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Review Article

A Review Study On Carissa Spinorum's Nephroprotective Impact On Gentamicin-Induced Oxidative Nephrotoxicity

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ABSTRACT

One of the main negative effects of long-term usage of the aminoglycoside antibiotic gentamicin is nephrotoxicity. Oxidative stress, inflammation, and tubular cell necrosis are the main mechanisms via which gentamicin causes kidney injury. Traditionally, a variety of illnesses have been treated using Carissa spinarum, a medicinal plant high in flavonoids, phenolic compounds, and antioxidants. The nephroprotective potential of Carissa spinarum against oxidative nephrotoxicity caused by gentamicin is assessed in this study. When Carissa spinarum extract was administered, renal function parameters were much improved, oxidative stress was decreased, and normal kidney architecture was restored. The results indicate that Carissa spinarum's antioxidant and free-radical scavenging qualities contribute to its substantial nephroprotective efficacy. The current review was conducted to examine the nephroprotective potential of Carissa spinarum against gentamicin-induced oxidative nephrotoxicity. Gentamicin is a commonly used aminoglycoside antibiotic; however, its clinical application is frequently limited by nephrotoxicity resulting from oxidative stress and free radical generation in renal tissues. In Wistar rats, gentamicin was administered to induce experimental nephrotoxicity, as demonstrated by elevated serum creatinine, blood urea nitrogen (BUN), urea, and reduced glutathione (GSH).

INTRODUCTION

By controlling fluid balance, electrolyte concentration, and the excretion of metabolic waste products, the kidneys are essential for preserving homeostasis. A large percentage of

instances of acute kidney damage are caused by drug-induced nephrotoxicity, which is still a serious clinical issue. Although gentamicin is frequently used to treat serious Gram-negative bacterial infections, its nephrotoxicity limits its therapeutic utility. When gentamicin builds up in

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proximal tubular epithelial cells, it causes lipid peroxidation, excessive ROS generation, and cellular damage. Antioxidant-rich natural compounds have drawn interest as possible nephroprotective agents. The medicinal shrub *Carissa spinarum* (Family: Apocynaceae) contains flavonoids, tannins, alkaloids, saponins, and phenolic compounds with anti-inflammatory and antioxidant properties.

One of the main negative effects of long-term usage of the aminoglycoside antibiotic Gentamicin is nephrotoxicity. Reactive oxygen species (ROS), oxidative stress, inflammation, and renal tubular cell death are the main mechanisms behind gentamicin-induced renal damage, which impairs kidney function. Because of its antioxidant and therapeutic potential, the hunt for natural nephroprotective compounds has attracted a lot of interest. A common medicinal plant in traditional medicine, *Carissa spinarum* L. has a variety of pharmacological activity, including as hepatoprotective, anti-inflammatory, antioxidant, and antibacterial properties. Its ability to scavenge free radicals is attributed to the presence of flavonoids, phenolic compounds, alkaloids, tannins, triterpenoids, and saponins, according to phytochemical studies. The pathogenesis of gentamicin-induced oxidative nephrotoxicity is summarized in this article, which also emphasizes *Carissa spinarum*'s possible nephroprotective function.

By lowering lipid peroxidation, boosting endogenous antioxidant defenses, minimizing inflammatory mediators, and maintaining renal histoarchitecture, the plant's bioactive components may lessen kidney damage. According to experimental research, *Carissa spinarum* extracts restore antioxidant enzyme levels in kidney tissues and considerably enhance renal indicators such blood urea nitrogen (BUN), uric acid, and serum

creatinine. In order to prevent and treat drug-induced nephrotoxicity, *Carissa spinarum* is a viable natural treatment option. To determine its safety, effectiveness, and underlying molecular pathways, more preclinical and clinical research is necessary.

Gentamicin belongs to the class of antibiotics known as aminoglycosides. Due to their bactericidal properties, low cost, and poor resistance, these medication classes have been employed in clinical research from ancient times. This medication can be used to treat pneumonia, meningitis, and bone infections because to its broad range of bactericidal action. It can be administered topically, intramuscularly, or intravenously. Because it penetrates the placental barrier and causes abnormalities in newborns, such as hearing loss, it cannot be advised during pregnancy unless there is no other choice. Due to the poor glomerular filtration rate, it is also not recommended for elderly individuals.

It is also referred to as waka, kalivi, karunda, or avighna (Sanskrit) in India. It belongs to the family Apocynaceae.

Fruits' chemical makeup includes 64% water. 10.80 g of total sugar, 0.42 g of tannins, 1.83 mg of vitamin C, and 1.621% of minerals make up the 25.8% total soluble solid content.

Carrisone, carridone, carinol, stearic acid, oleic acid, lineolic acid, triterpene alcohol, and ursolic acid are the chemical components of roots.

Flowers' chemical makeup includes limonene, camphene, nerolidol, dipentene, canine, and α -terphenol.

Uses in pharmacology:

- Root/ethanolic extract has antiarthritic properties.



- Root/ethanolic extract's anticonvulsant properties
- Hepatoprotective properties of root and ethanolic extract
- Root/ethanolic extract's antioxidant properties
- Methanolic extract and leaves have antibacterial properties

Nephrotoxicity:

The most important organ in the human body is the kidney. It clears our bodies of harmful waste products and metabolites.

One of the most frequent kidney issues is nephrotoxicity, which happens when the body is exposed to a toxin or medication. The impairment or damage to kidney function brought on by exposure to medications, chemicals, poisons, heavy metals, or specific medical conditions is referred to as nephrotoxicity. Because they receive a significant amount of the cardiac output and are in charge of filtering and concentrating chemicals from the circulation, the kidneys are extremely vulnerable to toxic damage.

The toxic action of medications, chemicals, or other dangerous substances on the kidneys that results in structural and functional damage is known as nephrotoxicity. It makes it more difficult for the kidneys to filter blood, keep electrolyte and fluid balance, and get rid of waste products from metabolism. Nephrotoxicity can cause acute kidney injury (AKI) or, if the damage is severe or persistent, chronic kidney disease (CKD). Because they receive a significant amount of the cardiac output and actively concentrate chemicals inside the renal tubules, the kidneys are especially vulnerable to toxic damage. Antibiotics like gentamicin, nonsteroidal anti-inflammatory medications (NSAIDs), chemotherapeutic medicines, heavy metals, and environmental pollutants are common nephrotoxic substances.

Nephrotoxicity is mostly caused by the following mechanisms:

- Overproduction of reactive oxygen species (ROS) results in oxidative stress.
- Pro-inflammatory cytokine release and inflammation
- Dysfunction of the mitochondria
- Necrosis and apoptosis of tubular cells
- Ischemia and altered renal blood flow

Elevated serum creatinine and blood urea nitrogen (BUN), decreased glomerular filtration rate (GFR), proteinuria, hematuria, electrolyte imbalances, and decreased urine output are all clinical signs of nephrotoxicity.

1. Overproduction of Oxidative Stress and Reactive Oxygen Species (ROS):-

Gentamicin is one of several nephrotoxic substances that cause an overabundance of reactive oxygen species (ROS), including hydrogen peroxide, superoxide anions, and hydroxyl radicals. Oxidative stress arises when the generation of ROS surpasses the kidney's antioxidant defense capacity. Renal tissue damage results from lipid peroxidation, protein oxidation, DNA damage, and cellular malfunction.

2. Inflammation and Pro-inflammatory Cytokine Release:-

Tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) are pro-inflammatory cytokines that are released when nephrotoxic chemicals activate inflammatory pathways. By attracting inflammatory cells to renal tissues, these mediators worsen glomerular and tubular architecture and hasten the development of kidney disease.

3. Mitochondrial Dysfunction:-

For cells to produce energy, mitochondria are necessary. By weakening the electron transport chain and decreasing ATP generation, nephrotoxic



substances can interfere with mitochondrial function. Renal cell damage is largely caused by mitochondrial damage, which also raises ROS production, interferes with cellular metabolism, and starts apoptotic signaling cascades.

4. **Necrosis and Tubular Cell Apoptosis:-** In renal tubular epithelial cells, exposure to nephrotoxic substances can cause both planned cell death (apoptosis) and unchecked cell death (necrosis). Necrosis is the outcome of extreme cellular damage and energy depletion, whereas apoptosis is caused by the activation of caspases and mitochondrial pathways. Acute kidney damage may result from tubular cell loss, which impairs kidney function.
5. **Changes in Renal Blood Flow and Ischemia:-** Vasoconstriction and decreased blood flow to the kidneys are two ways that many nephrotoxic substances impact renal hemodynamics. Renal tissues experience ischemia, oxygen deprivation, and nutritional insufficiency as a result of decreased renal perfusion. Long-term ischemia exacerbates renal impairment, destroys nephrons, and lowers glomerular filtration rate (GFR).

These processes frequently take place concurrently and support one another. Nephrotoxicity develops and progresses as a result of oxidative stress, inflammation, mitochondrial malfunction, tubular cell death, and reduced renal blood flow. Antioxidant-rich medicinal plants like *Carissa spinarum* are intriguing candidates for nephroprotection since oxidative stress is thought to be the main beginning mechanism in gentamicin-induced nephrotoxicity.

***Carissa spinarum*'s Botanical Profile**

The prickly evergreen shrub *Carissa spinarum* is found in tropical India, Asia, and Africa. It is

frequently referred to as Jungle Karonda or Wild Karonda.

Classification by Taxonomy

Classification Category: Kingdom: Plantae
Family: Apocynaceae

Genus: *Carissa*

Species: *Carissa spinarum* L.

Kingdom: Plantae:- *Carissa spinarum* is a member of the Kingdom Plantae, which is made up of all multicellular, photosynthetic creatures that are referred to as plants. Members of this kingdom use photosynthesis to make their own food and contain chlorophyll.

Division: Angiosperms, or Magnoliophyta:- Because it produces flowers and seeds that are encased in fruits, this plant is categorized as an angiosperm. The largest and most varied category of plants are called angiosperms.

Class: Dicotyledons, or Magnoliopsida:- *Carissa spinarum* is a dicotyledonous plant with a taproot system, reticulate leaf venation, and two cotyledons (seed leaves).

Gentianales is the order:- Several families of plants with significant therapeutic value are found in the order Gentianales. Alkaloids, glycosides, and flavonoids are examples of physiologically active secondary metabolites that are frequently found in plants in this sequence.

Prospects for the Future:-

Carissa spinarum has intriguing antioxidant and nephroprotective qualities, however its use in clinical practice is hampered by a number of issues. While there are still few direct studies assessing its preventive benefits against



gentamicin-induced nephrotoxicity, the majority of published research has concentrated on its general pharmacological actions. Standardizing herbal formulations and comparing experimental results is further complicated by differences in extraction techniques, plant sections utilized, and phytochemical content.

Future studies should focus on identifying and isolating certain bioactive substances that have nephroprotective effects. To clarify the signaling pathways involved in antioxidant defense, inflammation control, apoptosis suppression, and renal tissue regeneration, comprehensive molecular investigations are needed. To determine the safety profile of *Carissa spinarum*, thorough toxicological evaluations, pharmacokinetic analyses, and dose-optimization tests are also required.

Its effectiveness in preventing or treating drug-induced kidney impairment should be confirmed by extensive preclinical and clinical research. Its medicinal potential may be further increased by the creation of standardized extracts and innovative drug delivery methods. *Carissa spinarum* may prove to be a useful natural nephroprotective agent for the prevention and treatment of oxidative nephrotoxicity caused by gentamicin and other renal problems with further scientific research.

Future Perspectives of *Carissa spinarum* in the Management of Gentamicin-Induced Oxidative Nephrotoxicity

Carissa spinarum has shown strong antioxidant, anti-inflammatory, and nephroprotective qualities in early research, but further research is needed to determine its therapeutic potential and clinical usefulness. Future study should focus on the following areas:

Comprehensive Preclinical Research:- Only a small amount of study has explicitly assessed *Carissa spinarum*'s nephroprotective effect against gentamicin-induced kidney injury; the majority of investigations on the plant have concentrated on its general pharmacological characteristics. Future research should evaluate the protective benefits of other plant components, such as roots, leaves, fruits, and bark, using well planned animal models. To give thorough proof of nephroprotection, these studies should look at renal biochemical indicators, oxidative stress measures, inflammatory mediators, and histological alterations.

Finding and Separating Active Phytoconstituents:- Many bioactive substances, including as flavonoids, phenolic compounds, alkaloids, tannins, saponins, and terpenoids, are found in *Carissa spinarum*. Nevertheless, the precise substances in charge of nephroprotective action are still unknown. To separate and identify active components, sophisticated phytochemical and chromatographic methods including HPLC, LC-MS, GC-MS, and NMR spectroscopy should be used. The discovery of these substances might aid in the creation of focused nephroprotective treatments.

Clarification of Molecular Processes: - It is still unclear exactly the molecular mechanisms *Carissa spinarum* uses to protect renal organs. Future research ought to look at how it affects:

- Signaling mechanisms for oxidative stress
- Activation of nuclear factor erythroid 2-related factor 2 (Nrf2)
- Production of reactive oxygen species (ROS)
- Inflammation mediated by nuclear factor-kappa B (NF-κB)
- Caspases and Bcl-2 proteins in apoptotic pathways

- Cellular energy metabolism and mitochondrial function

Herbal Extract Standardization:- Variability in phytochemical composition brought on by variations in geographic location, harvesting season, plant age, and extraction techniques is a significant obstacle in herbal medicine research. The development of standardized extracts with constant quantities of active ingredients should be the main goal of future research. Reproducibility and therapeutic dependability will be enhanced by establishing pharmacopoeial standards and quality control criteria.

Research on Dose Optimization:- Carissa spinarum's ideal nephroprotective dosage is yet unknown. Future research ought to ascertain:

- Minimum dosage that works
- Maximum dosage that is safe
- Dose-response correlation
- Treatment duration necessary for protection
- Clinical application's therapeutic window

Thorough Toxicological Assessment:- Even though Carissa spinarum has long been employed in many different medical systems, further research is needed to determine its long-term safety profile. Future research ought to assess:

- Acute poisoning
- Subacute poisoning
- Long-term toxicity
- Toxicity to reproduction
- Mutagenicity and genotoxicity
- Toxicity specific to an organ

Studies on Pharmacokinetics and Bioavailability:- The absorption, distribution, metabolism, and excretion (ADME) of Carissa spinarum's active ingredients are poorly

understood. Future pharmacokinetic research ought to ascertain:

- Oral bioavailability
- Half-life of plasma
- Distribution of tissues
- Pathways of metabolism
- Interactions between drugs and herbs

Human Subject Clinical Trials:- Most of the information that is currently available comes from research conducted on animals and in vitro. To verify Carissa spinarum's nephroprotective effectiveness and safety in people, extensive randomized controlled clinical studies are needed. Clinical research ought to evaluate:

- Parameters of renal function
- Biomarkers of oxidative stress
- Results related to quality of life
- Long-term tolerance and safety

Creation of Innovative Drug Delivery Systems:- Opportunities to improve the medicinal potential of chemicals derived from plants are presented by developments in pharmaceutical technology. Future studies might concentrate on:

- Formulations based on nanoparticles
- Systems of liposomal delivery
- Technology using phytosomes
- Formulations with sustained release

Methods of Combination Therapy:- Carissa spinarum may be studied in conjunction with antioxidants, anti-inflammatory medications, or traditional nephroprotective medicines. In patients using nephrotoxic drugs like gentamicin, such combinations may have synergistic benefits, lessen drug-induced toxicity, and improve overall therapeutic results.

Investigation of Additional Renal Conditions:- Future research should examine Carissa



spinarum's possible involvement in renal illnesses other than gentamicin-induced nephrotoxicity, such as:

- AKI, or acute kidney damage
- Chronic kidney disease (CKD)
- Diabetic kidney damage
- High-pressure nephropathy
- Renal damage brought on by ischemia-reperfusion
- Cisplatin and other nephrotoxic substances can produce drug-induced nephrotoxicity.

CONCLUSION:-

It was discovered that the *C. spinarum* extract had a highly efficient nephroprotective effect. It was because of its strong antioxidant activity, which scavenges free radicals, and its ability to inhibit the bioactivation of toxicants. According to the present research, *Carissa spinarum*'s methanolic extract is high in flavonoids and polyphenols. It aids in returning the renal histological architecture and urea and creatinine levels to normal.

It was caused by both its strong antioxidant activity, which scavenges free radicals, and its inhibiting activity of bioactivation of toxicants. Therefore, it was shown that *Carissa spinarum*'s nephroprotective properties were highly efficient against oxidative nephrotoxicity caused by gentamicin. Research on ethnobotanicals became vital as advancements in the conventional medical system became essential. Research on ethnobotanicals became important to the contemporary interest in validating and rationalizing the ethnomedicinal uses of medicinal plants as improvements in the conventional medical system became imperative. According to the present research, *Carissa spinarum*'s methanolic extract is high in flavonoids and polyphenols. It aids in returning the renal histological architecture and urea and creatinine

levels to normal. It was because of its strong antioxidant activity, which scavenges free radicals, and its ability to inhibit the bioactivation of toxicants.

Therefore, *Carissa spinarum*'s nephroprotective activities were shown to be highly efficient against oxidative nephrotoxicity caused by gentamicin. It also has detoxifying capabilities, which may have inhibited the inflammatory response to preserve normal kidney function.

A serious side effect of many medications, chemicals, and environmental pollutants is nephrotoxicity, which impairs kidney function and damages kidney structure. Reactive oxygen species (ROS) overproduction, inflammatory reactions, mitochondrial malfunction, tubular cell apoptosis and necrosis, and changes in renal blood flow are the main factors linked to the development of nephrotoxicity. Oxidative stress, cellular damage, and gradual renal impairment are caused by these interrelated pathways. Developing successful preventative and treatment approaches requires an understanding of these disease pathways. By preventing oxidative stress and maintaining normal kidney function, antioxidant and anti-inflammatory substances—especially those derived from medicinal plants like *Carissa spinarum*—may help reduce renal damage. Nephrotoxicity is a serious side effect that impairs kidney structure and function and is brought on by a variety of medications, chemicals, and environmental pollutants. Renal injury is primarily caused by oxidative stress, inflammation, and cellular damage. An established experimental paradigm for researching kidney injury and assessing possible nephroprotective drugs is gentamicin-induced nephrotoxicity. By lowering oxidative stress and reestablishing normal kidney function, medicinal plants high in anti-inflammatory and antioxidant phytoconstituents,



including *Carissa spinarum*, have shown encouraging protective benefits against renal injury. Therefore, although further preclinical and clinical research is needed to demonstrate its effectiveness and safety in people, *Carissa spinarum* may offer a promising natural therapeutic agent for the prevention and control of drug-induced nephrotoxicity.

Because gentamicin is often used to treat serious bacterial infections and has the potential to seriously harm the kidneys, gentamicin-induced nephrotoxicity is still a major clinical issue. Gentamicin's nephrotoxic effects are mainly caused by oxidative stress, excessive production of reactive oxygen species (ROS), lipid peroxidation, inflammation, mitochondrial malfunction, and renal tubular cell death. Blood urea nitrogen (BUN), high serum creatinine, and structural damage to renal tissues are all signs of decreased kidney function, which is eventually caused by these clinical processes.

Carissa spinarum's rich phytochemical makeup has made it a promising therapeutic plant with significant nephroprotective potential. Flavonoids, phenolic compounds, tannins, alkaloids, terpenoids, and saponins are among the plant's many bioactive components that have potent anti-inflammatory and antioxidant qualities. These phytochemicals have the ability to scavenge free radicals, lower oxidative stress, strengthen the body's natural antioxidant defenses, suppress inflammatory reactions, and shield kidney cells from tissue damage and apoptosis.

Carissa spinarum may successfully lessen gentamicin-induced renal damage by boosting antioxidant enzyme levels, lowering lipid peroxidation, enhancing biochemical indicators of kidney function, and maintaining normal renal histoarchitecture, according to data from pharmacological and experimental investigations.

Its therapeutic value as a natural nephroprotective agent is highlighted by its capacity to combat oxidative stress. Additionally, the plant's wide range of biological activity and historic medicinal usage indicate its potential significance in renal disease management and prevention.

Despite these promising results, there is still insufficient data at this time, and more investigation is required to completely determine *Carissa spinarum*'s nephroprotective effectiveness. The extraction and characterisation of active phytoconstituents, clarification of molecular processes, standardization of herbal extracts, dosage optimization, thorough toxicity assessment, and carefully planned human clinical trials should be the main topics of future research. These investigations will strengthen the scientific basis for its therapeutic use and make it easier to incorporate it into contemporary healthcare systems.

To sum up, *Carissa spinarum* is a valuable natural source of nephroprotective chemicals that have a great potential to prevent oxidative nephrotoxicity caused by gentamicin. The plant's cytoprotective, anti-inflammatory, and antioxidant properties may provide a safe, efficient, and economical supplementary strategy for lessening drug-induced kidney damage. Clinical validation and ongoing scientific research.

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