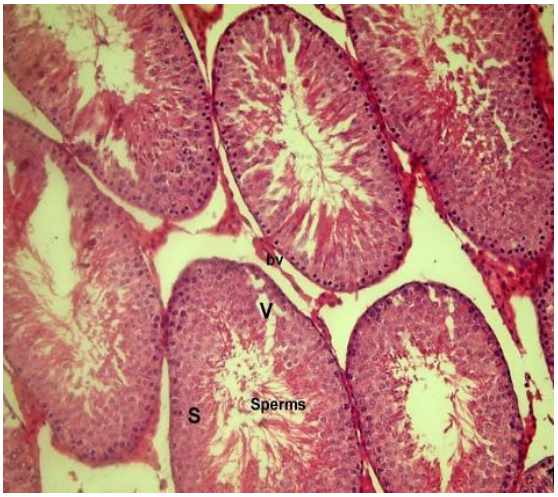

Fig. (5): A photomicrograph of a section in the testis of the cyclosporine+NAC treated group showing most of seminefrous tubules are more or less similar to the control group with intact spermatogenic cells (S) and the lumen full of sperms apart from some vaculation (V) compared to cyclosporine treated group. No congestion of blood vessels (bv) in the interstetium. H&E X 200

Discussion

Testicles as a part of the male reproductive system are responsible for production and nutrition of spermatozoa on puberty, and synthesis of testosterone that is the main male sex hormone *(Junqueria, 2010).*

Cyclosporine is a potent immunosuppressive drug used after transplantation surgery. It helps to increase the survival rate and quality of life of transplant patients. However, its use is associated with many hazards one of them is reprotoxicity *(Najafi et al., 2016).*

Cyclosporine A effects on the male reproductive system are; reduction of organs weight, sperm counts, motility, and fertility. In addition, it decreases testosterone and LH levels *(Seethalakshmi et al., 1990).*

Despite that the exact mechanism of cyslosporine toxicity on organs is still unclear; the formation of reactive oxygen species (ROS) and membrane lipid peroxidation are considered the causes by which cyclosporine induce toxicities. Additionally, cyclosporine induces testicular toxicity by affection of the hypothalamic–pituitary–gonadal axis and decrease of Sertoli cell phagocytic activity *(*Türk *et al., 2007 & Najafi et al., 2016).*

The peroxidation of lipids of sperm membrane results in its damage with rapid loss of intracellular ATP which leads to axonemal destruction, decrease sperm viability and increase mid-piece morphological defects. In addition, it may fully prevent spermatogenesis in severe cases *(Baykalir et al., 2016).*

Testosterone is the main hormone responsible of spermatogenesis. Testosterone is secreted from Leydig cells which are regulated by LH secreted by the pituitary gland *(Ray et al., 1992).*

In the present study, cyclosporine treatment for 4 weeks by a dose of 25mg/kg had decreased serum testosterone levels significantly compared to the negative control group animals.

The results of the present study were in accordance with Chen et al. (2013) who stated that cyclosporine or sirolimus administration in unilateral nephrectomized rats associated with significant decrease in testosterone level and increase of estradiol level.

Also Gawish et al. (2016) reported that treatment of rats with 20 mg/kg/day cyclosporine resulted in significant decrease in testicular weight, sperm count, serum testosterone level and fertility.

Cyclosporine A causes mutagenic changes in the shape and count of sperms. This is due to the cyclosporine effect on the serum testosterone level so the reproductive ability of the male is affected *(Gawish et al., 2016).*

Cyclosporine treatment decreases the testosterone levels as it reduces the mitochondria number which is the organelle responsible of testosterone synthesis *(Ali et al., 2009).*

In the present study pathological changes were observed in the rat testis when cyclosporine was given orally in a dose of 25mg/kg. These pathological changes were in the form of degeneration of the seminefrous tubules with irregular outlines. spermatogenic cells were degenerated with vaculation with absence of sperms and dislocation of germ cells into the lumen of the tubules. The interstitial tissue showed degeneration of leydig cells and congested blood capillaries.

These results go in harmony with Türk et al. (2010) who found that cyclosporine caused DST atrophy, necrosis and degeneration in germinal cells, interstitial edema, capillary congestion with spillage of immature spermatogonia and spermatocytes in seminiferous tubules lumen.

The present finding were in accordance with the results recorded by Alazouny et al. (2014) where Examination of the seminiferous tubules showed disruption of their architecture and some tubules were empty with no germinal epithelium and others contained sloughed germ cells. Blood vessels congestion was also present.

Also, Chen et al. (2013) stated that in cyclosporine and sirolimus treated groups there was seminiferous tubules atrophy with disruption of germ cell layers, reduced spermatocytes and capillary congestion. There was also an interstitial edema and fibrosis.

Cyclosporine inhibits spermatogonia type B mitosis and prolongs G1 phase of their cell cycle resulting in thinning of the germinal epithelium and decreased sperm formation. Clinically, this leads to oligospermia or azospermia and infertility *(Rezzani 2006 & Jedlinska-Krakowska et al., 2006).*

Free radicals affect cell membrane by oxidative phosphorylation leading to loss of its integrity. Additionally, these free radicals enhance lysosomal enzymes release in the cytoplasm and oxidation of cellular protein leading to their disruption. All these effects lead to appearance of vacuoles due to degeneration of germ cells and increased spaces between Sertoli cells *(Alazouny et al., 2014).*

Recently, attention has been directed to the use of antioxidants to counter the reproductive toxicity induced by cyclosporine effects. One of the antioxidants is the ellagic acid which has been found to attenuate cyclosporine induced testicular damage and spermatotoxicity. Also, lycopene has a highly antioxidant effect against cyclosporine induced testicular toxicity as it can restore the oxidant/antioxidant balance *(Najafi et al., 2016).*

Alpha-lipoic acid is a powerful antioxidant, anti-inflammatory and anti-apoptotic agent. It can inhibit the oxidative damage induced by cyclosporine on the testis and epididymis and improve fertility ability *(Kabel et al., 2020).*

Also, costus afer extract has an ameliorative effect on CsA induced testicular toxicity due to its antioxidant ability. This antioxidant ability may be because it contains strong antioxidants such as flavonoids, saponins and phenols which counter act testicular damage induced by CsA treatment due to ROS formation *(Khattab & Mansoury, 2020).*

In the present study testosterone level increased significantly in the group treated with cyclosporine plus NAC compared to the cyclosporine alone treated group. To the best of our knowledge, no previous studies discussing this correlation.

In the present study combination of NAC with cyclosporine attenuate the pathological changes compared to the cyclosporine treated group as most of tubules were more or less similar to control group with intact spermatogenic cells and the lumen full of sperms apart from some tubules showed degeneration and vaculation. The interstitial tissue, leydig cells and blood capillaries were similar to control group. To the best of our knowledge, no previous studies discussing this correlation.

Conclusion

It has been found that cyclosporine has toxic effects on the testis functionally and pathologically. These effects attributed to oxidative stress. N-acetylcystein is an antioxidant and has the ability to attenuate testicular toxicity induced by cyclosporine but not provide full protection.

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الدور الوقائي للأسيتيلسيستين من التأثيرات السامة للسيكلوسبورن على الخصية في ذكور الفئران البيضاء

مى مصطفى عبد القادر[١], و مها عبد الحميد هلال[١], و عبد الرحمن وجيه تركى[٢], و هدى محمد السيد[٣], و ولاء احمد علام[١]

الملخص العربي

المقدمة: السيكلوسبورين هو أحد الأدوية الأكثر استخدامًا في زراعة الأعضاء ومرضى الأورام. كما أنه يستخدم ايضا في علاج أمراض المناعة الذاتية. وبالرغم من ذلك، فإن استخدامه محدود بسبب العديد من الآثار الجانبية، أحد هذه الآثار الجانبية هو التاثير السام على الخصية. الاسيتيلسيستين هو أحد مضادات الأكسدة التى تستخدم للحد من سمية السيكلوسبورن.

الهدف من الدراسة: تحديد تأثير التعرض للسيكلوسبورين على الخصيتين والتحقق من الدور الوقائي للاسيتيلسيستيين.

طريقة البحث: اجريت الدراسة على ٥٠ من ذكور الفئران البيضاء البالغة لمدة ٤ أسابيع مقسمة إلى ٥ مجموعات، المجموعة الضابطة السلبية ، مجموعة زيت الزيتون (٠.٥ مل / يوم عن طريق الفم) ، مجموعة السيكلوسبورين (٢٥ مجم / كجم / يوم عن طريق الفم) ، مجموعة الاسيتيلسيستين ٦٠٠مجم / كجم /يوم عن طريق الفم) ومجموعة السيكلوسبورين + الاسيتيلسيستين .تم إجراء التحليل الكيميائي الحيوي والفحص النسيجى فى نهاية البحث.

نتائج البحث: يؤثر السيكلوسبورين بشكل كبير على الخصية ويسبب العديد من التغيرات المورفولوجية على هيئة تكسر فى الخلايا الجنينية لانابيب الخصية واحتقان النسيج البينى. كما يؤدى ايضا الى انخفاض نسبة التيستوستيرون. ولكن تناول الاسيتيلسيستين يحد من سمية السيكلوسبورن.

الخلاصة: يتسبب السيكلوسبورين في تلف الخصيتين عن طريق الإجهاد التأكسدي ولكن الاسيتيلسيستين كاحد مضادات الاكسدة يحد من التأثير السام للسيكلوسبورن ولكن لا يوفر الحماية الكاملة.

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٢. قسم الطب الشرعى والسموم, كلية الطب, جامعة حلوان, جمهورية مصر العربية.

٣. قسم علم الأنسجة, كلية الطب جامعة سوهاج, جمهورية مصر العربية