

Evaluation of The Antidotal Activity Of Aged Garlic Extract On Aluminum Induced Male Reproductive Toxicity In Albino Rats

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ABSTRACT

The effect of aluminum (Al) on male fertility was assessed by weighing the testis and epididymal spermatozoal examination. For this purpose, twenty mature male rats were divided into four equal groups each of five animals. The first group used as negative control group and orally administered deionized water daily for 9 weeks. The second group orally administered 1 gm/kg b.wt. of AGE daily for 9 weeks (placebo group). The third group orally administered 320 mg/kg b.wt. of aluminum nitrate nonahydrate daily for 9 weeks (positive control group). The fourth group orally administered 1 gm/kg b.wt. of AGE two hours before administration of 320 mg/kg b.wt of aluminum nitrate nonahydrate daily throughout the experimental period.

At the 9th week, both treated and control male rats were sacrificed. The testis and epididymis were dissected out and examined macroscopically and weighed.

The results showed that there was a significant decrease in epididymal sperm cell count (2.4 ± 0.83), live sperm percentage (21.0 ± 3.67) and individual motility percentage (16.00 ± 3.67) in the group administered aluminum only. On the other hand, it elicited a non significant increase in total sperm abnormalities (19.07 ± 2.52). Group administered AGE (1 g/kg b.wt orally) and aluminum nitrate daily throughout the whole experimental period 9 weeks showed a significant increase in epididymal sperm cell count (17.50 ± 6.37), live sperm percentage (76.85 ± 1.12) and individual motility percentage (67.00 ± 2.00). AGE ameliorate the histopathological changes induced by $Al(NO_3)_3$ in the brain, kidney, testes and spleen.

INTRODUCTION

Aluminum was long considered virtually innocuous to human (1), and in the past few decades its impact on biological systems have been the subject of much controversy (2), but since initial reports, Al has received considerable attention as a potential neurotoxic factor in neurological disorders such as Alzheimer's disease (3). Since then a wealth of intensive research efforts have been carried out to investigate Al toxicity. Systemic aluminum toxicity has an effects on bone (4), hematopoietic tissue (5), and kidney (6).

Desferrioxamine (DFO) is one of drugs used to treat Al accumulation and toxicity but it is not orally effective, rather expensive and has a teratogenic effects (7).

fresh garlic, is not for everyone, it can cause indigestion and its pungent odor that lingers on the breath and skin is a social deterrent. These disagreeable effects of fresh garlic are due to *allicin*, an oxidant, released

upon cutting or chewing the clove. Scientific studies, however, showed that garlic does not have to be fresh to be effective nor its smell required for its health benefits. An alternate source of garlic, that is odorless and richer in antioxidants than the fresh bulb is the dietary supplement *Aged Garlic Extract* (AGE). AGE has been found to help prevention of atherosclerosis and protect against cardiovascular disease, increase circulation and immunity and have antiaging effects, improving memory, endurance and learning (8).

The purpose of our study was carried out to investigate the antidotal effect of Aged Garlic Extract (AGE) against the effect of aluminum nitrate nonahydrate on semen quality in male albino rats.

MATERIALS AND METHODS

Chemicals and AGE

Aluminum nitrate nonahydrate, a product

of LOBA CHEMICA, Mumbai-India was administered orally via stomach tube.

Preparation of AGE was carried out as previously described (9). We used the Egyptian garlic cloves (*Allium sativum*) which were sliced and then soaked in 20% ethanol (water/ethanol mixture) in dark colored glass bottles and naturally aged for 20 months at room temperature. The alcohol found to have no effect, except to inhibit bacterial growth (10). The concentration of garlic in water / ethanol mixture was 1 ml of water ethanol mixture contains 200 mg garlic.

The extract was then filtered and tested bacteriologically and was found to be bacteriologically negative on neutral agar.

The filtrate was concentrated to dryness (lyophilization) in clean, dry and sterilized ampoules. Each ampoule contains 2 ml of liquid extract which is concentrated to dryness to become 0.2 gm. The lyophilized powder was used and reconstituted when dosing to 0.2 gm/ml.

Lyophilization was carried out in the lyophilization unit, Serum and Vaccine Institute, Abbassia, Cairo, Egypt.

Experimental animals and Treatment

twenty mature male rats were divided into four equal groups each of five animals. The first group used as negative control group and orally administered deionized water daily for 9 weeks. The second group orally administered 1 gm/kg b.wt. of AGE daily for 9 weeks (placebo group). The third group orally administered 320 mg/kg b.wt. of aluminum nitrate nonahydrate daily for 9 weeks (positive control group). The fourth group orally

administered 1 gm/kg b.wt. AGE two hours before administration of 320 mg/kg b.wt of aluminum nitrate nonahydrate daily throughout the experimental period.

At the end of 9th week of administration, both treated and control male rats were sacrificed. The testis and epididymis were dissected out and examined macroscopically and weighed. Samples from the brain, kidney, spleen, and testes were taken for histopathological examination (11).

Statistical analysis

The obtained data were statistically analyzed using the procedure of statistical analysis system (SAS) computer program (12). $P \leq 0.05$ was considered the level of significance.

RESULTS

Aluminum nitrate administration evoked a significant decrease in epididymal sperm cell count (2.4 ± 0.83), live sperm percentage (21.0 ± 3.67) and individual motility percentage (16.00 ± 3.67). on the other hand, it elicited a non significant increase in total sperm abnormalities (19.07 ± 2.52) as compared with control groups (Table 1).

The group administered AGE and aluminum nitrate daily showed a significant increase in epididymal sperm cell count (17.50 ± 6.37), live sperm percentage (76.85 ± 1.12) and individual motility percentage (67.00 ± 2.00). On the other hand, it elicited a non-significant changes in the total sperm abnormalities as compared with the positive control group administered aluminum nitrate only (Table 1).

Table 1. The antidotal effect of AGE on the effect of oral administration of aluminium nitrate nonahydrate on semen quality in male albino rats throughout the experimental period (9 weeks) (mean \pm S.E).

Group N=5	Treatment	Dose	Sperm cell conc. ($\times 10^6$)	Live sperms	Motility	Abnormalities	Testicular weight
I	Deionized water (negative control group)	-	26.25 \pm 2.40 ^a	89.28 \pm 2.81 ^a	88.00 \pm 1.22 ^a	11.96 \pm 2.03 ^a	4.14 \pm 0.29 ^a
II	AG	1 g / kg b.t	25.94 \pm 2.5 ^a	87.83 \pm 1.74 ^a	89.40 \pm 1.04 ^a	10.97 \pm 2.93 ^a	4.17 \pm 0.27 ^a
III	Aluminium nitrate nonahydrate	720 mg/kg b.wt	2.40 \pm 0.83 ^c	21.0 \pm 3.67 ^c	16.00 \pm 3.67 ^c	19.07 \pm 2.52 ^a	3.18 \pm 0.11 ^b
IV	Aluminium nitrate + AGE	720 mg/kg b.wt + 1 g / kg b.t	17.50 \pm 6.37 ^b	76.58 \pm 1.12 ^b	67.00 \pm 2.00 ^b	19.55 \pm 2.86 ^a	4.04 \pm 0.22 ^a

Histopathological Examination

Testes

The testes the group administered aluminium nitrate thickened tunica albuginea by hyalinized fibrous tissue. The majority of seminiferous tubules had little or no spermatogenesis manifested by absence of spermatozoa with absence or vacuolation in spermatogonial, primary and secondary spermatocytes and Sertoli cells. Some lumina of seminiferous tubules revealed absence of spermatozoa with the presence of necrotic debris, lymphocytes, macrophages and spermatid giant cells (fig.1). Edematous stroma was detected in some examined testes.

Active spermatogenesis represented by numerous spermatozoa inside the lumina of seminiferous tubules and nourished cells was observed after administration of AGE (fig. 2).

Brain

The majority of pyramidal cells in cerebral cortex showed shrinkage and become rounded with losing of their processes beside perineuronal edema. Demyelination in nerve axons with focal areas of encephalomalacia could be seen (fig 3), were seen in the group administered ALN.

The brain lesions were minimal and characterized by a few degenerated neurons. Moreover, little pericellular and meningeal edema beside dilated meningeal blood vessels were encountered. A few lymphocytes

could be seen in the meninges particularly around blood vessels was observed after administration of AGE (fig.4).

Kidney

Hypercellularity or distortion of some glomeruli with necrotic changes in the surrounding renal tubules could be seen mainly in the renal cortex in the positive control group (fig.5).

The renal parenchyma revealed an improvement in their microscopical lesions after administration of AGE. A few reversible changes summarized by slightly dilated glomerular spaces with vacuolation of some tubular epithelia in renal cortex. The remaining segments of nephrons were apparently normal (fig. 6).

Spleen

Lymphoid depletion of white pulps and sub-capsular sinuses were common. Extensive haemosiderosis with proliferations of megakaryocytes (extramedullary hematopoiesis). Some central arteriols had hyalinized and edematous vascular wall (fig. 7).

The splenic structures were apparently normal beside mild activation of extramedullary haematopoiesis and hyperplastic white pulps was observed after administration of AGE (fig. 8).

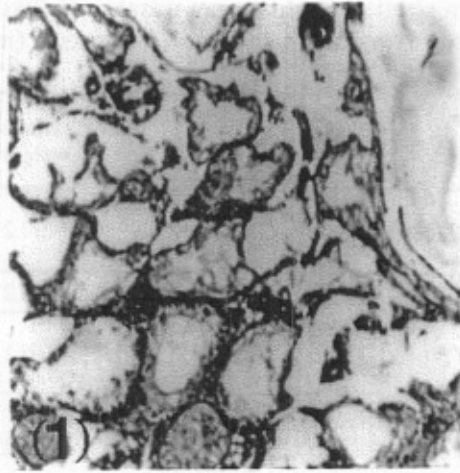


Fig. 1. Arrest of spermatogenesis and vacuolation in the layers of seminiferous tubules in the testes of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) daily for nine weeks (H & E x300).

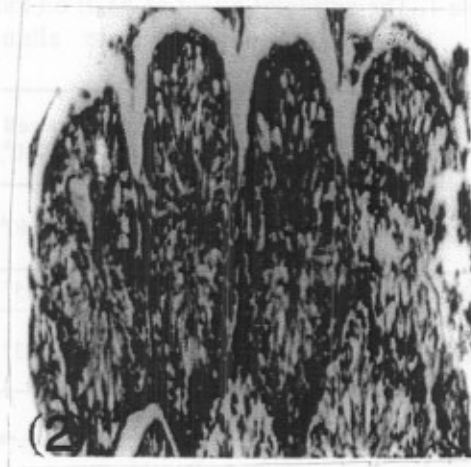


Fig. 2. Active spermatogenesis in the testes of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) and AGE (1 gm/kg b.wt) daily for nine weeks (H & E x 300).

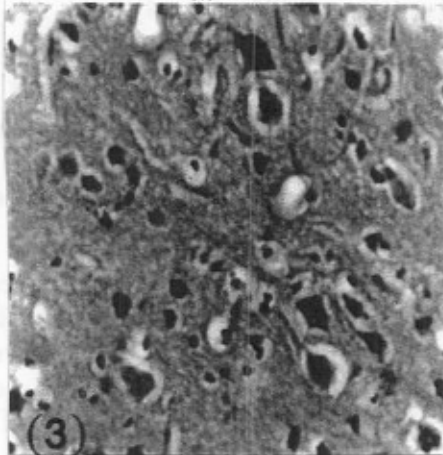


Fig. 3. Shrunken and rounded pyramidal cells with perineuronal edema in the brain of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) daily for nine weeks (H & E x300).

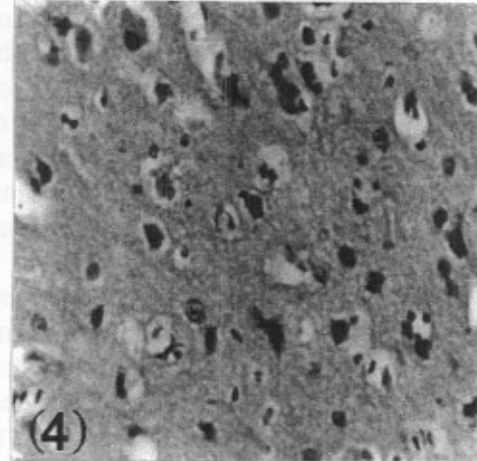


Fig. 4. Few degenerated neurons, mild satellitosis and neurophagia in the brain of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) and AGE (1 gm / kg b.wt) daily for nine weeks (H & E x300).

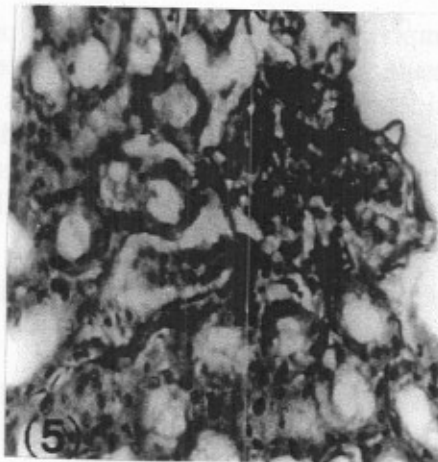


Fig. 5. Hypercellularity of glomeruli with necrotic renal tubules in the kidney of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) daily for nine weeks (H & E x300).

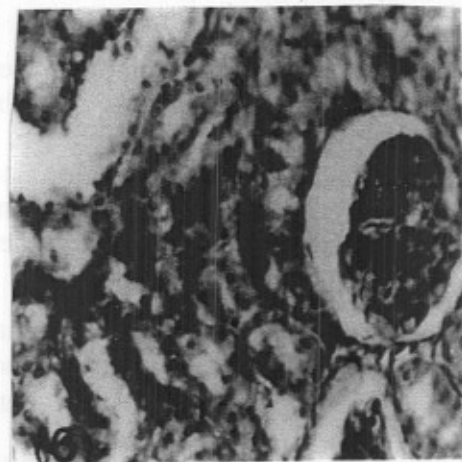


Fig. 6. Apparently normal renal parenchyma in the kidney of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) and AGE (1 gm/kg b.wt) daily for nine weeks (H & E x300).



Fig. 7. Lymphoid depletion in the spleen of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) daily for nine weeks (H & E x300).

DISCUSSION

In Japan, the pharmacological activities of AGE was studied in comparison with raw garlic juice (RGJ), heated garlic juice (HGJ), and dehydrated garlic powder (DGP). Results suggested that among the four garlic preparations, AGE could be the most useful garlic preparation (9). With over 350 scientific studies conducted on AGE since its development in 1955, showing its effectiveness for number of health conditions. Japanese scientists developed AGE about 30 years ago. In addition, AGE is an appropriate solution as it provides therapeutic level of fresh garlic without offensive odor and irritability of the stomach. From the previous evident it can be concluded that fresh garlic is not for everyone, as it can cause indigestion and its pungent odor that lingers on breath and skin is a social deterrent. These disagreeable effect of fresh garlic which is due to *allicine*, a volatile and reactive oxidant, released upon cutting or chewing the clove lead us to prepare and use AGE during our study.

In the present study, it has been obvious that oral administration of AL in a dose of 320 mg/kg b.wt daily throughout 9 weeks to male albino rats evoked a significant decrease in epididymal cell count, live sperm percentage and individual motility percent, and testicular weight and a non-significant increase in total sperm abnormalities as compared with that of control groups.

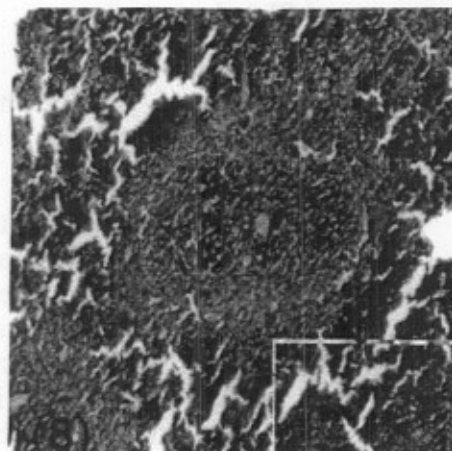


Fig. 8. Hyperplastic white pulps in the spleen of male rat orally administered aluminum nitrate nonahydrate (320 mg/kg b.wt) and AGE (1 gm/kg b.wt) daily for nine weeks (H & E x300).

Blood-testis barrier (BTB) protected germ cells from harmful influences, it prevents the delivery of xenobiotics to the testis (13).

Intratesticular testosterone, secreted by the leydig cells is necessary for spermatogenesis. Intratesticular testosterone was mainly bound to androgen-binding protein and secreted into the seminiferous tubules. Suppression of testosterone produced by leydig cells would result in a deficient spermatogenesis (14). Evidence indicates that, AL produces its adverse effects on semen picture by many ways. Firstly, decreases or suppress the testosterone hormone produced by leydig cells by means of stimulating NO production (15-17) that results in a deficient spermatogenesis (14). Secondly, AL induces excessive production of NO which might changes BTB and increases the permeability of testicular membrane (18). Thirdly AL induces the formation of thiobarbituric acid reactive substance (markers of oxidative stress) in seminal plasma which can induce a negative effects on sperm motility (19).

Interestingly enough, our findings revealed that AL provoked an adverse effect on semen picture the same results are recorded previously by several investigators (14-19). AL evoked a significant increase in sperm cell abnormalities and a highly significant decrease in sperm cell motility, live / dead sperm and sperm cell concentration and a significant decrease in serum and testicular testosterone. AL caused degenerative changes in the

seminefrous tubules epithelia with arrested spermatogenesis at the stage of spermatid formation (15, 16,18, 20).

In the present study, the oral administration of AGE in AL-treated male albino rats abolished the adverse effects of AL on semen picture. These animals showed a significant increase in epididymal sperm cell count, live sperm percentage and individual motility percent and testicular weight. On the other hand, it elicited a non-significant decrease in total sperm abnormalities as compared with group administered AL only throughout the experimental period.

AGE acts as an antidote against the adverse effects of AL on semen picture and testicular weight may be explained by several previously cited investigations. Firstly, it inhibits protein, lipid peroxidation and production of ROS and oxidative DNA damage (sperm DNA) (7). Secondly, improvement in peripheral circulation which would likely result in improved nutrition and thus, spermatogenesis (21,8). Our results are in accordance with those reported by previous investigators (22,23,7). The authors reported that daily intake of garlic extract provoked significant increase in the weight of male reproductive organs, enhancing spermatogenesis and a significant elevation of sperm cell count, live sperm percentage, sperm motility percentage and significant decrease in sperm abnormalities. In addition to the beneficial effects of AGE on male reproduction, the present study showed that oral administration of AGE in Al-treated male albino rats revealed minimal brain lesions indicating the ameliorating effect of AGE on Al toxicity.

These results are consistent with those reported that AGE and its constituents reduce or even inhibit apoptosis and neuronal cell death due to the accumulation of amyloid-B protein in the brain which associated with senile plaques encountered in AD and can be triggered by ROS damage. They also reported that AGE possesses neurotrophic effects and its ability to enhance nerve growth (24).

The kidney is the major pathway of Al excretion from the body and Al form insoluble complex formed by combination of Al and phosphorus. This complex accumulated in kidney during its excretion (25).

In the present study, oral administration of aluminum revealed several histopathologic lesions in kidneys in the form of distortion of some renal glomeruli and hydropic degeneration and cellular or hyaline cast were encountered. These results are consistent by those which found that Al produce severe degenerative changes, necrosis of renal tissue (26,27).

The oral administration of AGE improved the renal parenchymal microscopical lesions. These results are in accordance with the fact that AGE ameliorates renal dysfunction and morphological changes induced by the administration of cyclosporin A (CsA) (28), which in turn induce oxidative stress and lipid peroxidation through ROS production and so, the ameliorating action of AGE is due to its potent antioxidative and free radicals scavenging abilities in various diseases conditions.

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الملخص العربي

تقييم النشاط التريباتي لمستخلص الثوم المعتق على التأثير الناجم عن التسمم بواسطة نيترات الألومنيوم المائية في ذكور الجرزان البيضاء

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قسم الطب الشرعي والسموم – كلية الطب البيطري – جامعة الزقازيق

يهدف البحث إلى دراسة تأثير مستخلص الثوم المعتق على حماية الحيوانات المنوية من تأثير من أثير التسمم بالألومنيوم وكذلك دراعسة التأثير الترياقى للثوم المعتق على التغيرات الهستوباثولوجية الناجمة عن التسمم بالألومنيوم في الكلى والطحال والمخ وكذا الخصية . استخدم في هذه التجربة عدد ٢٠ من ذكور الجرزان البيضاء حيث قسمت إلى ٤ مجموعات كل مجموعة مكونة من ٥ حيوانات وتم استخدام مسار التجريع عن طريق الفم بواسطة أنبوب إلى المعدة في جميع حالات المعالجة وكانت المجموعة الأولى تمثل مجموعة ضابطة سالبة والمجموعة الثانية اعطيت هذه المجموعة مستخلص الثوم المعتق بجرعة يومية مقدارها ١ جم/كجم من وزن الجسم لمدة ٦٥ يوم "Placebo group". المجموعة الثالثة اعطيت هذه المجموعة نيترات الألومنيوم المائية بجرعة يومية مقدارها ٣٢٠ مجم/كجم من وزن الجسم لمدة ٦٥ يوم "مجموعة ضابطة موجبة" المجموعة الرابعة اعطيت هذه المجموعة نيترات الألومنيوم المائية كما هو مبين في المجموعة الثالثة بالإضافة الى مستخلص الثوم المعتق كما هبين في المجموعة الثانية. وفي اليوم ٦٥ من عمر التجربة تم ذبح جميع الجرزان في كل المجموعات وتم فحص محتوى كل حويصلة خصوية من حيث عدد الحيوانات المنوية ونسبة الحيوانات المنوية الحية ونسبة حركتها والتشوهات الموجودة بها بالإضافة لدراسة التأثيرات الهستوباثولوجية في الخصية في كل المجموعات. وعدد فحص خصائص السائل المنوي وجد أن المجموعة التي اعطيت مستخلص الثوم المعتق فقط طوال فترة التجربة وجد انها لا تختلف اختلافا ذو دلالة إحصائية عن المجموعة الضابطة السالبة والمجموعة التي اعطيت نيترات الألومنيوم المائية وجد أنه يؤدي الى نقص شديد في عدد الحيوانات المنوية ونسبة الحيوانات المنوية الحية وكذلك نسبة الحركة بالإضافة لوجود زيادة في تشوهات الحيوانات المنوية مقارنة بالمجموعات الضابطة. والمجموعة التي اعطيت مستخلص الثوم المعتق مع نيترات الألومنيوم المائية وجد أن التأثير السلبي للألومنيوم على خصائص السائل المنوي قد نقص بصورة ملحوظة. كما اظهرت التغيرات الهستوباثولوجية أن الحيوانات التي اعطيت نيترات الألومنيوم وجد أن الألومنيوم يؤدي الى حدوث بعض التغيرات التحطيمية والتركزة في خلايا المخ ووجود انكماش في الخلايا الهرمية مع اختفاء الغشاء النخاعي المغلف للليف العصبي ووجود تجمعات لخلايا الأغشية السحائية. وعند إعطاء مستخلص الثوم المعتق مع الألومنيوم لجميع الجرزان وجد أن التأثيرات التحطيمية قد اندثرت الى حد كبير. كما ان الحيوانات التي اعطيت نيترات الألومنيوم المائية وجد أنه يؤدي الى حدوث تفرغ أو نزح ليفي للباب الأبيض الخاص بالطحال ووجود تخليق لكرات الدم الحمراء خارج اللب. وعند إعطاء مستخلص الثوم المعتق مع نيترات الألومنيوم المائية لجميع الجرزان وجد أن التأثيرات الضارة للألومنيوم قد اندثرت الى حد كبير ووجد أن نسيج الطحال أصبح الى حد ما طبيعياً. أما الحيوانات التي اعطيت نيترات الألومنيوم المائية وجد أنه يؤدي الى حدوث بعض التغيرات التحطيمية وتتركز في الأنابيب الكلوية مع تشوية في العصافة الكلوية وذلك بزيادة عدد خلاياها. بعض الأنابيب المجمععة تعاني من فساد حبنى مع وجود قوالب بلورية بداخلها.

وعند إعطاء مستخلص الثوم المعتق مع نيترات الألومنيوم المائية لجميع الجرزان وجد أن التأثيرات الهستوباثولوجية قد اندثرت الى حد كبير حيث يوجد تحسن في الأفات الميكروسكوبية في النسيج الكلوي والناجمة عن التسمم بالألومنيوم. كما أوضحت الدراسة أن نيترات الألومنيوم المائية عند إعطاؤه لذكور الجرزان البيضاء يسبب ضمور في عملية تخليق الحيوانات المنوية داخل النبيتات الخصوية وكذلك وجد أن الألومنيوم يسبب تحطيمية متقدمة في الخصية.

وفحص النسيج الخصوى وجد به شبه غياب تام للحيوانات المنوية مع وجود تغيرات تحطيمية وتتركز للغشاء الطلائى له. كما يوجد زيادة في سمك الغلالة البيضاء المحيطة بالخصية.

وعند اعطاء مستخلص الثوم المعتق مع الألومنيوم لذكور الجرزان البيضاء وجد أن التأثيرات التحطيمية للألومنيوم قد اندثرت لحد كبير مع تحسن في صورة السائل المنوي وكذا نسيج الخصية.