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Research paper

The possible protective effects of saccharum officinarum l. (sugar cane) juice co-supplementation on gentamicin induced acute renal toxicity in adult albino rats

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Abstract

Gentamicin (GM) is an effective and probably the most commonly used aminoglycosides antibiotic, however the risk of causing nephrotoxicity limits its use. In the present study, the possible protective effects of Saccharum officinarum L. (sugar cane juice) on gentamicin induced acute oxidative renal injury in experimental rats were investigated. Twenty adult albino rats were randomly allocated into four groups (5 rats in each) and treated once daily for a period of 7 days as follows; group A being the negative control and was injected intraperitoneal with normal saline, group B (sugar cane juice treated group) was given sugar cane juice orally at a dose of 15 ml/kg/day, group C (GM treated group) and group D (sugar cane juice + GM treated group) were the experimental groups and were injected intraperitoneal with (80 mg/kg/day GM) & (sugar cane juice 15 ml/kg/day orally + 80 mg/kg/day GM intraperitoneal) respectively. By the end of the experiment, the biochemical kidney functions tests (urinary cystatin C and kidney injury molecule-1, blood urea and creatinine) were investigated. Also, oxidative stress parameters (malondialdehyde [MDA] level, superoxide dismutase [SOD] & glutathione peroxidase [GPX] enzymatic activity) in renal tissue were evaluated. Histopathological examinations of kidney were done to assess the degree of renal protection induced by sugarcane juice, Gentamicin treated rats showed; marked significant rise in the biochemical kidney functions tests and lipid peroxidation (MDA) parameter in renal tissues, along with significant reduction in renal tissue antioxidant enzymatic activity of both SOD & GPX. However, co-administration of sugar cane juice in group D leading to marked reduction in previous biochemical markers and MDA levels together with significant elevated renal SOD &GPX enzymatic activity which nearly tend to return to normal values. The histopathological examination of groups A and B showed normal kidney structure which was deranged in group C (GM treated), whereas group D showed significant recovery in histological structures. Gentamicin induced acute renal injury and oxidative damage. Co-administration of sugar cane juice may reduce this damage by improving antioxidant defense and tissue integrity in experimental albino rats.

Keywords: *Histopathology; Gentamicin; Nephrotoxicity; Oxidative Stress and Sugar Cane Juice.*

1. Introduction

The kidney is a vital organ in both health & disease. Many environmental pollutants and chemicals, including drugs alter its functions (Mahmood and Waters, 1994). Acute renal failure (ARF) refers to a sudden & almost reversible loss of renal functions, which develops over a period of days or weeks. Among the causes of acute renal failure is acute tubular necrosis which occurs due to ischemia or nephrotoxic drugs such as cisplatin & gentamicin (Jain et al., 2013). The capacity of the kidney to extract and concentrate toxic substances by highly specialized cells together with its high blood flow rate which nearly account 21% of cardiac output, make it a common target for toxic xenobiotics (Martínez-Salgado et al., 2007).

Aminoglycosides are traditional antibacterial medications that inhibit protein synthesis. They are used, either alone or in combination with cell membrane-active compounds, for the treatment of severe and life-threatening infectious diseases (Mingeot-Leclercq et al., 1999; Choi et al., 2011).

Among all of the aminoglycosides, gentamicin (GM) is considered the most commonly used & studied type. However, the ability of GM to cause nephrotoxicity and ototoxicity remain major problems for its effective long term clinical use (Khan et al. 2009; Awodele et al., 2015). The specificity of GM to produce nephrotoxicity is apparently related to its accumulation and deposition in the renal proximal convoluted tubules (Laurent et al., 1999), and the oxidative stress damage caused by generation of reactive oxygen species (Tavafi et al., 2012). Previous studies concluded that the natural antioxidants from medicinal plants and herbs can prevent GM induced nephrotoxicity (Seckiner et al., 2014).

Saccharum officinarum L. (sugarcane) is a tall grass native to tropical regions of Asia (Pal et al., 2006). In Ayurvedic medicine, sugarcane is used to treat bronchitis, cough, anemia, constipation, urinary tract infections, loss of milk production as well as general debility (Kadam et al., 2008). Also, it has been documented to possess anticancerous, antiproliferative and antioxidant properties which attributed to high polyphenolics compounds predominantly flavonoids (Genovese and Lajolo, 2002; Maurício Duarte-Almeida et al., 2006; Pallavi et al., 2012).

Hence, the current study was aimed to evaluate the possible protective effect of Saccharum officinarum L (sugar cane) juice on nephrotoxicity induced by gentamicin.

2. Materials and methods

2.1. Preparation of sugar cane juice

Sugar cane juice was prepared according to method descried by Yasmin et al. (2010) and Khan et al. (2015). Sugar cane stems were cut into equal lengths, washed with a plain water to remove any contaminants, then a three-roller power crusher was used to extract the juice. The fresh juice then filtered by a muslin cloth & poured in a sterilized container (without addition of ice) and pasteurized at 85–90 °C for five minutes with pH adjusted to ≤4.00. After that all the waxy material was removed and the juice filled in sterilized glass bottles with air tight plastic caps without addition of any conventional food preservative. Bottles were stored in the refrigerator at 3–4 °C.

2.2. Animals

Twenty adult albino rats weighing 180-200 g were obtained from the animal breeding house, faculty of veterinary medicine, Moshtohor, Banha university. The animals were maintained on stock diet and kept under fixed appropriate conditions of housing and handling. All experiments were carried out in accordance with the research protocols according to the Ethics Committee of Scientific Research, Faculty of Medicine, Banha University which followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.3. Experimental design and treatments

Two weeks after acclimatization, all 20 rats were equally divided into 4 groups of 5 rats each. The animals of Group A served as negative control and injected with normal saline, intraperitoneal for 7 days. Group B received an oral administration of sugarcane juice at a dose of 15 ml/kg/day for 7 days and served as sugar cane juice group. Group C was injected intraperitoneal with gentamicin sulfate (GM) (Memphis Company for Pharmaceutical and Chemical Industries, Cairo, Egypt) 80 mg/kg/day of for consecutive 7 days and served as GM treated group. Group D was injected with GM intraperitoneal at a dose of 80 mg/kg/day and orally administered sugar cane juice at a dose of 15 ml/kg/day for 7 days concomitantly with GM and served as. GM + sugar cane juice group.

2.4. Sampling

2.4.1. Urine Samples:
At the 7th day of the experiment, the rats were placed individually in metabolic cages to collect of 24 h urine for estimation of urinary nephrotoxic markers; cystatin C & kidney injury molecule-1 (KIM-1)
2.4.2. Blood Samples:
At the end of the experimental period, all animals were sacrificed under anesthesia. Blood samples were rapidly obtained from their hearts by 5ml syringes and kept in a dry sterilized centrifuge tube to coagulate for 30 min at room temperature, then centrifuged at 3000 rpm for 15 min (4°C) for separation of the serum. The clear non-hemolyzed supernatant sera was quickly removed and stored at 20°C as aliquots for the quantitative estimation of both blood urea and serum creatinine.
2.4.3. Tissue Samples:
Immediately after scarification, both kidneys were rapidly removed and divided equally into two longitudinal sections. One half was stored at -80°C till preparation of tissue homogenate for estimation of malondialdehyde (MDA) as a marker of lipid peroxidation (LPO), and assaying activity of renal antioxidant enzymes: glutathione peroxidase (GPX), and superoxide dismutase (SOD). The other half was preserved in neutral 10% formaldehyde solution then processed for histopathological analysis.

2.5. Biochemical analysis

2.5.1. Renal function parameters

Measurement of urinary cystatin C and kidney injury molecule-1 (KIM-1) were done using (Rat cystatin C ELISA Kit, My BioSource. Com & Rat KIM-1 ELISA kit, tech@cusabio.com respectively)), following the instructions of the manufacturer (Pirttila et al., 2005).
Serum creatinine concentration was measured by creatinine- colorimetric method using the commercial kit (Jaffe. Colorimetric- Kinetic, Spin react Company, Spain), following the instructions of the manufacturer. Blood urea was quantitatively estimated by urease- colorimetric method using the (urease-GLDH, Kinetic UV from Spin react Company, Spain (Burtis et al., 2007).

2.5.2. Kidney oxidant/ antioxidant parameters

Malondialdehyde(MDA) was assessed as a marker of lipid peroxidation in renal tissue by measuring thiobarbituric acid reactive substances (TBARS) according to Chattopadhyay et al., (2003) principle. Measurement of MDA depends on the determination of thiobarbituric acid reactive substances (TBARS) with thiobarbituric acid to produce a pink colored complex, which can be read colorimetrically at 532 nm.
The activity of renal tissue superoxide dismutase (SOD) was assayed according to the method of Kakkar et al. (1984), based on the inhibition of formation of NADH-phenazinemethosulfate – nitrobluetetrazolium-formazon. The color formed at the end of the reaction can be extracted into butanol and measured at 560nm.
The method proposed by Reddy et al. (1995) was adopted for assaying the activity of Glutathione peroxidase (GPX). In the presence of hydrogen donor pyrogallol or dianisidine, peroxidase converts H2O2 to H2O and O2. The oxidation of pyrogallol or dianisidine to a colored product called purpurogalli can be followed spectrophotometrically at 430nm.

2.6. Histological study

Histological studies were done according to Bancroft and Layton (2019). At the end of the experimental period, kidney specimens were rapidly excised and small pieces were preserved and fixed in 10 % neutral formalin solution. The fixed specimens were trimmed, dehydrated in ascending grades of alcohol, cleared in xylene. They were embedded in paraffin boxes, sectioned at 4-6 microns' thickness and stained with Hematoxylin and Eosin (H&E). The histopathological changes were evaluated in several sections from each group using a light microscope.

2.7. Statistical analysis

Using the SPSS (Statistical Package for the Social Sciences, version 16.0 software, Spss Inc., Chicago, ILL Company) computer program, the obtained data were statistically analyzed and the results were presented as (mean ± SD). Data were tested for normality using Shapiro-Wilks test assuming normality at P>0.05, it was proved to be normally distributed, so The differences between the mean values among groups were determined by analysis of variance (ANOVA). Significant ANOVA was followed by post hoc multiple comparison using Bonferroni test to detect the significant pairs. P≤0.05 was considered significant. Means with different letters are significantly different.

3. Results

1) Biochemical Study

Sugar cane juice treated group demonstrated normal biochemical (cystatin C, kidney injury molecules-1 [KIM-1], blood urea and serum creatinine) and oxidative stress parameters (malondialdehyde [MDA)], the enzymatic activity of both superoxide dimutase [SOD] & glutathione peroxidase [GPX]) in comparison with control values. However, Injection of rats with 80 mg/kg /day gentamicin (GM) once daily for 7 consecutive days caused a marked significant increase in previous urinary and blood nephrotoxic parameters (cystatin C, KIM-1, blood urea and creatinine) in addition to malondialdehyde (MDA) level in renal tissue together with a significant reduction in the enzymatic activity of renal tissue superoxide dimutase (SOD) & glutathione peroxidase (GPX) when compared with control values. On the contrary, addition of sugar cane juice to GM in group D lead to markable reduction in urinary and blood nephrotoxic parameters and a significant elevation in the enzymatic activity of both superoxide dimutase (SOD) & glutathione peroxidase (GPX) in renal tissue as compared with GM treated rats (table 1).

2) Histopathological Study

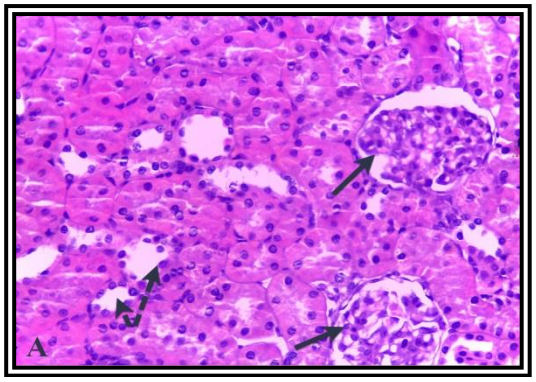
Histopathological examinations of sections from the rats' kidneys for evaluation of nephrotoxic effects of GM and the protecting role of co- administration of sugar cane juice were shown in (Fg.1).

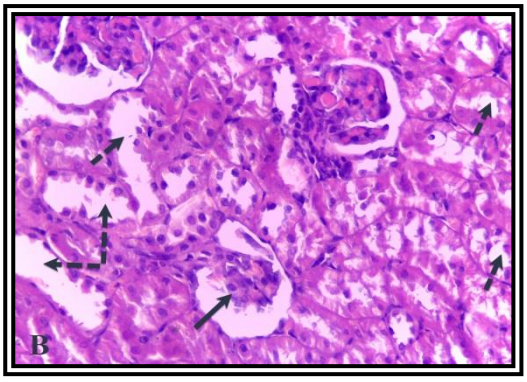
Table 1: Evaluation of the Effects of Sugar Cane Juice Oral Administration on Nephrotoxic Markers and Renal Tissues Oxidative Stress Parameters in Gentamicin Induced Acute Renal Toxicity in Experimental Rats (N=5) by ANOVA One-Way Statistical Comparison Test

Groups	Control	Sugar cane juice	Gentamicin	Sugar cane juice + Gentamicin	ANOVA	P
cystatin C (ng/ml)	8.0± 0.524	8.26±0.861	20.2^{abc} ±5.84	11.20 ±1.75	17.2	<0.001 (HS)
KIM-1 (ng/ml)	6.52±1.07	6.86±0.87	16.6^{abc} ±3.76	9.64 ± 1.24	24.8	<0.001 (HS)
Urea (mg/dl)	22.2±1.30	21.8±2.16	46.6^{ab} ± 9.12	37.8^{ab} + 6.45	22.7	<0.001 (HS)
Creatinine (mg/dl)	0.49±0.043	0.47±0.047	1.98^{abc} ± 0.797	1.01 ±0.257	14.2	<0.001 (HS)
MDA (nmol MDA/g tissue)	47.4±5.92	47.8 ±5.18	78.9^{ab} ± 8.41	71.9^{ab} ± 9.61	23.6	<0.001 (HS)
SOD (U/mg protein)	56.7+5.90	58.6+4.45	32.1^{abc} +4.58	50.7+7.69	21.7	<0.001 (HS)
GpX (nmol/mg tissue)	31.1+1.38	30.7+1.11	12.9^{abc} +2.45	24.7^{ab} +4.07	55.6	<0.001 (HS)

Different letter within the same row indicates significant differences (p<0.05) between experimental groups for the same blood & tissue chemical parameter.

Highly significant P (<0.001). KIM-1 = kidney injury molecules-1. MDA = malondialdehyde, SOD = superoxide dimutase, GPX= glutathione peroxidase.





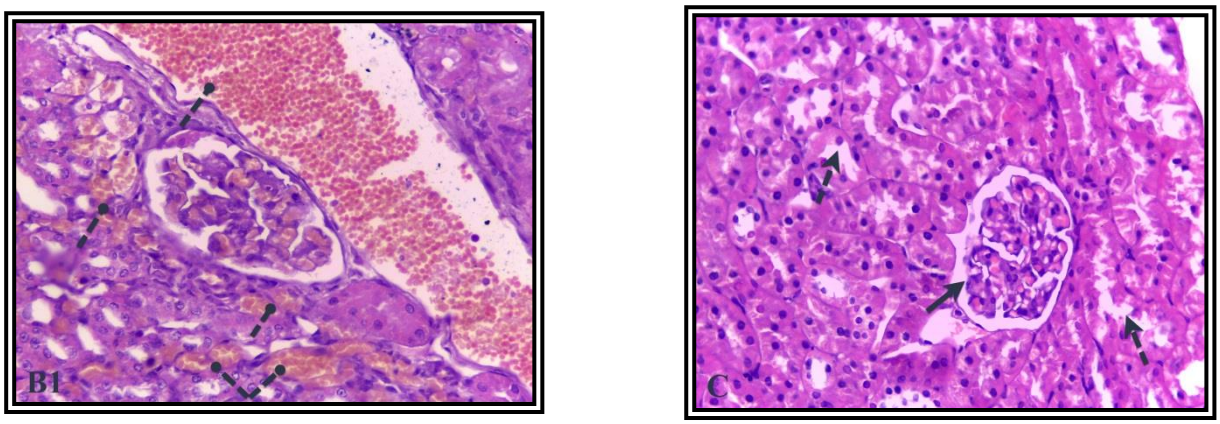


Fig. 1: A Photomicrograph Sections of the Studied Rat's Renal Tissues Demonstrated Renoprotective Effect of Sugar Cane Juice on Histopathological Changes of Renal Tissue in Rats Injected with GM. All [Hematoxylin and Eosin (H& E) X 400]. (A) Renal Tissue of Control Rats Revealed Normal Renal Corpuscle Contained Tuft of Blood Capillaries and Glomeruli & Surrounded by Two Layers of Bowman's capsule. The Renal Tubules Consisted of Proximal Convoluted Tubules Lined with Large Pyramidal, the Distal Convoluted Tubules Lined with Simple Cuboidal Cells). (B & B1) Renal Tissue Of GM Treated Rats Showing Marked Tubular Vacuolar Degeneration with Widening in Their Lumen (⇢), Sever Glomerular Atrophy (→) in Form of Retraction of Glomerular Tuft & Widening of Bowman's Space), Marked Congestion& Hemorrhage (⇢). (C) Renal Tissue of Rats Treated with Sugar Cane Juice Concomitantly with GM Showing Mild Tubular Vacuolar Degeneration (→) and Mild Glomerular Atrophy (⇢).

4. Discussion

Gentamicin (GM) nephrotoxicity is one of the most common causes of acute renal failure. Several studied have documented the role of oxidative stress in renal damage (Singh AP et al., 2012; Mestry et al., 2017).

In the current study, control (group A) and sugar cane juice (group B) treated rats were demonstrated normal kidney functions parameters (normal cystatin C, kidney injury molecule-1[KIM-1], serum creatinine and blood urea. Also, histopathological sections of the same both groups reflected normal renal structure.

The nephrotoxic effects of gentamicin (GM) in Group C (GM treated rats) were manifested by a marked significant elevation in the levels of cystatin C. These results were in line with other studies that revealed changes in both serum and urinary levels of cystatin C in various models of kidney injury (Parikh et al.

2010; Vaidya et al. 2008; Zhang et al. 2011). Additionally, the present study revealed marked significant increase in urinary KIM-1 in gentamicin treated group as compared to control group. These results agreed with the study of Cunha and Schor (2002) who illustrated that, in the dose-response study, urinary KIM-1 and kidney KIM-1/Havcr1 mRNA expression are very sensitive to the renal injury produced by gentamicin. These results may be explained by the fact that gentamicin accumulates in the epithelial cells of renal proximal tubules, leading to structural changes and functional impairments of the plasma membrane, mitochondria, and lysosome (Ali, 1995).

Functionally, the levels of blood urea and serum creatinine in Group C (GM treated group) in also showed markable significant increases. Similar degrees of GM toxicity have been reported by Karahan et al. (2005); Soliman et al. (2007); Moghaddam et al. (2010); Sivachandran and Hariharan (2012) who found that the gentamicin nephrotoxicity is functionally characterized by increase in serum creatinine, urea, and blood urea nitrogen. Also, Padmini and Kumar (2012) reported that treatment with gentamicin at dose level 80mg/kg. B.W. for 10 days produced an increase in the concentration of serum urea, creatinine and uric acid in rats.

Regarding oxidative stress parameters, the current work illustrate that GM-induced nephrotoxicity generates reactive oxygen species (ROS). This is manifested by a significant increase in renal tissue lipid peroxidation product malondialdehyde (MDA) level, together with a significant reduction in superoxide dismutase (SOD), and glutathione peroxidase (GPX) activities. These results are in agreement with the reports by Shalaby and Hammoda (2014) who revealed that intraperitoneal injection of GM in rats led to an increase MDA and reduction in reduced glutathione (GSH) and superoxide dismutase.

The biochemical analysis of the current research is confirmed by the histopathological examination of the renal tissue, where GM injected rats demonstrated glomerular atrophy (retraction of glomerular tuft & widening in Bowman's space), renal tubular vacuolar degeneration and hemorrhage. These results are in accordance with the findings reported by Soliman et al. (2007).

The specificity of GM to induce nephrotoxicity was attributed to its deposition and accumulation in the renal convoluted tubules and lysosomes leading to cytotoxicity (Laurent et al., 1999), The mechanism of GM induced nephrotoxicity may be explained by increased production of reactive oxygen species (ROS) leading to cytotoxicity due to oxidative stress (Tavafi et al., 2012).

However, co-administration of sugar cane juice with GM in group D revealed reno-protective effects manifested by the considerable reduction in urinary nephrotoxic markers (Cystatin-C and KIM-1), along with renal functions tests (serum creatinine & blood urea), renal lipid peroxidation product (MDA), and increased in renal antioxidants parameters (SOD & GPX) as compared to GM treated rats and these results were statistically significant. Such results were reported by Karahan et al., (2005); Farombi and Ekor, (2006); Polat et al. (2006) who studying the effects of different antioxidant compounds on gentamicin nephrotoxicity. Furthermore, the histopathological examination of renal tissue in group D (sugar cane juice + GM treated rats) revealed improvement effects of sugar cane juice and showed mild tubular vacuolar degeneration and mild glomerular atrophy.

The renoprotective effect of sugar cane juice may attributed to its high content of the antioxidant components. Polyphenolic compounds and flavonoids; apigenin, luteolin and tricin were found in the highest quantities. Bioactivity of tricin along with apigenin and luteolin have been proposed to be synergistic or additive in sugar cane juice (Duarte-Almeida et al., 2007).

5. Conclusions

Sugar cane juice possess a significant antioxidant protective effect against gentamicin induced acute renal injury and oxidative damage in experimental albino rats. However, further human studies are required to demonstrate the antioxidant effects of sugar cane juice on renal

diseases. Nevertheless, Saccharum officinarum L. (sugar cane) juice may offer an inexpensive, nontoxic and effective antioxidant intervention strategy in subjects with a risk for GM induced nephrotoxicity.

6. Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

[1] Ali BH (1995). Gentamicin nephrotoxicity in humans and animals: Some recent research. Gen Pharmacol. 26(7), 1477–1487. https://doi.org/10.1016/0306-3623(95)00049-6.

[2] Awodele O, Tomoye OP, Quashie NB, Amagon KI and Ogunnowo SA (2015). Gentamicin nephrotoxicity: Animal experimental correlate with human pharmaco vigilance outcome. Biomed J. 38(2), 125-130. https://doi.org/10.4103/2319-4170.131387.

[3] Bancroft JD & Layton C (2019). The hematoxylins and eosin. In: Bancroft's THEORYand PRACTICE of HISTOLOGICAL TECHNIQUES, (Suvarna SK, Layton C & Bancroft JD eds.), 8th ed. ELSEVIER, China, Chapter (10), pp. 126-183.

[4] Burtis CA (2007). tietz fundamentals of clinical chemistry. By: Burtis CA, (Ashwood ER and Bruns DE eds.). 6th edition, St. Louis: Saunders Elsevier, pp.29-150.

[5] Chattopadhyay A, Biswas S, Bandyopadhyay D, Sarkar C & Datta AG (2003): Effect of isoproterenol on lipid peroxidation and antioxidant enzymes of myocardial tissue of mice and protection by quinidine. Mol Cell Biochm. 245 (1-2), 43-49. https://doi.org/10.1023/A:1022808224917.

[6] Choi JJ, Moffett BS, McDade EJ & Palazzi DL (2011). Altered gentamicin serum concentrations in obese pediatric patients. Pediatr Infect Dis J. 30 (4), 347–349. https://doi.org/10.1097/INF.0b013e3181ff023e.

[7] Cunha MA & Schor N (2002): Effects of gentamicin, lipopolysaccharide, and contrast media on immortalized proximal tubular cells. Ren Fail. 24(6), 687–690. https://doi.org/10.1081/JDI-120015662.

[8] Duarte-Almeida JM, Negri G, Salatino A, de Carvalho JE & Lajolo FM (2007). Antiproliferative and antioxidant activities of a tricin acylated glycoside from sugarcane (Saccharum officinarum) juice. Phytochemistry. 68(8), 1165–1171. https://doi.org/10.1016/j.phytochem.2007.01.015.

[9] Farombi EO & Ekor M (2006). Curcumin attenuates gentamicin-induced renal oxidative damage in rats. Food Chem Toxicol. 44 (9), 1443-1448. https://doi.org/10.1016/j.fct.2006.05.005.

[10] Genovese MI & Lajolo FM (2002). Isoflavones in soy-based foods consumed in Brazil: levels, distribution and estimated intake. J Agric Food Chem. 50 (21), 5987–5993. https://doi.org/10.1021/jf0202990.

[11] Jain A, Nahata A & Singhai AK (2013). Effect of Tephrosia purpurea (L.) leaves on gentamicin-induced nephrotoxicity in rats. Sci Pharm. 81(4). 1071-1087. https://doi: 10.3797/scipharm.1302-09. https://doi.org/10.3797/scipharm.1302-09.

[12] Kadam US, Ghosh SB, Strayo D, Suprasanna P, Devasagayam TPA & Bapat VA (2008). Antioxidant activity in sugarcane juice and its protective role against radiation induced DNA damage. Food Chemistry. 106 (3), 1154–1160. https://doi.org/10.1016/j.foodchem.2007.07.066.

[13] Kakkar P, Das B & Viswanathan PN (1984). A modified spectrophotometric assay of superoxide dismutase. Indian J Biochem Biophys. 21(2), 130- 132. http://hdl.handle.net/123456789/19932.

[14] Karahan I, Atessahin A, Yilmaz S, Ceribasi AO, Sakin F (2005). Protective effect of lycopene on gentamicin-induced oxidative stress and nephrotoxicity in rats. Toxicology. 215 (3), 198-204. https://doi.org/10.1016/j.tox.2005.07.007.

[15] Khan SA, Priyamvada S, Farooq N, Khan S, Wasim KM, Yusufi ANK (2009). Protective effect of green tea extract on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney. Pharmacol Res. 59: 254-262. https://doi.org/10.1016/j.phrs.2008.12.009.

[16] Khan SW, Tahir M, Lone KP, Munir B & Latif W (2015). PROTECTIVE EFFECT OF SACCHARUM OFFICINARUM L. (SUGAR CANE) JUICE ON ISONIAZID INDUCED HEPATOTOXICITY IN MALE ALBINO MICE. J Ayub Med Coll Abbottabad. 27(2), 346-350.

[17] Laurent G, Kishore BK & Tulkens PM (1999). Aminoglycoside-induced renal phospho-lipidosis and nephrotoxicity. Biochem Pharmacol. 40 (11), 2383-2392. https://doi.org/10.1016/0006-2952(90)90078-Y.

[18] Mahmood I & Waters DH (1994). Comparative study of uranyl nitrate and cisplatin induced renal failure in rate.Eur J Drug Metab Pharmacokinet.19(4), 327-336. https://doi.org/10.1007/BF03188859.

[19] Martínez-Salgado C, López-Hernández FJ & López-Novoa JM (2007). Glomerular nephrotoxicity of aminonucleosides. Toxicol Appl Pharmacol. 223(1), 86-98. PubMed] [Google Scholar]. https://doi.org/10.1016/j.taap.2007.05.004.

[20] Maurício Duarte-Almeida J, Novoa AV, Linares AF, Lajolo FM & Inés Genovese M (2006). Antioxidant Activity of Phenolics Compounds from Sugar Cane (Saccharum officinarum L.) Juice. Plant Foods Hum Nutr. 61(4), 187–192. https://doi.org/10.1007/s11130-006-0032-6.

[21] Mestry SN, Gawali NB, Pai SA, Gursahani MS, Dhodi JB, Munshi R, Juvekar AR (2017). Punica granatum improves renal function in gentamicin-induced nephropathy in rats via attenuation of oxidative stress, J Ayurveda Integr Med. XXX, 1-9. https://doi.org/10.1016/j.jaim.2017.09.006.

[22] Mingeot-Leclercq MP, Glupczynski Y & Tulkens PM (1999). Aminoglycosides: activity and resistance. Antimicrob Agents Chemother.43(4):727-37. https://doi.org/10.1128/AAC.43.4.727.

[23] Moghaddam AH, Javaheiri M, Nabavi SF, Mohdavi MR, Nabavi SM & Ebrahimzadeh MA (2010). Protective role of pleurotus porrigens (AngelHs wings) against gentamicin-induced nephrotoxicity in mice. Eur Rev Med Pharmacol. 14(12), 1011-1014.

[24] Padmini MP & Kumar JV (2012). A histopathological study on gentamycin induced nephrotoxicity in experimental albino rats. IOSRJDMS.1 (1), 14-17. https://doi.org/10.9790/0853-0111417.

[25] Pal R, Vaiphei K, Sikander A, Singh K & Rana SV (2006). Effect of garlic on isoniazid and rifampicin-induced hepatic injury in rats. World J Gastroenterol. 12(4), 636–639. https://doi.org/10.3748/wjg.v12.i4.636.

[26] Pallavi R, Elakkiya S, Tennety SSR & Suganya Devi P (2012). Anthocyanin analysis and its Anticancer Property from Sugarcane (Saccharum officinarum L) Peel. IJRPC. 2(2), 338–345.

[27] Parikh CR, Lu JC, Coca SG & Devarajan P (2010). Tubular proteinuria in acute kidney injury: a critical evaluation of current status and future promise. Ann Clin Biochem. 47 (Pt4), 301–312. https://doi.org/10.1258/acb.2010.010076.

[28] Pirttila TJ, Manninen A, Jutila L, Nissinen J, Kalviainen R, Vapalahti M, Immonen A, Paljarvi L, Karkola K, Alafuzoff I, Mervaala E & Pitkanen A (2005). Cystatin C expression is associated with granule cell dispersion in epilepsy. Ann Neurol. 58(2), 211-223. https://doi.org/10.1002/ana.20545.

[29] Polat A, Parlakpinar H, Tasdemir S, Colak C, Vardi N, Ucar M, Emre MH & Acet A(2006). Protective role of aminoguanidine on gentamicin-induced acute renal failure in rats. Acta Histochem. 108 (5) ,365-371. https://doi.org/10.1016/j.acthis.2006.06.005.

[30] Reddy KP, Subhani SM, Khan PA & Kumar KB (1995). Effect of light and benzyl adenine and dark - treated graving rice (Oryza sativa) leaves - changes in peroxidases activity. Plant Cell Physiol. 26, 987 – 994. https://doi.org/10.1093/oxfordjournals.pcp.a077018.

[31] Seckiner I, Bayrak O, Can M, Mungan AG & Mungan NA (2014). Garlic supplemented diet attenuates gentamicin nephrotoxicity in rats. Int Braz J Urol. 40(4), 562-567. https://doi.org/10.1590/S1677-5538.IBJU.2014.04.17.

[32] Shalaby MA & Hammoda A A (2014). Evaluation of nephroprotective and diuretic effects of parsley and turmeric herbs on gentamicin nephrotoxic rats. World journal of pharmacy and pharmaceutical sciences, 3(12), 1729-1744. https://doi.org/10.5455/jice.20131130022009.

[33] Singh AP, Junemann A, Muthuraman A, Jaggi AS, Singh N, Grover K, Dhawan R.(2012). Animal models of acute renal failure. Pharmacol Rep. 64(1):31-44. https://doi.org/10.1016/S1734-1140(12)70728-4.

[34] Sivachandran M & Hariharan P (2012). Renoprotective effect of terminalia chebula on gentamicin induced toxicity in rats. Int J Vet Sci.1 (2), 76-79.
[35] Soliman KM, Abdul-hamid M & Othman AI (2007). Effect of carnosine on gentamicin induced nephrotoxicity. Med Sci Monit. 13(3), BR73-83.
[36] Tavafi M, Ahmadvand H & Toolabi P (2012). Inhibitory effect of olive leaf extract on gentamicin-induced nephrotoxicity in rats. Iran J Kidney Dis. 6 (1), 25-32.
[37] Vaidya VS, Ferguson MA & Bonventre JV (2008). Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol. 48, 463–493. https://doi.org/10.1146/annurev.pharmtox.48.113006.094615.
[38] Yasmin A, Masood S, Abid H (2010). Biochemical analysis and sensory evaluation of naturally preserved sugarcane juice. Pak J Biochem Mol Biol. 43 (3), 144–145.
[39] Zhang Z, Lu B, Sheng X & Jin N (2011). Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis. 58(3), 356–365. https://doi.org/10.1053/j.ajkd.2011.02.389.