

# Arabic Gum Role in Ameliorating Cyclosporine- A Initiated Nephrotoxicity in Rats

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## Original Article

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## ABSTRACT

**Background:** Recently many researchers reported that treatment using cyclosporine A in extended period in order to avoid the rejection of allograft is connected with renal impairment progress. Arabic gum is a valuable antioxidant and anti-carcinogenic factor with a protective effect against renal intoxications.

**Aim:** This research aims at assessing the improving function of Arabic gum in ameliorating nephrotoxicity of cyclosporine A in adult rats by measuring urea and creatinine as renal function tests and histopathological changes plus redox status parameters.

**Materials and Methods:** 80 mature rats males and females were classified into four groups during the period of experiment (45 days) first one act as control given saline; the second one was given 7.5gm/kg/day of Arabic gum, while third group was given cyclosporine A (25 mg/kg/day) finally the fourth one was given 7.5gm/kg/day of Arabic gum together with the 25 mg/kg/day of cyclosporine A.

**Results:** Cyclosporine A group three rats had renal impairment beside injury, when reported by elevated values of urea and creatinine and renal pathological changes, relative to the first group (control) with high level of cyclosporine A in blood and bad parameters of redox status. Receiving of (Arabic gum) accompanied with (cyclosporine A) ameliorating renal damage by decreasing the level of urea and creatinine in the blood, renal histopathological amelioration, moreover the improved parameters of antioxidant. The levels of catalase, glutathione, peroxidase and superoxide dismutase were statistically reduced as regard group three G3 (cyclosporine) which was significant relative to the control & second groups G1, G2 although significantly elevated in the fourth group which given cyclosporine plus Arabic gum when compared with the third group (cyclosporine).

**Conclusion:** Arabic gum has likely to behave like natural agent opposing cyclosporine A -provoked nephrotoxicity.

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**Key Words:** Arabic gum, cyclosporine A., renal impairment.

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## INTRODUCTION

In the most recent decades many researchers detected that the greatest recent tendency in the treatment of many variable diseases as end-stage of liver and kidney dysfunction and injury is the organ transplantation. Also great risk of the failure of transplanted organ is the main problem in front of researchers which treated by taking immunosuppressive drugs clinically<sup>[1]</sup>.

Cyclosporine- A is an immunosuppressive drug which has become most strong popular immunosuppressive of choice for renal, liver, pancreatic, and cardiac transplantation, one of its side effects of long period clinical use is nephrotoxicity which consists of a reversible, raise in serum creatinine, hyperkalemia, hypertension, metabolic acidosis, and chronic interstitial nephritis with irreversible worsening in renal function<sup>[2]</sup>.

Despite results of acute and chronic cyclosporine-A -induced impairment of renal function mechanism is controversial, but accurate mechanisms concerned in these toxic manifestations of cyclosporine-A on the function of kidney are not well understood, even though they may reveal tubular toxicity, particularly in the proximal tubule in its straight segment<sup>[3]</sup>. Also it has direct effect on inhibition of calcineurin, excessive expression of fibrous intermediaries, like the transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1), and vascular insufficiency, including angiotensin II, thromboxane A (TXA) nitric oxide (NO), serotonin, leukotriene and catecholamine, in addition to elevating the production of reactive oxygen species (ROS) that results in oxidative hassle and distress<sup>[4,5]</sup>.

Plants and herbs are well thought-out as a folk medicine which has been handled as a previous style by the old grandfathers in order to manage various cases, moreover

they are recently considered as useful modulators of various agents intoxication like an original style in the current medicine<sup>[6,7,8]</sup>. In Middle Eastern countries, Arabic gum was long taken in Arab folk medicine to decrease equally the frequency and the call for hemodialysis in those complained of chronic renal impairment and used in the traditional medicinal practices. Moreover to that latest researches revealed that Arabic gum decreased the nitrogen excretion in urine by mounting urea removal inside large intestine plus decreasing urea level in the blood of rat and human. Treatment with Arabic gum (AG) was reported to rise creatinine removal, reduce the concentration of plasma phosphate, proteinuria and the excretion of phosphate as well as sodium in urine. Also many researches have detected the effect of Arabic gum (AG) on models of experiments of kidney diseases and revealed its role in limiting their sequence<sup>[9]</sup>.

These major effects might augment value of Arabic gum (AG) in dealing with chronic renal diseases like failure and diabetic nephropathy<sup>[10,11]</sup>.

Arabic gum (AG) is dietary fiber which is water-soluble and resultant from the dehydrated sticky exudates from the branches and the stems of *Acacia senegal* (Leguminosae), has magnesium, calcium, and salts of potassium of polysaccharide Arabic gum acid<sup>[11]</sup>. Conversely, a lack of information which giving scientific background about the folkloric claims of Arabic gum (AG) on renal function following renal injury is present. Recent researches revealed that (AG) has antioxidant, protection of nephron and other major anti-inflammatory roles on digestive system<sup>[12,13]</sup>.

So, our aim in this research was to determine the renoprotective role of Arabic gum in ameliorating cyclosporine-A initiated nephrotoxicity in adult rats which have renal damage and injure, and focus on its antioxidant properties.

## MATERIAL AND METHODS

80 adult rats (200 - 250 g) of both sexes were brought from the animal house of Alexandria University. The rats were under a day-night regimen of 12h/12h and easy contact. The rats were given food, water and balanced diet ad libitum through the experiment exactly forty five days. Animals were put into four groups (G) (n=20 each one); G1 given physiological saline as control group, G2 given 10 gm/kg/day of arabic gum<sup>[14]</sup>. G3 were given 25 mg/kg/day of cyclosporine dissolved in physiological saline<sup>[15]</sup>, at the same time G4 given 10 gm/kg/day of Arabic gum together with the same cyclosporine dose of the third group (25 mg/kg/day of cyclosporine dissolved in physiological saline).

Cyclosporine-A and Arabic gum were applied daily utilizing gastric gavage<sup>[14]</sup>. Cyclosporine-A was present in a soft gelatin capsule (50 mg) that was purchased from Novartis Pharma, while arabic gum was purchased from the market as spherical tears that were crushed and sieved in order to get tiny clean powder. The concentrate was 10

g/ 100 ml. then were put into warm water to dissolve them after that they were taken by the rats via mouth<sup>[14]</sup>.

### Blood Sample Collection

24 hours after the experiment, the animals were anesthetized using diethyl ether and weighted then withdrawal of blood from orbital sinus was done by (EDTA capillary tubes were used). Centrifugation of the blood was done to get the serum necessary for detection of (urea & creatinine) that were measured by the ordinary colorimetric ways<sup>[16]</sup>. Measuring of Cyclosporine level was determined in the blood which was obtained 12 hours after the last dose of the drug<sup>[15]</sup>.

### Histopathological examination

Dissection of kidneys from all groups was done then weighing them carefully, they were put in 10% formal saline for fixation, dehydrated in ascending grades of alcohol, cleared in xylene, after that embedded in paraffin, the tissue sections were stained with haematoxylin and eosin, periodic acid Schiff (PAS) and Mallory stain for light microscope examination<sup>[17]</sup>.

For ultrastructure studies fixation done at 4°C for 1.5 hours using 2.7% glutaraldehyde solution plus 0.1 M of phosphate buffer and then put in (0.15 M of phosphate buffer, pH 7.2), then fixed in osmic acid solution of 1% concentration in 0.15 M phosphate buffer during an hour under 4 °C. Dehydration was done by ascending grades of acetone after that embedding in epoxy resin Epon 812. After blocking, they were sectioned with an ultramicrotome type LKB at 70 nm thickness. Double contrasting of the sections with solutions of uranyl acetate and lead citrate occurred for examination by the use of transmission electron microscope<sup>[17]</sup>.

### Tissue preparation

Homogenization of 500 mg of renal samples was occurred in 4 ml of the buffer solution (phosphate buffered saline with PH 7.4) whereas centrifugation the homogenates were done at 10,000 xg (time:15 minutes at 4°C). The resultant was ready and utilized in detecting peroxidative stress markers like malondialdehyde ("MDA") plus antioxidant enzymes assay like catalase "CAT", peroxidase, glutathione "GSH", Nitric oxide and superoxide dismutase "SOD",<sup>[18]</sup>.

### Statistical analysis

For statistical study, (SPSS of version 17) was utilized. Outcomes were reported, using of (one-way ANOVA, post-hoc multiple comparisons test (TUKEY)) to detect any variation within various groupings. Mean + SD expressed as results variability while *P value* that equals to 0.05 or less was reported as statistically significant.

### Ethical considerations

suitable species of rats were selected during the present study. An elevated level of well-being rat is improved at

all times. The best size of sample was intended utilizing the lowest number of adult rats to get accurate results. Procedures causing pain done by the effect of anesthesia to inhibit any painful sensation and stress. animal safety with handling standards went parallel to the appropriate international rules and policy. There was approval from the ethics committee with a resolution no of 7703

## RESULTS

### *changes of the weight of both body and kidney in various experimental groups*

A significant reduction in the weight of rats of third group relative to group 1 and group 2. While, the rats' body weight of G4 had a significant rise relative to that of G3 (Figure 1).

kidneys of rats of third group (cyclosporine) revealed significant reduce in weight relative to the control and second groups, but kidneys of rats of group 4 had a significant rise statistically relative to the second group (Figure 2).

A significant result was found statistically among groups. when  $P < 0.001$ .

### *Measuring of cyclosporine level*

Level of Cyclosporine-A in the serum of rats of third group was elevated with a significant difference relative to group 1 and group 2 although the cyclosporine blood level of rats of fourth group showed statistically significant difference When compared with the third group (Figure 3).

A significant result statistically was present among groups when  $P < 0.001$ .

### *Biochemical results*

#### *I-Urea & creatinine*

Urea and creatinine values of cyclosporine-A in group 3 had a significant increase relative to G1 but the levels of urea and creatinine of G2 and G4 had statistically significant decrease in relation to G3 (Table 1).

#### *II- Redox status parameters*

A significant reduce in the levels of catalase, peroxidase, glutathione and superoxide dismutase in group 3 in relation to the control and second groups G1&G2 but significantly increased levels in G4 relative to G3 Although, the levels of malondialdehyde (MDA) and nitric oxide were significantly raised in G3 when compared with G1&G2. while it significantly reduced in G4 when compared with G3 (Table 2).

### *Histopathological results*

#### *A- Light microscopic results*

Microscopic observation of tissues of cortical tissues in rats of G1 and G2 revealed normal appearance (Figures 4,7), periodic acid Schiff (PAS) stain in glomeruli

and tubules (brush borders) was positive (Figure 10) But, specimens from rats of group 3 which were treated with cyclosporine, revealed atrophy and damage of cells plus cystic dilatation of the tubules, the epithelium of Bowman's capsule was injured with large size glomeruli (Figures 5,8) and fibrosis among the interstitium positive periodic acid Schiff reaction (weak reaction) was detected in vascular media, capillaries of glomeruli and renal tissues. (Figure 11) As regard the forth group, the cortical tissue showed restoration of histological normal appearance, the cytoplasm of cells of renal tubules was strong acidophilic and the nuclei were vesicular (Figures 6,9), there was strong positive (PAS) stain in glomeruli and tubules(brush borders) of kidney of the G4 (Figure 12).

### *B- transmission electron microscopic results*

G1&G2 revealed normal ultrastructure appearance (Figure 13) But, renal cellular structures of G3 revealed nuclear shrinkage in the cells of proximal convoluted tubules, most of cytoplasmic organelles were degenerated with several vacuoles of multiple sizes, obvious swollen few mitochondria, the basement membrane of tubules was thick and disturbed microvilli in brush border (Figure 14) On the other hand, rats of G4 showed nearly the same ultrastructure of G1 and G2 whereas mitochondria and the nucleus were almost normal with well-formed microvilli (Figure 15).

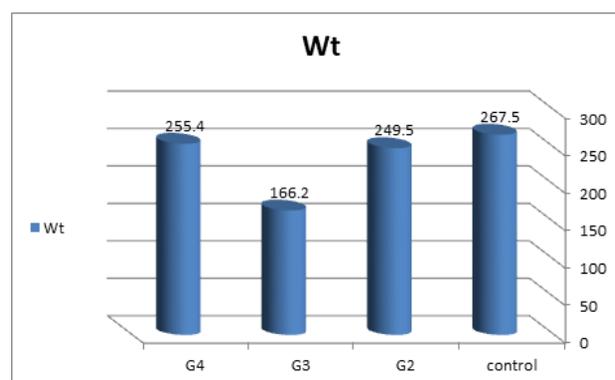


Fig. 1. Body weight among different groups  
G1: (control group). - G2: Arabic gum (AG).  
G3: Cyclosporine (CsA). - G4: Cyclosporine and Arabic gum (CsA+ AG).

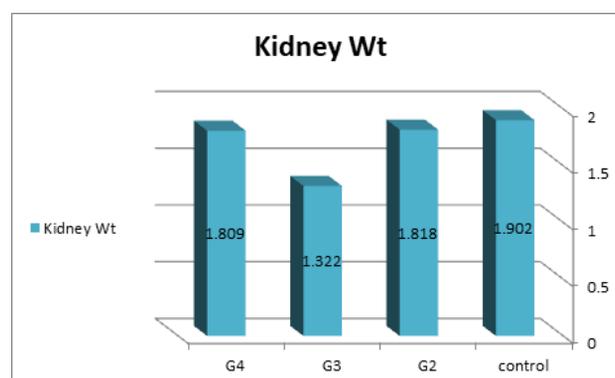
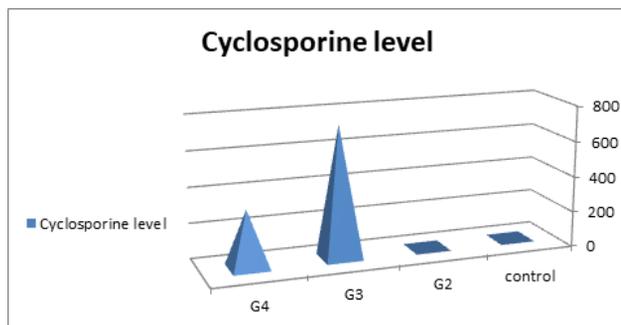
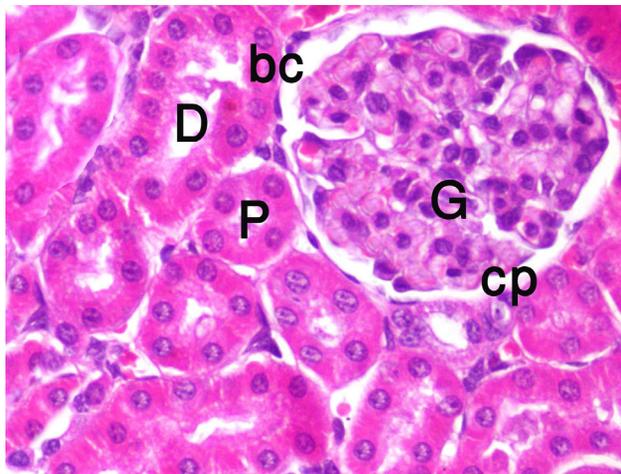


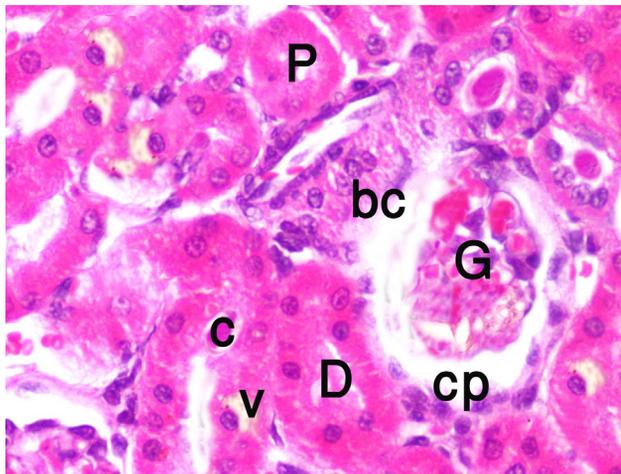
Fig 2: The rats' kidney weight among the four groups



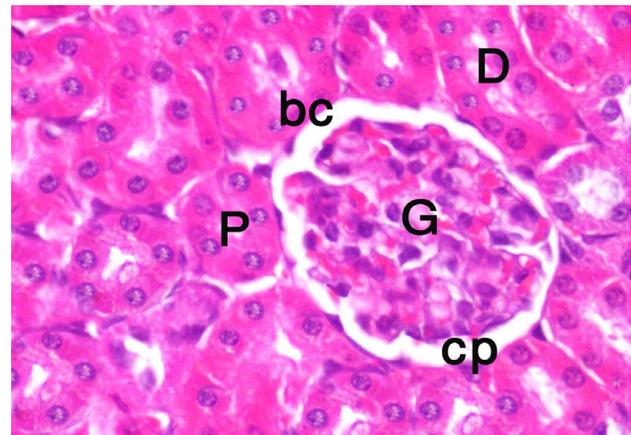
**Fig. 3:** Rats' cyclosporine blood level among the four groups



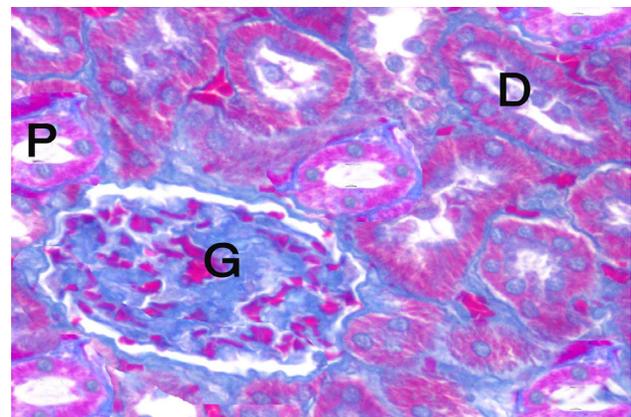
**Fig. 4:** A photomicrograph of G1(G2 showed the same results) kidney section showing typical glomeruli (G), obvious capsular space (cp), a flat epithelium of the glomerular capsule (bc), glomerular capsular space (CP), thickened cubical epithelium of the proximal convoluted tubules (P) and a low simple cubic epithelium of the distal convoluted tubules (D).(H&E X400)



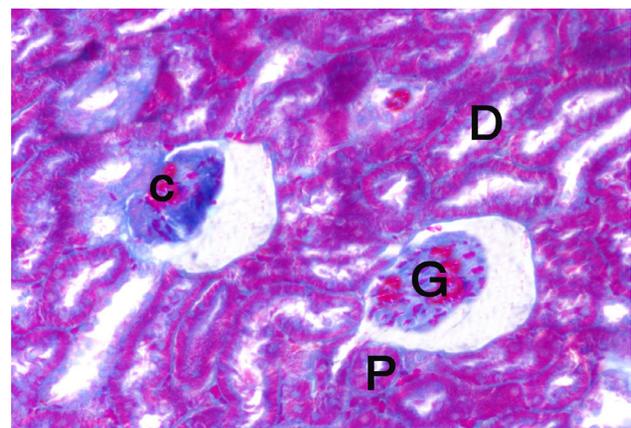
**Fig. 5:** A photomicrograph of G3 kidney section showing necrosis and glomerular atrophy (G). great vacuoles (v) in the epithelium of tubules, distinct glomerular capsular space (cp), destroyed flat epithelium that lines Bowman's capsule (bc), tubular cellular atrophy of proximal (P) and distal tubules (D), beside the presence of tubular casts (c).(H&E X400)



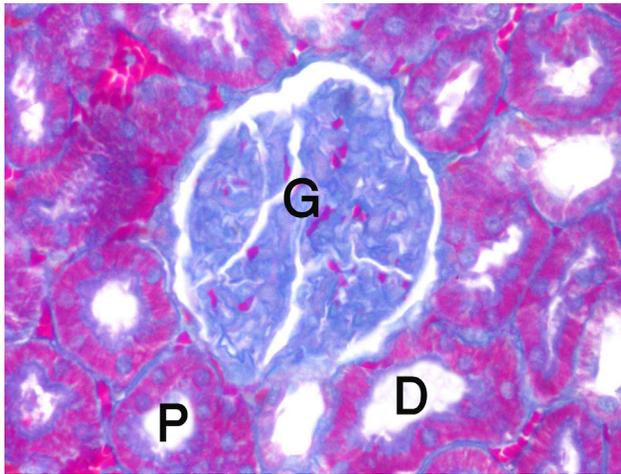
**Fig. 6:** a photomicrograph of section in G4 rat kidney revealing almost typical glomeruli (G), a flat epithelium lining of the glomerular capsule (bc), obvious capsular space (cp), normal proximal (P) and distal (D) convoluted tubules. (H&E X400)



**Fig. 7:** A photomicrograph of G1(G2 showed the same results) kidney section showing typical normal histological appearance of glomeruli (G), typical normal proximal (P) and distal (D) convoluted tubules, interstitial tissues contain few connective tissue.(Mallory X400)



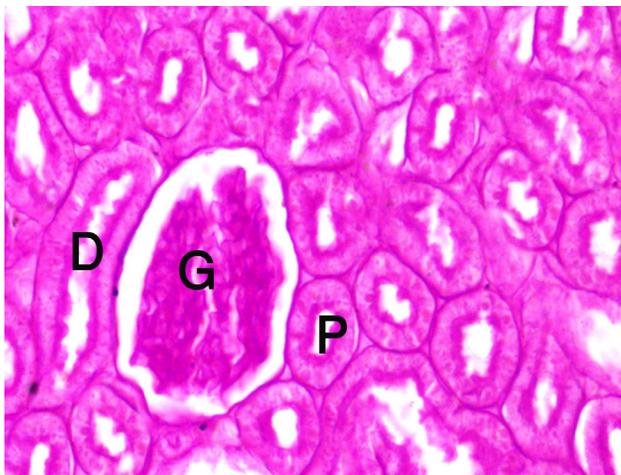
**Fig. 8:** A photomicrograph of G3 kidney section showing congestion (c) of vessels of glomeruli (G) with several foci of interstitial fibrosis. proximal (P) and distal (D) convoluted tubules. (Mallory X400)



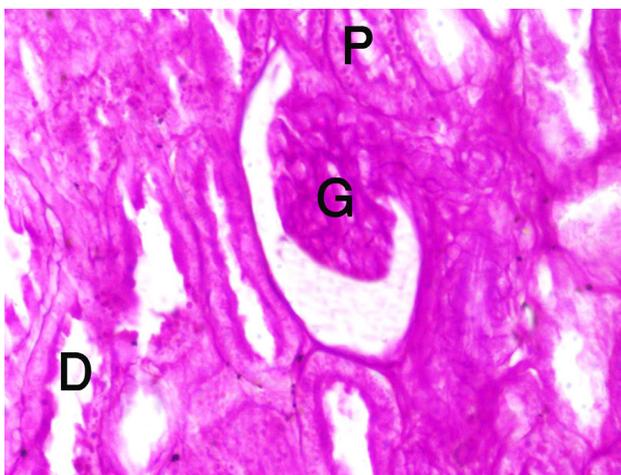
**Fig. 9:** A photomicrograph of G4 kidney section showing almost typical glomeruli (G), proximal (P) and distal (D) convoluted tubules. The interstitial tissues contain few connective tissue.(Mallory X400)



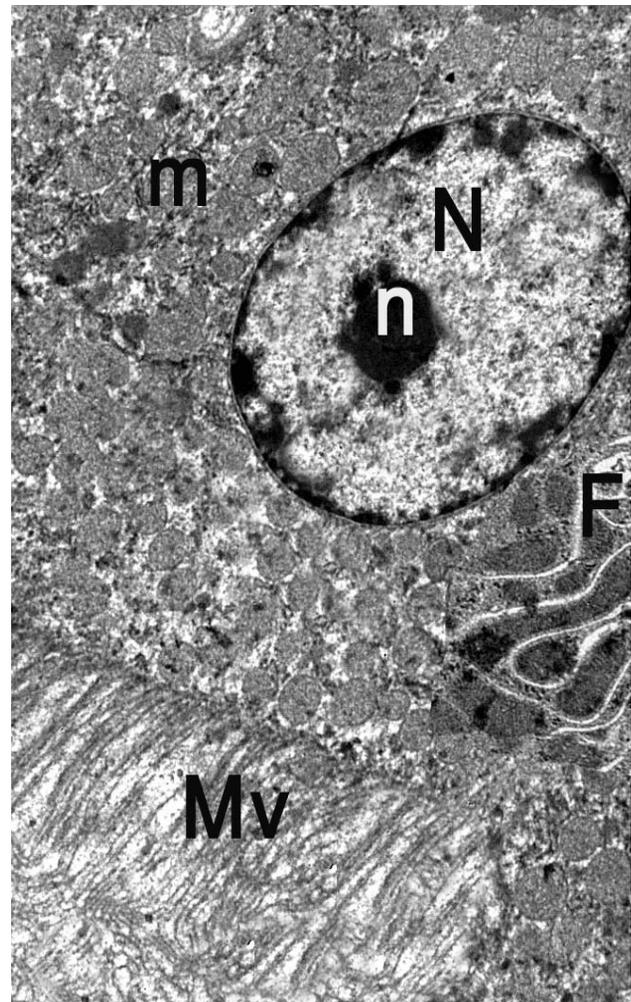
**Fig. 12:** A photomicrograph of G4 kidney section showing strong positive reaction in renal glomeruli (G) and the brush border of tubules of kidney either proximal (P) or distal (D) .(PAS X400)



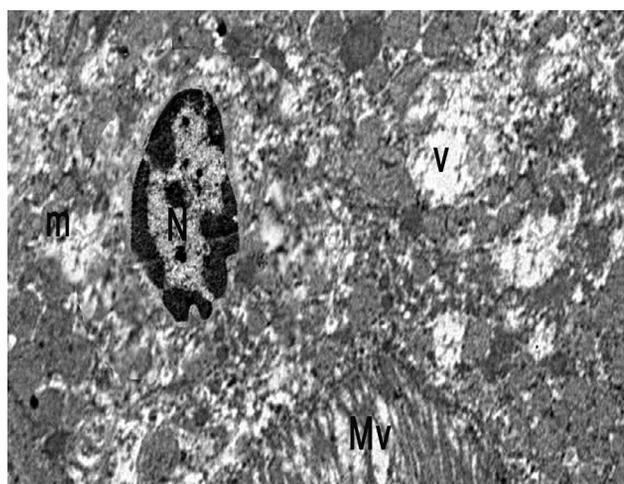
**Fig. 10:** A photomicrograph of G1(G2) kidney section showing strong positive reaction in the glomeruli (G), brush border of the convoluted tubules: proximal (P) and distal (D) (PAS X400)



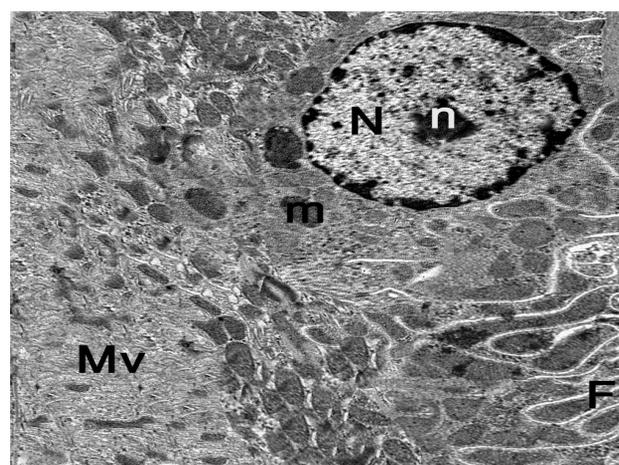
**Fig. 11:** A photomicrograph of G3 kidney section showed weak positive reaction in renal glomeruli (G) and moderate reaction in the renal tubules: proximal (P) and distal (D) . (PAS X400)



**Fig. 13:** An electron micrograph of a section in Proximal convoluted tubules of G1(G2) of rat kidney showing a great spherical nucleus (N) with a little nucleolus (n), basal enfolding (F) with almost healthy microvilli (Mv) and many mitochondria (m). (X12000)



**Fig. 14:** An electron micrograph of a section in convoluted tubules of G3 of rat kidney revealing disturbance of many cytoplasmic organelles with the existence of vacuoles (v), distended mitochondria (m), disrupted microvilli (Mv) and shrunken small nucleus (N). (X12000)



**Fig. 15:** An electron micrograph of a section in convoluted tubules of G4 of rat kidney revealing almost a typical nucleus (N) with a tiny nucleolus (n), basal enfolding (F) with almost healthy microvilli (Mv) and many mitochondria (m). (X12000)

**Table 1:** Showing urea and creatinine levels among various groups

	First Control	Second Arabic Gum	Third CsA	Fourth CsA+ Arabic gum	F
Urea(M±SD)	28.21±6.34	27.4±4.02**	81.2±6.06*	27.12±1.56**	356.406
Creatinine(M±SD)	0.91±0.11	0.88±0.17**	6.12±0.45*	0.89±0.034**	3.597

SD: Standard deviation

\*  $P < 0.001$  refers to Significant result when compared with G1

\*\*  $P < 0.001$  refers to Significant result when compared with G3

F: The value of the difference between the groups.

**Table 2:** Showing the redox status parameters of four groups of rat

	G1	G2	G3	G4	F
C	38.84±1.66	37.58±2.31**	11.01±1.98*	39.58±1.25**	555.513
P	15.51±1.22	14.98±1.09**	6.09±1.05*	13.84±2.17**	164.854
GSH	93.32±1.51	89.89±2.86**	51.01±5.02*	92.52±1.08**	447.757
MDA	23.78±0.59	25.12±1.95**	61.3±1.77*	24.15±0.83**	1.031
N.O	48.66±4.35	41.92±2.82**	62.12±4.78*	46.92±2.22**	68.208
S.D	25.41±1.78	25.98±1.21**	12.01±0.66*	25.12±1.65**	196.237

C: Catalase

P: Peroxidase

GSH: Glutathione

MDA: Malondialdehyde

N.O: Nitric oxide

S.D: Superoxide Dismutase

\*  $P < 0.001$  refers to significant result when compared with the G1

\*\*  $P < 0.001$  refers to significant result when compared with the third group

F: The value of the difference between the groups.

## DISCUSSION

Cyclosporine-A has an immunosuppressive action but it is still the initial selected treatment in case of transplanted organ problems and rejection. The most complication of its prolonged use is a nephrotoxicity whereas modern studies had to get a way out for this renal damage by means of various substances which are naturally present. There is not enough experimental studies on the effect of Arabic Gum on the cellular state of renal tissues during the use of cyclosporine. The aim of this present work was to determine the use of Arabic gum to overcome the side effects of cyclosporine by improving the nephrotoxicity caused by it in trial to know the pathogenesis of the drug.

The present study reported that a statistical significant reduce was present in the rats' weights of both body and kidney of group III which was given cyclosporine-A when compared with group I and group II due to toxicity of cyclosporine, this happened due to anorexia and catabolic effect causing the loss of body weight, these results were in agreement with<sup>[15,19,20]</sup> who revealed renal apoptosis as a reason of renal weight decrease.

A statistical significant increase of weight of both kidney and body in the rats of fourth group which given Arabic gum plus cyclosporine-A was present due to its antioxidant role which opposes effects of cyclosporine-A caused loss of the weight of both body and kidneys, these results went in agreement with<sup>[9,10]</sup> who detected that Arabic gum enhanced the weight of both body and kidneys in the rats which were given adenine-induced failure of kidneys

The present work concluded that cyclosporine-A caused significant raise of urea & creatinine in the blood, these results were parallel with the results of<sup>[15,21,22]</sup>. The present study showed renal cells apoptosis, these results were in agreement with<sup>[15,23]</sup>. According to<sup>[15,24]</sup>, renal pathological results and impairment due to cyclosporine intoxication produced oxidative stress which leads to reactive oxygen species (ROS) causing peroxidation of lipids in constant with<sup>[15,25]</sup> and our results revealed that raise in all of the oxidative parameters such as (malondialdehyde "MDA" and nitric oxide), and statistical significant reduce in (glutathione) and other enzymes like (catalase, superoxide dismutase and peroxidase) as a cause of elevated blood value of cyclosporine which produces oxidative stress for example enzyme inhibition and inactivation, disturbance of mitochondria beside cellular necrosis according to<sup>[26]</sup>. The present research showed that cyclosporine-A caused histopathological and ultrastructural deteriorations in the renal tissues of rats, these results were parallel to<sup>[15,21,22]</sup>.

This present work revealed that treatment by the use of both Arabic gum and cyclosporine together could cause improvement of the results of cyclosporine-A intoxication when compared with group II that given cyclosporine only and this was parallel to the results of<sup>[14]</sup> who showed that Arabic gum improved the toxic manifestations of indomethacin on renal tissues of rat. Moreover<sup>[27,28]</sup>, added that Arabic gum improved renal histopathological and

ultrastructural pathological deteriorations of cisplatin-evoked Nephrotoxicity in Rats.

## CONCLUSION

Prolonged period of cyclosporine-A administration may result in oxidative stress and injury of renal tissues and deteriorations of renal function which were detected by histological and biochemical studies through the oxidative stress. The utilize of Arabic gum accompanied with cyclosporine-A produced amelioration in renal damage manifestations due to its obvious antioxidant effect

## RECOMMENDATIONS

The dual intake of Arabic gum as dietary natural substance during the period of extended intake of cyclosporine is suggested in patients with organ transplantation to adjust and improve the nephrotoxicity caused by it.

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## CONFLICT OF INTERESTS

There are no conflicts of interest.

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## الملخص العربي

## التأثيرات الكلوية للعلكة العربية ضد السيكلوسبورين - المسبب للسمية الكلوية في الفئران

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**المقدمة:** أفاد العديد من الباحثين مؤخرًا أن العلاج باستخدام السيكلوسبورين أ في فتره ممتده لتجنب رفض زرع الاعضاء يرتبط بتقدم السمية الكلوية. الصمغ العربي من مضادات الأكسدة القيمة والعامل المضاد للسرطان مع تأثير وقائي ضد التسمم الكلوي.

**الهدف:** تهدف هذه الدراسة إلى تقييم الدور الوقائي للصمغ العربي في تحسين السمية الكلوية للسيكلوسبورين أ في الجرذان البالغة عن طريق قياس الوظيفة الكلوية والآفات النسيجية، ومعلومات حالة الأكسدة. مواد وطرق البحث تم تقسيم ثمانين من الفئران البالغة من الذكور والإناث إلى أربع مجموعات خلال ٤٥ يومًا من انتهاء التجربه؛ تعمل المجموعة الأولى كمجموعه ضابطه؛ المجموعة الثانية المعالجة ب ٧,٥ جم / كجم / يوم من الصمغ العربي، تلقت المجموعة الثالثة ٢٥ مجم / كجم / يوم من السيكلوسبورين أ بينما تلقت المجموعة الرابعة ٧,٥ جم / كجم / يوم من الصمغ العربي مع ٢٥ مجم / كجم / يوم من الصمغ العربي. من السيكلوسبورين أ.

**النتائج:** كان لدى الفئران المعالجة بالسيكلوسبورين أ خلل وظيفي كلوي، كما تم الإبلاغ عنه من خلال علامات عالية في قيم الوظائف الكلوية والتغيرات النسيجية الكلوية، عند مقارنتها بالمجموعة الضابطة مع زيادة مستوى السيكلوسبورين أ وضعف معلومات حالة الأكسدة. استخدام الصمغ العربي مع السيكلوسبورين أ - ادي الي تخفيف السمية الكلوية عن طريق خفض مستويات اليوريا في الدم والكرياتينين، وتحسين أمراض الكلى، بالإضافة إلى تحسين معايير مضادات الأكسدة. هناك انخفاض إحصائي مهم في قيم الكاتالاز، البيروكسيديز، الجلوتاثيون وفوق الأكسيد الفائق في المجموعة الثالثة) السيكلوسبورين (مقارنة بالمجموعة الضابطة والمجموعات الثانية بينما زاد بشكل ملحوظ في المجموعة الرابعة) السيكلوسبورين والصمغ العربي (بالمقارنة مع المجموعة الثالثة) السيكلوسبورين.

**الاستنتاج:** من المحتمل أن يعمل الصمغ العربي كعامل طبيعي للوقاية من السكلوسبورين أ المسبب لسميه كلويه.