Original Article

COMPARISON OF POTENTIAL PROTECTIVE EFFECTS OF APOCYNIN AND MELATONIN AGAINST GENTAMICIN-INDUCED NEPHROTOXICITY IN ADULT MALE ALBINO RATS

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ABSTRACT

Background: Gentamicin (GNT) as an aminoglycoside antibiotic is commonly used against life threatening bacterial infections, however, the risk of nephrotoxicity is the main limitation of GNT therapeutic indication. Aim of the Work: This study was designed to evaluate the potential protective effects of apocynin (APO) and melatonin (MEL) against GNT induced nephrotoxicity in rats. Material and Methods: This study was carried out on thirty-two adult male albino rats randomly divided into 4 equal groups, Group I (negative control), Group II (GNT group) each rat was given intraperitoneal (ip) injection of (100mg/kg) of GNT daily for 7 days, Group III (APO/GNT) each rat was given (ip) injection of (10mg/kg) APO for 7 days started before administration of GNT (100mg/kg) (ip) for another 7 days. Group IV (MEL/GNT) each rat was given (ip) injection of (15mg/kg) MEL for 7 days started before administration of MEL (15mg/kg) (ip) plus GNT (100mg/kg) (ip) for another 7 days. Results: Gentamicin induced nephrotoxicity, as rats received GNT significantly presented an increase in the 24 -h urine volume, renal somatic index (RSI), urine protein, creatinine (Cr), blood urea nitrogen (BUN), serum lactate dehydrogenase (LDH), and malondialdehyde (MDA). Furthermore, GNT induced a significant decrease in the body weight gain percentage, creatinine clearance (CCr), superoxide dismutase (SOD) and glutathione peroxidase (GPX) in comparison to control rats. Gentamicin also induced hypercellularity in mesangial cells and renal tubular epithelium degeneration. Either APO or MEL significantly decreased 24- h urine volume, RSI, urine protein, Cr,BUN, , LDH, and MDA additionally, either APO or MEL caused a significant increase in body weight gain percentage, CCr, SOD, and GPX when compared to GNT group, moreover, either APO or MEL showed renoprotective effects histopathologically.

Conclusion: Apocynin and melatonin can attenuate nephrotoxic effects in rats treated with GNT possibly through anti-oxidant effect and keeping normal renal tissue morphology. KeyWords: Apocynin,antioxidant,Gentamicin,melatonin,nephrotoxicity.

I. INTRODUCTION

Gentamicin (GNT) is a broad spectrum antibiotic described for treatment of serious infections. The rapid effect and affordable cost, make GNT a first line therapy for various infections (Ghaznavi et al., 2016), however, the nephrotoxicity is the most therapeutic limitations of GNT use. Gentamicin has been implicated in 30% of acute renal failure cases world- wide, specifically it is accumulated up to (5 to 50) times in renal convoluted tubules more
than in serum” (Abdel-Raheem et al., 2009 and Moreira et al., 2016). Therefore, a therapeutic approach to renal protection upon and before GNT therapy would have critical important consequences clinically. Several mechanisms could be related to GNT nephrotoxicity as, ischemia in renal tissue, inflammation, lipid peroxidation, and depletion of kidney antioxidant enzymes (El-Kashef et al., 2016).

Apocynin is extracted from (Himalayan herb Picrorhiza kurrooa). Apocynin is an inhibitor of the NADPH-oxidase complex (NOX) present in the cell membrane (Altintas et al., 2013). “Reactive oxygen species (ROS) are produced in the mitochondrial respiratory chain during cellular respiration and oxidative reactions, and catalyzed by (NOX), which is considered as the major enzyme used by NADPH to generate ROS and one of its efficient inhibitors is APO” (Wang et al., 2021). Apocynin can attenuate fibrosis in the models of heart failure that accompany myocardial infarction (Sánchez et al., 2021), APO has been described as one of the most encouraging therapies in experimental studies for neurodegenerative diseases and recently has been supplied commercially as a novel anti-aging agent, but its potential reno-protective effect against GNT has not been demonstrated (Abdelrahman, 2018).

Melatonin is a hormone produced by the pineal gland, bone marrow, retina, and the immune system with a major role in modulating the circadian rhythm. It also has an anti-inflammatory, immune-modulatory effect, and might have a protective effect against oxidative stress (Ahmed et al., 2021). Recently, the melatonin supplements are widely used not only to prevent insomnia, but also to attenuate the aging however, the mechanism of melatonin antioxidant activity is still unknown (Chrustek and Olszewska-Slonina, 2021).

The present study was carried out to investigate the potential protective effects of Apocynin and Melatonin against Gentamicin induced nephrotoxicity in adult male albino rats.

II. MATERIAL AND METHODS

II.1 MATERIALS

II.1.1. Drugs and chemicals

Apocynin and Melatonin (powders) were purchased from Sigma-Aldrich Co. (St. Louis, Missouri, USA), Gentamicin: (40 mg) ampoules were obtained from Alexandria Pharmaceutical and Chemical Industries Company, Egypt.

II.1.2. Experimental animals

The study was carried out on thirty -two adult male albino rats with average weight of (200-230 gm). They were obtained from the animal house of Zagazig Scientific & Medical Research Center of the Faculty of Medicine, Zagazig University. The study had been designed in the Faculty of Medicine, Zagazig University. Ethical consideration of experimental animals were according to recommendations of “Principles of Laboratory Animal Care” (NIH publication no. 85-23, revised 1985). The Rats were randomly divided into four equal groups (n=8) as:

-Group I: (negative control group) to determine the basic values of tested parameters and did not receive any solvent or drug.

-Group II: (GNT) group each rat injected by GNT (100mg/kg), (ip) for 7 days.

-Group III: (APO/GNT) group each rat injected by APO (10mg/kg) (ip) was dissolved in drinking water at a concentration of (1mg/ml) for 7 days then APO (10mg/kg)(ip) dissolved in drinking water at a concentration of (1mg/ml) plus GNT (100mg/kg)(ip) for another 7 days.

-Group IV: (MEL/GNT) group, each rat injected by MEL (15mg/kg)(ip) for 7 days dissolved in drinking water at a concentration of (1mg/ml) then MEL (15mg/kg)(ip) dissolved in drinking...
water at a concentration of (1mg/ml) plus GNT (100mg/kg)(ip) for another 7 days. The doses of gentamicin, melatonin, and apocynin were chosen according to the previous dose–response studies of Karahan, et al. (2005), Ghaznavi et al. (2016) and Abdelrahman (2018) respectively.

II.2. Methods:
Each rat was weighted at the start and at the end of experiment, weight difference was calculated then weight gain percentage was calculated by dividing the weight difference of each rat on its initial weight. After the last dose, rats were immediately kept in metabolic cages individually, for a collection of 24-h urine samples. Then urine samples were centrifuged for 15 min and kept at -20 °C until analyzed, then, by using ether, the rats were anesthetized. Blood samples were collected and allowed to clot, Then serum samples were produced through centrifugation and stored frozen for biochemical measures, then rats were sacrificed by cervical dislocation. The kidneys were rapidly and carefully removed, rinsed with saline, then weighed for calculation of renal somatic index (RSI). RSI = (the weight of kidney (gm))/(the final weight of the body (gm)× 100). The right kidneys were homogenized in phosphate buffer centrifuged, and then the supernatants were used for the biochemical measures.

II.2.1. Biochemical measurements in the serum:
The Serum creatinine (Cr) and (BUN) levels were assessed according to Bartels et al.(1972) and Fawcett and Scott,(1960) respectively. The Serum creatinine and BUN were expressed as milligrams per deciliter (mg/dl). In addition, the lactate dehydrogenase (LDH) was assessed according to method of Henry et al., (1960) and expressed as a unit per liter (U/L).

II.2.2. Biochemical measurements in urine:
The urine (Cr) and protein levels were measured according to method of Bartels et al.(1972) and Daughaday et al.(1952) respectively, and expressed as milligrams per deciliter and milligrams per day, respectively. “the Creatinine clearance (CCr) was used to assess the glomerular filtration rate, calculated using this formula, CCr = Cr in urine (mg/dl) × urine flow (ml/min)/Cr in serum (mg/dl).” Urine flow was calculated by dividing urine volume of 24 h by 1440 (the number of minutes in day) and expressed in milliliters per minute.

II.2.3. Biochemical measurements in kidney tissue homogenate
The end product of lipid peroxidation (MDA) levels were assayed through monitoring of thiobarbituric acid reactive substance, and the biomarkers of oxidative stress (SOD and GPX) activities were determined in renal homogenate according to Ohkawa et al. (1979) Sun et al. (1988) and Paglia and Valentine (1967), respectively and expressed as nanomoles per gram tissue (nmol/g. tissue), units per gram tissue (U/g.tissue) and unit per mg protein (U/mg prot).

II.2.4. Histological examinations:
Samples from right kidneys were routinely processed, embedded in paraffin blocks and sectioned at 5µ thick sections. Sections were stained with haematoxylin and eosin and examined by light microscope (Bancroft and Stevens, 1996).

II.2.5. Statistical analysis
The results are reported as mean ± SEM. The statistical analyses were performed using one-way analysis of variance (ANOVA) by SPSS software (version 20). Group differences were calculated by post hoc analysis using Tukey-Kramer test.

III. RESULTS:
III.1. Weight gain percentage

No deaths were observed in all groups. A decrease in weight gain percentage caused by GNT was significantly (p < 0.05) observed on comparison to percentage of weight gain in control group, while Pretreatment with either APO or MEL significantly (p < 0.05) attenuated the GNT-induced decrease in weight gain percentage, (Table 1).

III.2. Renal somatic index

(Table 1) shows a significant (p < 0.05) increase in RSI in GNT group on comparison to the control group. while pre and concomitant treatment with either APO or MEL significantly lowered the RSI when compared to GNT group.

III.3. 24 h urine volume

Gentamicin caused a significant (p < 0.05) increase the 24-h urine volume on comparison to the control group. The 24-h urine volume was significantly (p < 0.05) decreased in APO/GNT or MEL/GNT group when compared to GNT-treated rats (Table 1).

III.4. Biochemical results:

(Table 2) shows a significant (p < 0.05) increase in urine protein, serum, BUN and CR in GNT group on comparison to control group. however Pre and concomitant administration of either APO or MEL significantly (p < 0.05) attenuated the GNT-induced increase in these parameters. GNT caused a significant (p < 0.05) decrease in (CCr) when compared to the control group while The CCr was significantly (p < 0.05) increased in either APO/GNT or MEL/GNT group on comparison to GNT-related rats (Table 2).

(Figure 1,2) show that GNT significantly (p < 0.05) increased LDH and MDA on comparison to control rats while, Pre and concomitant injection with either APO or MEL in rats produced a significant (p < 0.05) decrease in LDH and MDA, when compared with (GNT) group. (Figure 3,4) show that GNT significantly (p < 0.05) decreased SOD and GPX when compared to control rats, while Pre and concomitant administration of either APO or MEL significantly (p < 0.05) increased SOD and GPX on comparison to GNT-treated rats. Furthermore, MEL/GNT group showed decrease in MDA and increase in SOD and GPX, however that decrease not reached statistically difference when compared to APO/GNT group yet.

III.4. Histopathological results:

Light microscopic examination of (H&E) stained renal sections of control groups showed normal glomeruli and normal renal tubules with normal lining epithelium (Figure 5). Light Microscopic examination of (H&E) stained renal sections of rats received (100mg/kg GNT ip for 7 days (group II), revealed prominent hypercellularity in mesangial cells with degeneration of renal tubular epithelium (Figure 6), while administration of either Apo or Mel 7 days before combined administration of either APO or MEL with GNT showed normal glomeruli and normal renal tubules with normal lining epithelium (Figure 7,8) respectively.
Table (1): Statistical comparison between tested groups regarding (weight gain percentage, renal somatic index and 24 h urine volume) by one-way ANOVA followed by Tukey-Kramer multiple comparisons post hoc test.

| Groups         | Percentage of weight gain% | renal_somatic index (gm) | 24 hours urine_vol (ml/100 g body weight) |
|----------------|----------------------------|--------------------------|------------------------------------------|
| negative control | 6.99 ± 0.79                | 0.49 ± 0.01              | 2.85 ± 0.17                               |
| GNT            | 1.95 ± 1.68 (a)            | 0.62 ± 0.03 (a)          | 5 ± 0.33(a)                               |
| APO /GNT       | 5.65 ± 0.87(b)             | 0.54 ± 0.03(b)           | 3.58 ± 0.35(b)                            |
| MEL/GNT        | 4.51 ± 1.19(b)             | 0.57 ± 0.03(b)           | 3.61 ± 0.26(b)                            |

GNT: gentamicin (100 mg/kg, i.p.); APO: apocynin (10 mg/kg, i.p.); MEL: melatonin (15mg/kg i.p.); SEM: standard error of the mean; ANOVA: analysis of variance. Data are expressed as mean ± SEM, n = 8. (a): p < 0.05, significantly different from control group; (b): p < 0.05, significantly different from GNT group.

Table (2): Statistical comparison between tested groups regarding (kidney functions tests) by one-way ANOVA followed by Tukey-Kramer multiple comparisons post hoc test.

| Group        | serum creatinine (mg/dl) | CCr (ml/min) | BUN (mg/dl) | Proteinuria (mg/day) |
|--------------|--------------------------|--------------|-------------|---------------------|
| negative control | 0.57 ± 0.03              | 0.28 ± 0.01  | 27.54 ±1.38 | 92.85 ± 2.82        |
| GNT          | 1.14 ± 0.12(a)           | 0.18 ± 0.01(a)| 47.34 ± 4.06(a) | 141.21 ± 11.53(a) |
| APO/GNT      | 0.95 ± 0.14(b)           | 0.21 ± 0.02(b)| 39.45 ± 4.48(b) | 121.3 ± 8.42(b)    |
| MEL/GNT      | 0.82 ± 0.09(b)           | 0.25 ± 0.02(b)| 35.41 ± 2.57(b) | 119.79 ± 7.04(b)   |

GNT: gentamicin (100 mg/kg, i.p.); APO: apocynin (10 mg/kg, i.p.); MEL: melatonin (15mg/kg i.p.). CCr: creatinine clearance; BUN: blood urea nitrogen; SEM: standard error of the mean; ANOVA: analysis of variance. Data are expressed as mean ± SEM, n = 8.

(a): p < 0.05, significantly different from control group; (b): p < 0.05, significantly different from GNT group.
Figure (1). Comparison of protective effects of APO and MEL against GNT-induced increase in serum LDH activity of rats. 
GNT: gentamicin, APO: apocynin; MEL: melatonin; SEM: standard error of the mean; ANOVA: analysis of variance. Data are expressed as mean ± SEM, n = 8. *p < 0.05, significantly different from control group. **p < 0.05, significantly different from GNT group.

Figure (2): Comparison of protective Effects of APO and MEL against GNT-induced increase in renal MDA activity of rats. GNT: gentamicin; APO: apocynin; MEL: melatonin. SEM: standard error of the mean; ANOVA: analysis of variance. Data are expressed as mean ± SEM, n = 8. *p < 0.05, significantly different from control group; **p < 0.05, significantly different from GNT group.
Figure (3): comparison of protective Effects of APO and MEL against GNT-induced decrease in renal SOD activity of rats. GNT: gentamicin. APO: (apocynin). MEL: (melatonin). SEM: standard error of the mean; ANOVA: analysis of variance. Data are expressed as mean ±SEM, n = 8; *p < 0.05, significantly different from control group; **p < 0.05, significantly different from GNT group.

Figure (4): comparison of protective Effects of APO and MEL against GNT-induced decrease in renal GPX activity of rats. GNT: gentamicin. APO: apocynin. MEL: melatonin. SEM: standard error of the mean; ANOVA: analysis of variance. Data are expressed as mean±SEM, n = 8; *p < 0.05, significantly different from control group; **p < 0.05, significantly different from GNT group.
Figure (5): A photomicrograph of a section in the kidney from a rat of control group showed normal glomeruli (g) and normal renal tubules (t) with normal lining renal tubular epithelium (H&E x200).

Figure (6): A photomicrograph of a section in the kidney from a rat of Gentamicin group: showed mesangial hypercellularity (arrow with degeneration of renal tubular epithelium (double arrows) (H&E x200).

Figure (7): A photomicrograph of a section in the kidney from a rat of (Apo/GNT) group, GNT: gentamicin; APO: apocynin showed normal glomeruli (double arrows) and normal renal tubules with normal lining renal tubular epithelium (arrow) (H&E x200).

Figure (8): A photomicrograph of a section in the kidney from a rat of MEL/GNT group: MEL: melatonin; GNT: gentamicin showed normal glomeruli (double arrows) and normal renal tubules with normal lining renal tubular epithelium (arrow)(H&E x200).
IV. DISCUSSION

This study shows that either APO or MEL could protect and forming GEN-iron couples, which can be the first step in GEN-induced ROS formation (Priuska and Schacht, 1995). Lipid peroxidation is a proximal event in the cascade of GNT-induced nephrotoxicity. This is supported by an increase in MDA level, an index of lipid peroxidation, and decreases in antioxidant enzyme activities such as, SOD and GPX (Parlakpinar et al., 2005).

Either APO or MEL has a safe drug profile in the animal studies and utilized for long time without any signs of toxicity (Yu et al., 2008, Rodriguez et al., 2004 and Allegra et al., 2003).

In this work, either APO or MEL pretreatment caused a significant increase in the body weight gain percentages and a significant decrease in the RSI when compared to the GNT group, that is may attributed to either APO’s or MEL’s anti-inflammatory effects plus reversing histopathological changes of kidney upon GNT treatment (Kim et al., 2012 and Ghaznavi et al., 2016). These results are against GNT-induced nephrotoxicity, that is presented by APO or MEL ability to attenuate elevation in the RSI, serum Cr, BUN, urine protein, 24-h urine volume, LDH, and renal MDA induced by GNT, in addition to attenuation of GNT induced decrease in CCr, renal SOD and GPX.

Gentamicin is an effective aminoglycoside antibiotic however; toxic effects of this category limit its therapeutic indication (Mohamed and Shenouda, 2021). In this work, GNT injection for 7 days at dose of (100mg/kg ip) caused a significant decrease in the body weight gain percentages of rats and a significant increase in the RSI in comparison to control group. This restricted weight gain may be due to injury in renal tubules directly, causing incapability of reabsorbing water by tubules, that led to dehydration and decrease in body weight (Ali et al., 2003).

The increase in weight of kidney in rats treated with GNT may be due to inflammation and edema (Erdem et al., 2003). Gentamicin is absorbed through the renal tubular cells by anion transportation. Gentamicin accumulation in tubular cells finally leads to morphological changes, and increase in (ROS) in the kidney promoting inflammatory process (Ahmadvand et al., 2020). The body weight loss and increase in the kidney weight after administration of gentamicin to rats were also noted in other studies (Elkashef et al., 2016 and Nasri et al., 2013).

This study shows that administration of GNT to rats induced a significance increase in Cr, BUN, and urine protein in comparison to control group. Moreover, GNT induced a significant decrease in CCr in comparison to control group, these results indicate both glomular and tubular damage.

The decrease in glomerular filtration rate results in a reduction of the kidney’s ability to filter Cr and the waste product of nonprotein is accumulated. Moreover, both urea and the urine protein also are increased which may pose to tubular dysfunction that impaired reabsorptive capacity of tubular protein (Abdelrahman, 2018) these results were also demonstrated in other studies (Christo et al., 2011 and El-kashef et al., 2016).

In the present study, GNT caused a significant increase in serum LDH on comparison to control groups that is may be
attributed to GNT induced renal inflammatory responses (Quiros et al., 2011). That increase in LDH upon GNT treatment also showed in El-Kashefe et al. (2015) study.

In this work, GNT induced a significant elevation in MDA and a significant decrease in SOD and GPX on comparison to control rats indicating GNT role in induction of oxidative stress. GNT is capable of generation of (ROS), and reactive nitrogen species (RNS). Several studies reported that GEN induces ROS formation by launching iron from mitochondria of renal cortex consistent with studies of Luchetti et al. (2010) and Connell et al. (2011).

In this study either APO or MEL pre and concomitant treatment with GNT caused a significant decrease in Cr, BUN, and urine protein and a significant increase in CCr when compared to GNT alone treatment. The ameliorative effect of APO on these kidney toxicity indicators may be attributed to the antioxidant effect and protection against both glomerular and tubular injury as “APO is a selective NOX inhibitor, which generates superoxide. The superoxide anion is a central ROS molecule and converts to more toxic reactive free radicals” (Altintas et al., 2013).

These findings come in line with Chirino et al., 2008 and Ghaznavi et al., 2016. The ameliorative effect of MEL may be also due to antioxidant effects. Several studies have demonstrated that the antioxidant effect of melatonin may be due to “its direct ability to detoxify free radicals and indirect antioxidant effect by increasing the activity and expression of antioxidative enzymes”. (Allegra et al., 2003 and Rodriguez et al., 2004).

In the present study Treatment of rats with either APO or MEL attenuated the increase in serum LDH caused by GNT; this may be due to the anti-inflammatory effects of either APO or MEL (Dam et al., 2012 and Ghaznavi et al., 2016).

In this study, either APO or MEL could protect the kidney against GNT induce oxidative stress, either APO or MEL induced a significant decrease in MDA and a significant increase in SOD and GPX on comparison to GNT rats. However in this study MEL is more efficient than APO in decreasing MDA and increasing both SOD and GPX yet, that effect difference not reached statistical difference, that may need longer duration and larger sample size to be fully investigated.

Apocynin attenuated cisplatin-induced nephrotoxicity through antioxidant-induced effect (Chirino et al., 2008). Additionally, APO prevented the increase in oxidative stress in lung after bleomycin exposure (Gutterridge et al., 1995).

“Melatonin also is an efficient for scavenging of ROS and RNS. Melatonin induces gene expression and activates multiple antioxidative enzymes as, GPX, and SOD (Reiter et al., 2003), SOD decreases free radical cellular damage that caused by producing H2O2, SOD converts H2O2 to water and oxygen; GPX also metabolize H2O2 to water (Lee et al., 2012).

Mitochondria has a major role in free radical generation. Superior ability of melatonin to accumulate into the mitochondria makes it an effective anti oxidant to treat oxidative stress related pathologies conversely to other
antioxidants with poor mitochondrial penetration (Raza and Naureen 2020).

The role of melatonin in scavenging (ROS), reducing (MDA) levels and promoting the production of antioxidant enzymes (SOD) and catalase (CAT) also documented by Tu et al.,(2021).

Many studies indicate that melatonin is able to attenuate the renal functional injury made by oxygen free radicals induced by cyclosporine in rats (Mun and suh, 2000) It has also decreased the renal oxidative insult caused by aluminum and lead (Mahieu et al., 2009) it has been shown that melatonin had protected against hamster kidney model of estradiol-induced DNA damage (Karbownik et al.,2001).

Histopathological investigation of the kidney of control rats showed normal glomeruli and normal renal tubules with normal lining renal tubular however ,GNT-induced hypercellularity in mesangial cells with degeneration of renal tubular epithelium in GNT group of rats, on other hand rats of either APO/GNT group or MEL/GNT group respectively showed normal glomeruli and normal renal tubules with normal lining renal tubular epithelium, these results point out the protective role of either APO or MEL against renal injury and reversing histopathological change induced by GNT through previous proven antioxidant and antiinflammatory effect . these findings also documented by Abdelrahman,(2018) and lee et al.,(2012).

V. CONCLUSION:

Either APO or MEL has a reno protective effect against GNT induced nephrotoxicity possibly through antioxidant effect (persevering antioxidant marker ) and improving renal tissue morphology.

VI. RECOMMENDATION:

Further studies should be conducted on the human to confirm the efficacy of novel antioxidants (Apocynin and Melatonin) as curative and protective agents against nephrotoxicity of Gentamicin.

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Conflicts of Interest:
The authors declared that they have no conflicts of interest.

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مقارنة الأثر الوقائي المحتمل لعقارى الأبثيونين والميلاتونين ضد التسمم الكلوي المصاحب

الل geliان البيضاء

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المقدمة البحث:
يدع عقار الجنتاميسين كم ائا ا العاتاا التسييت دم  لع العدئخ ال يلك ئلبم ياقع التسييتو الب خ
التصاحب لتنائل  مم اهو التحاذيل التع تحد مم است دام .

هدف البحث:
الهدف مم هذا الاحث ه
مقارنة الآثار الوقائيه المحتمله لعقارى الأبثيونين والميلاتونين ضد التسمم الكلوي المصاحب
لعقاري المصابين في الجرذان البيضاء البالغه.

طريقة البحث:
أجرى البحث على أثاثين وثلاثين جزء أبيض باللغة مثلى للإنسان.

المجموعة الأولي (مجموعة الضابطة السالبة): المجموعة الثانية (الجيناتاميسين) تم حق كل جرذ بريتانيا 100 مجم من الأثاثين بالحقن البوليني لمدة سبع أيام ثم حق كل جرذ بريتانيا 10 مجم من الأثاثين لمدة سبع أيام أخرى. المجموعة الثالثة (مجموعة الميلاتونين/ جنتاميسين) تم إعطاء كل جرذ 15 مجم / كجم من الميلاتونين بالحقن البوليني لمدة سبع أيام ثم حق كل فار بريتانيا 100 مجم من الميلاتونين مع 5 مجم من الجنتاميسين لمدة سبع أيام أخرى.

النتائج:
لقد تسياب الجنتاميسين لع ح ت التسييتو الب خ بالاللان التع تنائلت  حيث كان هناك زيادة ذو دلالة إحصائية في كل من (مؤشر وزن الكلى بالنسبة للجسم، حجم البول المجمع في 4 ساعات، الزيادة في الأثاثين بالبول) التي تغيرت بشكل معين من البداية إلى النهاية. يلاحظ أن الجنتاميسين يؤدي إلى تقليل معدل التأكسد في النسيج الولائي ضد التأكسد مع الدلالة الإحصائية في كل من (مؤشر وزن الكلى بالنسبة للجسم، حجم البول المجمع في 4 ساعات، الزيادة في الأثاثين بالبول).

الخلاصة:
تتلد ين تنائ آي من الأثاثين أو الميلاتونين تسبب في انخفاض ذو دلالة إحصائية في كل من (مؤشر وزن الكلى بالنسبة للجسم، حجم البول المجمع في 4 ساعات، الزيادة في الأثاثين بالبول) بالمقارنة مع مجموعة الفأر. كما أن تتأثر سيكون (مؤشر وزن الكلى بالنسبة للجسم، حجم البول المجمع في 4 ساعات) بالفأر ويكشف ذلك عن تأثير الفأر على تأثير الفأر على تأثير الفأر على تأثير الفأر على تأثير الفأر على تأثير الفأر على تأثير الفأر على تأثير الفأر.

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