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Efficacy of *Garcinia pedunculata* Fruit Extract in Preventing Drug-Induced Nephrotoxicity

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Abstract: The fruit rind of *Garcinia pedunculata* (GP) is a significant medicinal herb. Despite the numerous medicinal benefits attributed to this species, there is a lack of pharmacological research conducted on it. The objective of this study was to establish a standardised method for analysing the outer layer of the fruit of *Garcinia pedunculata*. Additionally, the study intends to assess the effectiveness of the fruit's ethanol extract in protecting the kidneys. This study performed macromicroscopic, physico-chemical, and preliminary phytochemical analyses using standardised pharmacopoeial processes. Gentamicin (80 mg/kg b wt. was given orally for 10 days. Also gentamicin (80 mg/kg b wt. and *Garcinia pedunculata* (200, 400 and 600 mg/kg b wt.) was given orally to other groups of rat for 10 days. The assessment of nephrotoxicity involved the examination of serum biochemical, antioxidant, and histological alterations in the kidney. The administration of gentamicin (GM) notably increased the levels of urea, creatinine, and lipid peroxidation in kidney tissue as compared to the control group. The gentamicin has caused necrotic alterations in the tubular epithelium, edematous alterations in the interstitial tissue, and localised infiltration of cells. The treatment of GP extract greatly reduced these modifications and effectively corrected the histological changes caused by gentamicin. The administration of gentamicin led to the deterioration of renal function indicators and histological alterations in the kidneys of rats. The co-administration of GM with GP mitigated the adverse effects of GM-induced nephrotoxicity and resulted in a significant reduction of all parameters in rats treated with gentamicin.

Keywords: *Garcinia pedunculata*, Nephrotoxicity, Gentamycin, Necrotic, Urea, Creatinine, Lipid peroxidation, BUN

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Introduction

On a daily basis, the kidneys perform the task of filtering around 200 litres of fluid from the bloodstream. This process enables the elimination of toxins, metabolic wastes, and excessive ions through urine, while simultaneously reabsorbing necessary elements back into the circulation (Debnath *et al.*, 2010). Similar to a water purification facility that ensures the drinkability of a city's water supply and manages waste disposal, the kidneys are often undervalued until they experience dysfunction, resulting in the contamination of bodily fluids. The kidneys are the primary organs responsible for excretion, although the lungs and skin also play a role. The kidneys not only carry out excretory tasks, but also play a crucial role in regulating the volume and chemical composition of the blood. They ensure a good balance between water and salts, as well as between acids and bases (Jayaprakasha *et al.*, 2006; Mundugaru *et al.*, 2014a).

Nephrotoxicity, a prevalent renal ailment, arises from the exposure of the body to a medicine or toxin. Several therapeutic agents can have detrimental effects on the kidney, leading to acute renal failure, chronic interstitial nephritis, and nephrotic syndrome (Meher *et al.*, 2016). This is due to the growing number of powerful therapeutic drugs, such as aminoglycoside antibiotics, NSAIDs, and chemotherapeutic agents that have been incorporated into the treatment options in recent times. Nephrotoxicity can be induced by exposure to chemical reagents such as ethylene glycol, carbon tetrachloride, sodium oxalate, as well as heavy metals like lead, mercury, cadmium, and arsenic. Early identification of the disease and discontinuation of the causative medications typically constitute the sole required treatment. Nephroprotective agents are compounds that have protective properties against nephrotoxicity (Mundugaru *et al.*, 2014a).

Garcinia pedunculata Roxb., a member of the Clusiaceae family, is a prevalent tree found in the deep woods of Northeast India and the Andaman Nicobar Islands. The desiccated pericarp of the

mature but not fully ripe fruits (FRGP) possesses significant therapeutic properties and is incorporated into the dietary practices of tribes residing in Assam and the North-Eastern states of India (Shalaby and Hammoda, 2014). It is employed in the treatment of several conditions including fever, cough, bronchitis, asthma, rheumatoid arthritis, obesity, and as a cardiogenic medication. The examination of phytochemicals in GP has demonstrated the presence of pedunculol, garcinol, cambogin3, and (-)-hydroxyl citric acid. The GP extracts obtained from hexane and chloroform shown antioxidant activity, free radical scavenging activity, and significant antimutagenic properties, however, the hexane extract exhibited higher activity compared to the chloroform extract (Jayaprakasha *et al.*, 2003).

Medicinal plants have healing capabilities as a result of the existence of diverse intricate chemical compounds. Ancient texts have recommended different medicines for treating kidney diseases. Concomitant use of diverse medicinal herbs with nephroprotective properties with various nephrotoxic drugs may mitigate their toxic effects (Keservani and Sharma, 2018). Renal failure refers to the inability of the kidneys to effectively remove nitrogenous waste products from the blood. Furthermore, there is a lack of proper regulation of fluid and electrolyte balance, coupled with endocrine dysfunction. Renal failure is primarily classified into acute and chronic renal failure. Acute renal failure is the abrupt and typically reversible decline in kidney function that occurs within a few days or weeks. Acute renal failure can be caused by various factors, with the most prevalent being acute tubular necrosis, which is responsible for approximately 85% of cases. Acute tubular necrosis primarily arises from either ischemia or exposure to toxins (Negi *et al.*, 2008).

The poisons can originate from external sources (exogenous) or from within the body (endogenous). The exogenous substances include radiocontrast agents, cyclosporine, antibiotics, chemotherapeutic agents, chemical solvents,

paracetamol, and illicit abortifacients. Chronic renal failure is a progressive and permanent decline in kidney function that often occurs over several years, resulting in the loss of the ability to excrete waste products and regulate hormones. Renal failure can be caused by various factors, including hypertension, diabetes mellitus, and antineoplastic drugs such as cyclophosphamide, vincristine, and cisplatin. In this investigation, we intend to utilise the fruit pulp extract of *Garcinia pedunculata*, which has been found to exhibit nephroprotective properties against Gentamicin-induced nephrotoxicity (Launay-Vacher *et al.*, 2008; Keservani *et al.*, 2017).

Materials and Methods

Material:

The substances used in this study include mature fruits of *Garcinia pedunculata*, ethanol, Mayer's reagent, Fehling's A and B solution, ferric chloride, sodium hydroxide, sulphuric acid, hydrochloric acid, mercuric chloride, nitric acid, gentamicin (Himedia Labs Pvt. Ltd.), ethyl ether, and formalin. All additional chemicals and reagents utilised were of analytical grade. *G. pedunculata* (GP) fruits were collected from North India in May 2022. The plant was recognised by its common name and verified by Dr. R. Murugan, a scientist from the Botanical Survey of India at Coimbatore.

Plant Extract Preparation:

The freshly harvested fruits were collected, sliced into small pieces, and dried for a duration of two weeks under direct sunshine. The dehydrated fruit was crushed into a fine powder and 150 g of it was extracted using 1000 ml of ethanol in a Soxhlet apparatus for a duration of two days. The extract was concentrated using distillation, and subsequently, the solvent was evaporated to complete dryness using a water bath (Talele *et al.*, 2021; Sable *et al.*, 2023).

Colour Study and Yield Determination:

The extract's hue was visually examined without the use of any aids. The extract's yield was determined using the following formula:

$$\% \text{ Yield} = \frac{\text{Weight of the Extract}}{\text{Weight of powder taken}} \times 100$$

Preliminary Evaluation:

The ethanolic extract of dried fruit pulp of *Garcinia pedunculata* was analysed to identify several compounds. Standard procedures were employed to ascertain the presence of phytochemicals (Nasri *et al.*, 2013; Sable *et al.*, 2023).

Animal Study:

The study utilised Wistar rats weighing between 120 and 150 g of either sex, obtained from the animals breeding station in Kerala, India. The rats were kept in polyethylene cages in a controlled conditions including 12 h of darkness and 12 h of light cycles, a temperature of 25°C, humidity ranging from 35% to 60%, and proper air circulation. They were provided with unlimited access to normal rat food and water. The animals had a two-week acclimatisation period to adapt to the environment prior to be used in the experiment. The animal experiments were carried out in accordance with the rules set by the Animal Welfare Board and with the previous approval of the animal ethical committee (Sunil Kumar *et al.*, 2016; Sable *et al.*, 2023).

Acute toxicity studies:

The acute toxicity tests were conducted in accordance with the guidelines outlined by the Organisation for Economic Co-operation and Development (OECD), specifically guideline 423. A cohort of Wistar rats, regardless of gender, was divided into three groups, each consisting of six individuals. The rats were given a single oral dose of dried fruit extract of *Garcinia pedunculata* at various dose levels of 50, 200, and 2000 mg/kg b wt. The animals were periodically monitored for any overall changes in behaviour, signs of toxicity, and mortality within the critical first four hours, as well as within 24 h and every day for the following 14 days (Gautam, *et al.*, 2015; Sable *et al.*, 2023).

Experimental design for administration of gentamicin and *Garcinia pedunculata* extract:

A total of thirty Wistar rats were randomly allocated into five groups, with each group consisting of six animals.

Group 1: Normal animals, orally received distilled water for 10 days.

Group 2: gentamicin treated rats, orally received gentamicin (80 mg/kg b wt.) for 10 days

Group 3: Rats received gentamicin (80 mg/kg b wt.) and *Garcinia pedunculata* dried fruit pulp extract (200 mg/kg b wt.) orally for 10 days.

Group 4: Gentamicin (80 mg/kg b wt.) and *Garcinia pedunculata* dried fruit pulp extract (400 mg/kg b wt.) were given to rats orally for 10 days.

Group 5: Rats orally received gentamicin (80 mg/kg b wt.) and dried fruit pulp of *Garcinia pedunculata* (600 mg/kg b wt.) for 10 days.

Biochemical Study:

Each group of rats were placed in separate metabolic cages for a duration of 24 h. On the 11th day following the therapy, urine samples were obtained from each rat. Urea and creatinine levels in urine were measured, and blood samples were obtained from rat that had fasted overnight. The samples were collected through the orbital route while the animals were under light ethyl ether anaesthesia. Urea, creatinine, uric acid, blood urea nitrogen (BUN), potassium, and sodium levels were measured in blood samples. The samples were collected in simple bottles. Subsequently, the animals from each group were euthanized. Various biochemical laboratory analysing methods were used to analyse serum and urine parameters (Bancroft and Gamble, 2008; Kumar *et al.*, 2016).

Histopathological studies:

Following the sacrifice of the animals, the rat kidneys were extirpated for histological analysis. After rinsing with normal saline, the kidney were fixed in 10% formalin. The tissues were processed by routine paraffin method. Sections were cut at 6 µm and stained with hematoxylin-eosin. It was then examined under a light microscope with the assistance of a veterinary pathologist (Kunle, *et al.*, 2006; Sable *et al.*, 2023).

Statistical Analysis:

The data are represented as the mean ± standard error of the mean (SEM). The data was analysed using one-way ANOVA, followed by Dunnett's test. A significance level of $p < 0.05$ was used to determine statistical significance.

Results

% Yield and colour identification of Plant Extract:

An ethanol extraction was performed on 150 g of powdered *Garcinia pedunculata* fruits using a Soxhlet equipment. The extraction process lasted for a duration of 48 h. The solvent was evaporated to obtain the extract devoid of any solvent. The extract's yield was 5.46% w/w. The extract exhibited a dark hue and possessed a viscous consistency.

Preliminary Study:

A qualitative phytochemical analysis was conducted on the ethanolic extract of *Garcinia pedunculata* fruits. The results revealed the presence of alkaloids, terpenoids, carbohydrates, saponins, quinines, proteins, and steroids. However, phenol, tannins (glycosides), and flavonoids were not detected.

Acute Toxicity Analysis:

Albino rats subjected to acute toxicity testing did not experience any deaths when administered a dosage of 2000mg/kg over a 14-day period. This meticulous investigation predicts that it is devoid of any form of toxicity and is completely safe. Consequently, a therapeutic lower dose of 200 mg/kg b wt., 400 mg/kg b wt., and 600 mg/kg b wt., were chosen in this investigation, representing non-mortality dose.

Effects of *Garcinia pedunculata* extract on plasma urea, creatinine, and uric acid:

The impact of different doses of *Garcinia pedunculata* on urea, creatinine, and uric acid levels was examined in rats treated with gentamicin. Gentamicin-induced renal damage resulted in substantial alterations in plasma renal markers, with urea levels increasing by 85.40%,

Table 1: Effects of GP on serum urea, creatinine, and uric acid against GM-induced nephrotoxicity in rats

Groups	Treatments	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)
1	Control	32.72 ± 2.81	0.631 ± 0.05	2.8 ± 0.14
2	Gentamicin (80 mg/kg b wt.)	58.28 ± 2.02	3.25 ± 0.06	4.41 ± 0.09
3	GM (80 mg/kg b wt.) + GP (200 mg/kg b wt.)	40 ± 0.23	2.45 ± 0.17	3.8 ± 0.09
4	GM (80 mg/kg b wt.) + GP (400 mg/kg b wt.)	35.41 ± 0.42	0.62 ± 0.06	3.03 ± 0.07
5	GM (80 mg/kg b wt.) + GP (600 mg/kg b wt.)	29.6 ± 2.61	0.36 ± 0.04	2.16 ± 0.06

Table 2: GP affects serum total protein, sodium, and potassium against GM-induced nephrotoxicity in rats

Groups	Treatments	Total protein (g/dl)	Sodium (meq/l)	Potassium (meq/l)
1	Control	7.27 ± 0.24	129.72 ± 2.88	4.8 ± 0.21
2	Gentamicin (80 mg/kg b wt.)	8.32 ± 0.24	160.22 ± 2.03	6.22 ± 0.20
3	GM (80 mg/kg b wt.) + GP (200 mg/kg b wt.)	7.81 ± 0.08	158.67 ± 2.16	7.60 ± 0.22
4	GM (80 mg/kg b wt.) + GP (400 mg/kg b wt.)	8.71 ± 0.25	143.6 ± 0.80	6.8 ± 0.20
5	GM (80 mg/kg b wt.) + GP (600 mg/kg b wt.)	7.32 ± 0.09	135.04 ± 2.82	4.2 ± 0.28

creatinine levels by 159.19%, and uric acid levels by 61.2% as compared to the control group. In the GP treated groups, the percentage protection for renal markers at a dose of 200 mg/kg is as follows: urea - 35.31%, creatinine - 28.62%, and uric acid - 12.61%. At a dose of 400 mg/kg, the percentage protection for urea is 39.32%, creatinine - 72.81%, and uric acid - 32.38% when compared to the toxic group. The highest percentage protection for renal markers is observed at a dose of 600 mg/kg: urea - 52.88%, creatinine - 84.62%, and uric acid - 52.14% (Table 1).

Effect of Garcinia pedunculata extract on serum sodium, potassium, and total protein:

The impact of different doses of *Garcinia pedunculata* on total protein, sodium, and potassium levels was investigated in rats treated with gentamicin. Gentamicin-induced renal damage resulted in significant alterations in serum total protein with a 47.49% increase, sodium levels with a 21.43% increase, and potassium

levels with a 82.8% increase as compared to the control group. In the GP treated groups, the percentage protection for renal markers at a dose of 200 mg/kg was as follows: total protein - 7.01%, sodium - 6.31%, and potassium - 7.99%. At a dose of 400 mg/kg, the percentage protection for total protein was 18.38%, for sodium - 14.23%, and for potassium - 7.25%. The maximum percentage protection for total protein, sodium, and potassium was observed at a dose of 600 mg/kg, with values of 34%, 19.33%, and 53.71%, respectively (Table 2).

Effects of Garcinia pedunculata extract on BUN:

A study was conducted to investigate the impact of different doses of *Garcinia pedunculata* on blood urea nitrogen levels in rats that were intoxicated with gentamicin. The administration of gentamicin resulted in a substantial alteration in BUN levels, with a 97.42% difference compared to the control group. The blood urea nitrogen protection percentages for the GP treated groups were

Table 3: GP effects on BUN, urine urea, and urine creatinine against GM-induced nephrotoxicity in rats

Groups	Treatments	BUN (mg/dl)	Urine urea (mg/dl)	Urine creatinine (mg/dl)
1	Control	13.77± 0.82	63.6 ±0.82	12.61± 0.31
2	Gentamicin (80 mg/kg b wt.)	24.56± 2.34	105.89± 2.21	32.62± 0.39
3	GM (80 mg/kg b wt.) + GP (200 mg/kg b wt.)	23.18 ±0.89	86.22 ±0.89	28.6± 0.69
4	GM (80 mg/kg b wt.) + GP (400 mg/kg b wt.)	20.79± 0.56	80.49 ±0.81	19.41± 0.91
5	GM (80 mg/kg b wt.) + GP (600 mg/kg b wt.)	15.85± 0.89	61.72± 2.88	11.60± 0.88

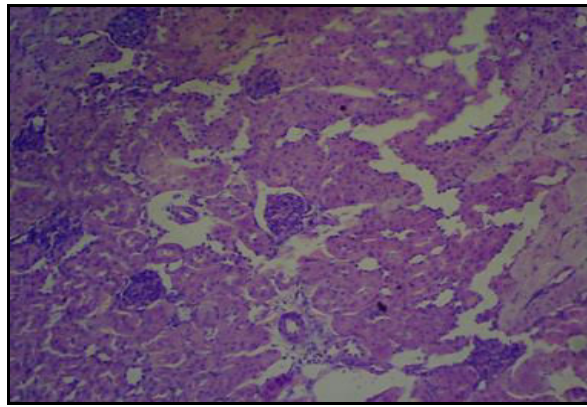


Fig. 1: Kidney of control rat.

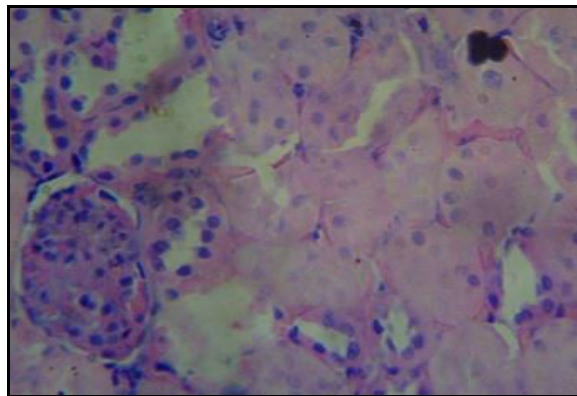


Fig. 2: Kidney of gentamicin-treated rat.

12.51% at a dose of 200 mg/kg and 21.71% at a dose of 400 mg/kg, compared to the gentamicin group. The highest blood urea nitrogen protection percentage was seen at a dose of 600 mg/kg, with a value of 41.45% (Table 3).

Urine urea and creatinine effects of Garcinia pedunculata extract:

The impact of different doses of *Garcinia pedunculata* on urine urea and creatinine levels in rats treated with gentamicin was investigated. The administration of gentamicin resulted in a substantial alteration in urine urea levels, with an increase of 70.92%, and creatinine levels, with an increase of 172.71%, as compared to the control

group. The GP treated groups showed a percentage protection of 20.28% for urea and 12.91% for creatinine at a dose of 200 mg/kg. At a higher dose of 400 mg/kg, the percentage protection increased to 25.58% for urea and 41.95% for creatinine when compared to the toxic group. The maximum protection was observed at a dose of 600 mg/kg, with urea showing a percentage protection of 43.21% and creatinine showing a percentage protection of 66.75% in urine (Table 3).

Histopathological Observations:

The nephrotoxicity was observed in gentamicin treated group which include tubular degeneration, desquamation, and necrosis, as well as glomerular blood vessel congestion and edoema (control-Fig.1; Gentamicin treated – Fig. 2). Administration of GP extract at doses of 200, 400, and 600 mg/kg body weight improved the adverse effects observed in the kidney.

Discussion

The use of herbal medicines that are derived from natural sources and are manufactured from a variety of medicinal plants has gained popularity in the field of health care. It is well known that herbal medicines are composed of more than one plant or active constituent, and that the therapeutic efficacy of these medicines is not derived from a single collection of compounds. It is possible that some of these compounds work in conjunction with one another to change the bioavailability and effectiveness of the active ingredient (Ramesh and Reeves, 2003). The bioactive molecule found in the medical product is considered to be safe, and because of this, it is frequently used for self-medication. However, the potential health advantages of the substance are mostly unknown. Nevertheless, there is a flaw in the toxicological data that pertains to certain combinations. It is therefore necessary to conduct an acute toxicity study in order to determine the range of dosages and the clinical symptoms that are likely to be induced by the test substance in the animal that is being investigated. In addition to that, it is a device that may be used to determine

the therapeutic index of a lead compound. *Garcinia pedunculata* fruit extract at a dose of 2,000 mg/kg, caused no morbidity or mortality in rats during the course of the observation period of fourteen days. Based on the findings of this acute investigation, it can be concluded that it does not contain any form of toxicity and that it is completely safe (Ramesh and Reeves, 2004).

Within the realm of chemotherapy, nephrotoxicity is a side effect that is generally undesirable. The vast majority of chemotherapy medications are directed against pathways that are necessary for cell division. There have been a number of studies that have demonstrated the significance of reactive oxygen metabolites in the renal damage that is caused by gentamicin. It is common for the medications to accumulate in the renal cortex, which is reliant on their affinity for the kidneys as well as the kinetics of the drug trapping process (Sharma and Kumar, 2011). Nephrotoxicity is typically connected with this buildup. It has been demonstrated beyond a reasonable doubt that aminoglycoside antibiotics, and in particular gentamicin, which is the molecule that is used most frequently, are nephrotoxic. According to the findings of a number of studies, oxygen free radicals are thought to play a significant role as intermediaries in the process of gentamicin-induced renal failure. Nephrotoxicity that is induced by gentamicin is characterised by elevated levels of urea, creatinine, uric acid, total protein, sodium and potassium in serum as well as urine urea and creatinine (Basist *et al.*, 2022). Additionally, severe proximal tubular necrosis and renal failure were found to be significantly increased in rats that were treated with only gentamicin. The administration of GP to rats that had been treated with GM resulted in a decrease in the levels of urea, creatinine, uric acid, total protein, sodium, and potassium in the blood, as well as in the levels of urea and creatinine in the urine. It appears from these data that renal function has substantially improved. GM treatment to rats resulted in a typical pattern of nephrotoxicity, which was characterized by a significant rise in serum BUN levels. It has been

shown that the levels of blood urea nitrogen decreased when GP was administered to rats that had been treated with GM (Venkataiah *et al.*, 2013).

Some researchers have reported histopathological findings that demonstrate structural alterations in renal tissue caused by aminoglycoside antibiotics like GM. The histopathological examination of kidney in rat that were treated with GM revealed desquamation, necrosis, and degeneration in the tubules, as well as congestion in the blood vessels and enlargement in the glomerulus. This was in contrast to the control groups (Mundugaru *et al.*, 2014b). Tubercular necrosis, karyopycnosis, and glomeruli displaying mesangial matrix expansion were observed in the groups that were administered GM and GP at a dosage of 200 mg/kg. Glomerular and tubular epithelial changes were significantly mild in groups that were treated with GM+400 mg/kg and GM+600 mg/kg. Animals that were treated with GP 400 mg/kg exhibited mild glomerular mesangial matrix expansion, mild tubular epithelial changes, and no congestion in blood vessels. On the other hand, animals that were treated with GP 600 mg/kg exhibited regeneration in tubular epithelial cells. Therefore, morphological alterations in the kidneys were caused by the administration of GM; however, these changes were often less in the treatment that included both GM and GP (Ali *et al.*, 2011; Ali *et al.*, 2017).

Conclusion

It can be concluded that renal function markers were impaired and histological alterations were observed in rats treated with gentamicin. In rats treated with gentamicin, the adverse effects of GM-induced nephrotoxicity were mitigated and all parameters showed a substantial decrease when GM and GP were administered together. One possible explanation for *Garcinia pedunculata*'s positive effects is that it improves renal function. The results demonstrated that *Garcinia pedunculata* ethanolic fruit extract protected the kidneys from gentamicin's harmful side effects. To

further develop therapeutically viable ways to treat patients with renal failure, additional research into the protective benefits of *Garcinia pedunculata* fruit extract against gentamicin-induced renal impairment is highly encouraged.

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