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Protective Effects of Herbal Drugs Against Gentamicin-Induced Nephrotoxicity: A Pharmacological Perspective

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Abstract

Gentamicin, an aminoglycoside antibiotic, is widely used to treat severe bacterial infections but is associated with nephrotoxicity, leading to acute kidney injury due to oxidative stress, mitochondrial dysfunction, and tubular cell damage. This study explores the nephroprotective potential of herbal drugs in mitigating gentamicin-induced renal toxicity. A comprehensive review of various medicinal plants with antioxidant, anti-inflammatory, and cytoprotective properties was conducted. Studies investigating the efficacy of herbal extracts and bioactive compounds in preventing or reducing gentamicin-induced nephrotoxicity were analyzed. Several herbal drugs, rich in flavonoids, polyphenols, and alkaloids, demonstrated significant nephroprotective effects by reducing oxidative stress, inhibiting inflammation, and promoting renal repair. These natural compounds exhibited protective effects by modulating key biochemical markers of kidney function, reducing histopathological damage, and restoring antioxidant enzyme levels. Herbal drugs show promising potential in counteracting gentamicin-induced nephrotoxicity through multiple protective mechanisms. Their integration into therapeutic strategies may offer a safer approach to managing drug-induced renal injury. However, further preclinical and clinical studies are necessary to confirm efficacy, establish standardized dosages, and evaluate long-term safety.

Keywords: Gentamicin, Nephrotoxicity, Herbal Drugs, Oxidative Stress, Nephroprotection, Medicinal Plants

Introduction

The kidneys are main excretory organ in human body known to perform various essential functions, including the regulation of extracellular fluid to maintain optimal hydration and acting as a primary site for the accumulation of xenobiotics, such as harmful environmental chemicals, attributed to its unique biochemical and physiological characteristics [1, 2]. With a high renal blood flow rate and a

capacity for accumulating diverse solutes during urine formation, the kidneys are particularly vulnerable to exposure to various toxic substances [3]. It is crucial in maintaining homeostasis and help to eliminate toxic metabolites from the body [4, 5]. Renal diseases are a significant health concern globally, with underlying pathological processes involves the role of oxidative stress, inflammation, apoptosis and fibrosis [6]. Nephrotoxicity can be defined as quick damage to the nephrons on exposure of harmful drugs and chemicals during filtration [7]. Some medicines can damage the kidneys in different ways, such as injuring the basic units in the kidneys that leading to inflammation or blocking the small blood vessels [8]. About 19–26% of kidney injuries in hospitals due to exposure of drugs or chemicals [9]. Some examples of the injuries include damage to the cells, changes in blood flow, inflammation, muscle breakdown, and blood clots in the fine vasculature of the kidneys [10].

Gentamicin (GM) is one of the most effective aminoglycosides against gram-negative bacterial infection in humans and animals [11]. One of the major complications associated with GM is nephrotoxicity/renal failure accounting for 10–30% of patients cases [12]. Nephrotoxicity induced by GM is a complex phenomenon characterized by an increase in plasma creatinine, urea level and severe proximal renal tubular necrosis, followed by deterioration of renal function [13]. The toxicity of aminoglycosides, including GM, is believed to be related to the generation of reactive oxygen species (ROS) in the kidneys [14].

Consequences of drug induced nephrotoxicity might include both glomerular and tubular injuries leading to acute or chronic functional changes [15]. The frequency of drug-induced nephrotoxicity is approximately 14-26% in adult populations as detailed in previous prospective cohort studies [16]. As earlier mentioned aminoglycosides used against many life threatening infections especially against gram negative bacterial infections, are one of the major cause for nephrotoxicity [17, 18]. Aminoglycosides are wide spectrum antibiotics because of certain properties such as rapid concentration dependent bactericidal effects, clinical effectiveness, a low rate of true resistance, synergism with other beta lactam antibiotics and low cost of therapy [19,20]. However, nephrotoxicity induced by them continue to be a challenge as it results in kidney damage by a direct dose dependent mechanism [21,22]. Gentamicin induced acute renal failure in rodents has proved to be an excellent working animal model for exploring the pathogenesis of drug induced acute renal failure and stimulus to develop therapeutic approaches to minimize or prevent its harmful effects in humans [23].

One of the key hallmark responsible for acute toxic effect on renal tissue is increased oxidative stress [24, 25]. Generation of reactive oxygen species (ROS) in the kidney have been implicated as the etiology for nephrotoxicity induced by aminoglycosides [26, 27]. The cellular antioxidants plays an important role in determining the susceptibility to oxidative damage which might alter in response to oxidative stress.[13] Several studies had claimed antioxidant property of drugs as crucial for their nephroprotective effects in gentamicin induced renal damage [28-31].

Gentamicin, a widely used aminoglycoside antibiotic, is highly effective against Gram-negative bacterial infections. However, its clinical use is often limited due to its dose-dependent nephrotoxicity, which leads to acute kidney injury (AKI) [11]. Gentamicin-induced nephrotoxicity is primarily associated with oxidative stress, mitochondrial dysfunction, apoptosis, and inflammatory responses in renal tubular cells. The accumulation of gentamicin in the proximal tubules results in increased production of reactive oxygen species (ROS), leading to lipid peroxidation, DNA damage, and renal dysfunction. To counteract gentamicin-induced renal toxicity, various protective strategies have been explored, including synthetic antioxidants and pharmaceutical agents. However, the increasing interest in herbal medicine has led to the investigation of plant-derived compounds as potential nephroprotective agents. Herbal drugs, rich in bioactive constituents such as flavonoids, polyphenols, alkaloids, and terpenoids, exhibit potent antioxidant, anti-inflammatory, and cytoprotective properties that can mitigate gentamicin-induced renal damage. This paper aims to explore the protective role of herbal drugs against gentamicin-induced nephrotoxicity, focusing on their mechanisms of action, efficacy, and potential clinical applications. Understanding the therapeutic potential of herbal remedies may contribute to the development of safer and more effective treatment strategies for preventing drug-induced kidney injury.

2. Structure of Nephron

The renal system is a very complex system, and is essential for normal body functions. The survival of human beings depends, to a large extent, on important functions performed by the kidneys. Some important functions of kidneys are regulating acid base balance, conserving nutrients, blood filtration, and metabolic waste products excretion and balancing solute concentration [32]. The renal system consists of 2 kidneys (produce urine), 2 ureters, 1 urinary bladder and 1 urethra [33]. The basic functioning unit of the kidney is known as nephron, and there are over one million nephrons in a single kidney. Each Nephron contains Bowman's capsule, glomerulus and renal tubules [34].

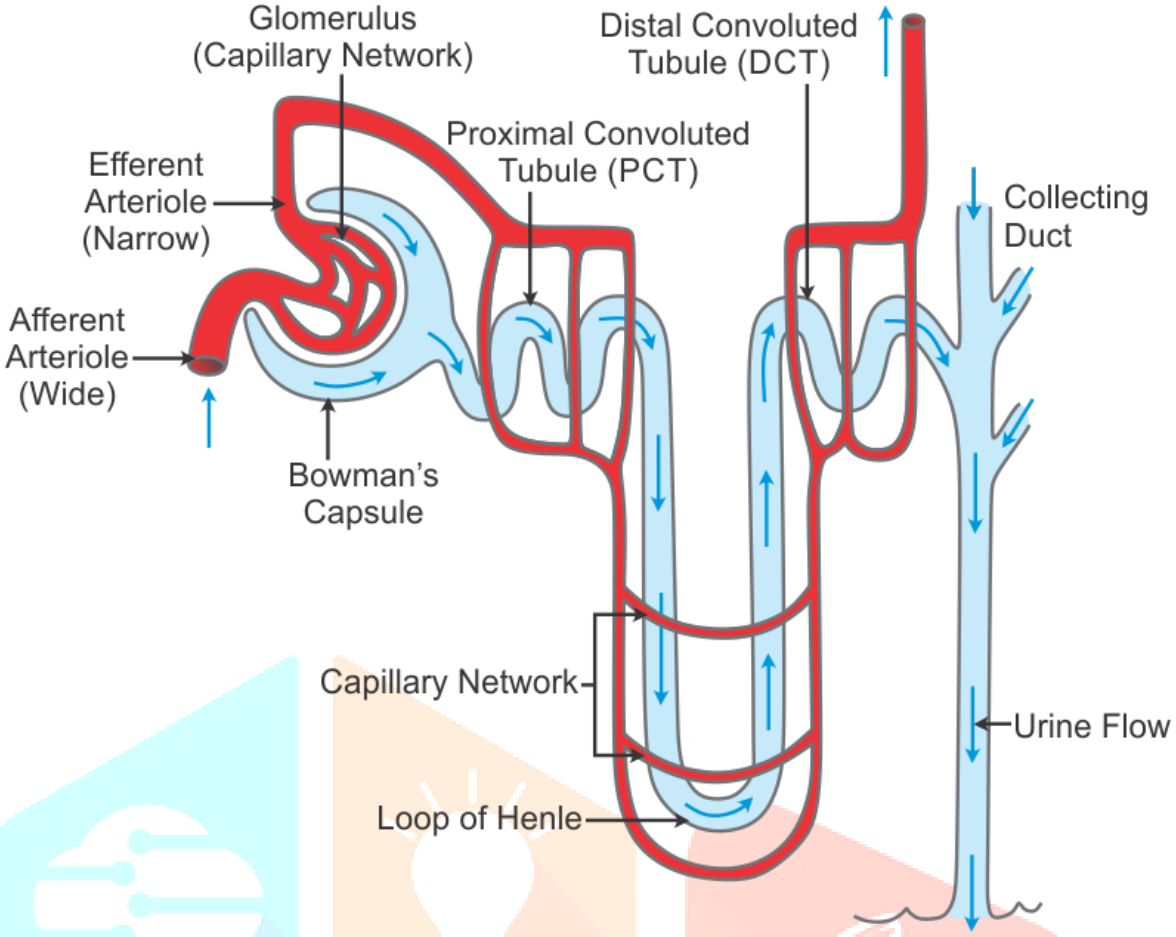

Figure No. 1. Structure of Nephron

2.1. Nephrotoxicity

The kidneys play a critical role in the metabolism and excretion of many drugs and foreign substances from the body. The functional units of the kidneys, known as nephrons, are responsible for the filtration and excretion of waste products and excess substances. Nephrotoxins are the compounds that have the potential to harm the kidneys. They can be drugs, chemicals, or environmental toxins [35,36]. These nephrotoxins can reach the nephrons through the renal arteries. Because nephrons are exposed to a high concentration of drugs and their metabolites during the filtration process, the cells of nephrons are more vulnerable to drug-related toxic responses. There is an evidence that acute kidney injury (AKI) is a serious adverse effect that has been associated with various drugs, industrial compounds, and diagnostic agents like radiocontrast media [37]. Particular drug administration-related kidney injury might result in either idiosyncratic dose-independent toxicity or cumulative dose-dependent toxicity. Damage to the renal infrastructure was indicated by changes in the normal nephron structures found in the morphological examination of the kidney biopsy induced by nephrotoxic substance. Drug induced renal failure can be further characterized depending upon the site affected with toxicity as acute tubular necrosis, interstitial nephritis, glomerulonephritis, renal vascular damage, and intrarenal obstruction. The most prevalent cause of intrarenal failure is acute tubular necrosis, which can also result from ischemia, sepsis, diabetes, and atherosclerosis, as well as from protracted exposure to nephrotoxins [38].

2.2. Prevalence

Drug induced renal failure has a high risk in older patients is about 60% responsible for AKI in which 19-26% of hospitalized cases [39]. In India, about 20% of all cases of acute kidney injury are drug induced; in which 40% are associated with aminoglycosides induced [57]. Aging is associated with the progression of AKI into CKD [58, 59].

2.3. Etiology of nephrotoxicity

There are numerous causes reported for the induction of nephrotoxicity. Some of which are describe below:

2.3.1. Ischemia/Reperfusion injury

Renal ischemia is defined as the decrease in supply of blood or oxygen to the kidneys, due to congestion or blockade of blood vessel of renal supply. A major clinical consequence that may cause AKI is renal ischemia/reperfusion injury (IRI) [60].

Increased ROS generation during reperfusion results in cell damage and apoptosis [61]. Injured and necrotic cells emit endogenous DAMPs that cause host cells to secrete chemotactic and pro-inflammatory cytokines, which causes an influx of innate immune cells The pathology of IRI-induced AKI is caused by the interaction between the innate immune response and the adaptive immune system, which involves effector cells like neutrophils, natural killer (NK) cells, dendritic cells (DCs), monocytes/macrophages, natural killer T (NKT) cells, and lymphocytes. These mechanisms result in renal tubular cell dysfunction, a decline in glomerular filtration rate (GFR), and ultimately AKI [62].

2.3.2. Diabetes mellitus

Diabetes mellitus is defined as the increased blood glucose level either due to the insulin deficiency or decreased ability of insulin to perfuse the glucose into cell. Extra glucose in bloodstream may damage the glomerular membranes as well as other parts of the nephron lead to nephrotoxicity. [56].

2.3.3. Hypertension

Hypertension is both a cause and a consequence of chronic kidney disease hypertension in the setting of chronic kidney disease has a multifactorial pathogenesis, which includes increased sympathetic nervous system and renin–angiotensin–aldosterone system activity as a result of the reduced number of functioning nephrons. The accumulation of uraemic toxins associated with deteriorating renal function stimulates renal afferent nerves, which in turn leads to reflex activation of efferent nerves driving hypertension Several studies have highlighted the role of activation of the renin–angiotensin–aldosterone system in the progression of underlying chronic kidney disease demonstrated that the renal injury seen in animal models of type 2 diabetes was associated with an increase in intrarenal levels of angiotensin II .[63]

2.3.4. Renal cell carcinoma (RCC)

Common cause of renal cell carcinoma is smoking, obesity, use of phenacetin containing analgesics, exposure to industrial waste, lack of physical activity, hypertension, and hyperglycaemia [64]. RCC risk increases with BMI elevation. This relation recommends that obesity is the major cause of malignancies to renal and cardiovascular disease [65]. Concentration of circulating vitamin D-binding protein (VDBP) also play an important role in the development of several cancers, by directly and indirectly by modifying connection between the risk of disease and circulating vitamin D [66].

2.4. Drug Induced Nephrotoxicity

Kidney damage or dysfunction by the use of specific pharmaceuticals or medications is referred to as drug-induced nephrotoxicity. Reabsorption and secretion of material mainly occur in the renal tubule [67]. and these parts of kidney are highly sensitive to drug accumulations and cause drug induced nephrotoxicity [68]. At the initial stage of drug induced nephrotoxicity the diagnosis is very difficult. The detection of nephrotoxicity is tough until the change in biomarkers is very high, like increase in serum creatinine level and increase in level of blood urea nitrogen. Drug induced nephrotoxicity is generally dose dependent [69].

The common classes of medicaments which are responsible for drug induced renal toxicity are NSAIDs, alkylating agents, antibiotics and some other drugs. These drugs mostly cause inflammation in various parts of nephrons like glomerulus, extracellular matrix and tubules (mainly the proximal tubules), after that fiberizing of kidney tissue [70-71].

The pathophysiological mechanism of drug induced nephrotoxicity is very complex and most frequently brought on by changes in intraglomerular blood flow, decreased tubular secretion, inflammatory processes and thrombotic microangiopathy [71,73]. The three basic mechanisms by which drugs cause nephrotoxicity are as follows:

1. Proximal tubule injury

2. Blockade of the tubules by crystals of drugs

3. Interstitial nephritis

2.4.1. Aminoglycosides induced nephrotoxicity

Certain of the first antibiotics to be used to treat severe infections brought on by gram negative and certain gram-positive bacteria were aminoglycosides, which were created in the 1940s [74]. The earliest aminoglycosides were discovered in the soil and came from *Micromonospora spp*. and *Streptomyces spp*. [75].

2.4.2. Cisplatin induced nephrotoxicity

One of the remarkable breakthroughs in "the war on cancer" is the drug cisplatin. Since its unintentional discovery more than 50 years ago, cisplatin was used extensively in chemotherapy [77]. The adverse effects of cisplatin, are neurotoxicity, ototoxicity, nausea and vomiting, and nephrotoxicity, on normal tissues are another important aspect that restricts its use. Numerous studies have demonstrated that cisplatin causes nuclear factor kappa (NF-k) light-chain-enhancer of activated B cells (NF-kB) to become active, and that inhibiting NF-kß transcriptional activity reduces the production of RIP1/RIP3 and pro-inflammatory mediators, which in turn reduces the severity of cisplatin-induced AKI [78]. One tactic is to create novel cisplatin analogues that are less harmful to healthy tissues and screen them for potential use. Numerous cisplatin analogues with milder side effects, such carboplatin, have been discovered in this direction [79].

2.5. Gentamicin

One of the earliest classes of antibiotics to be discovered and applied in medicine was the aminoglycoside [80]. Aminoglycoside antibiotics, which are used to treat gram-negative infections that recur often, tuberculosis, life-threatening infections in newborns, and cystic fibrosis patients, can cause acute renal injury and permanent hearing loss [81]. The mechanism to kill the bacteria by attaching to the 30s ribosomal subunit, it blocks the formation of an initiation complex with mRNA and reduces the production of bacterial proteins [82]. Gentamicin, kanamycin, and streptomycin are examples of the relatively recent class of natural compounds known as the aminocyclitol family, and it is obtained from the *micromonospora purpurea* by the process of fermentation [84, 85]. Gentamicin is a suitable alternative to treat a few common infections because of its bactericidal effectiveness against aerobic gram-negative bacteria [86]. It is useful in the treatment of various bacterial infections like infection in blood, bones, abdomen, skin, urinary tract (UT) and in meningitis. Gentamicin is often administered by parenteral methods, including systemic, ocular forms, and topical, as stomach absorption is low [87]. It can also be administered intrathecally or intravenously. There is very little binding to plasma proteins. Nephrotoxicity and ototoxicity are the frequent adverse effects of aminoglycoside. The kidney is affected by the drugs ability to enter the proximal tubule and

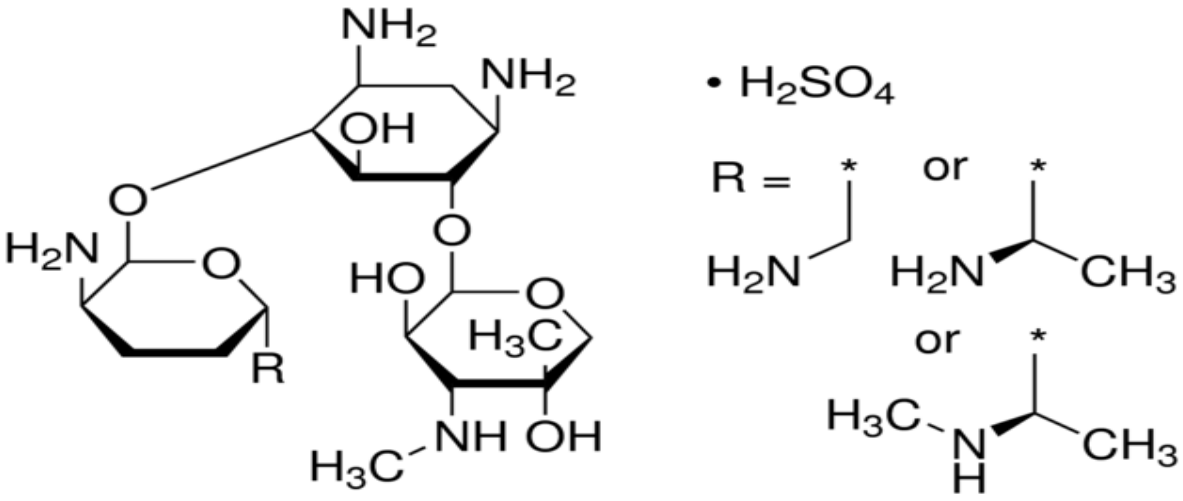

Figure 2: Chemical structure of gentamicin

cause a buildup of phospholipids in the lysosomes, inhibiting their function. The mechanism of ototoxicity is through the drugs ability to freely pass into hair cells and cause reactive oxygen species to damage the mitochondria, resulting in cell death [87]. It does not pass through the blood-brain barrier to enter the central nervous system or the eye, but it does traverse the placenta. A kidney's glomerular filtration handles almost all of the elimination, and it excreted in the active form [88]. Unfortunately, the rise and spread of resistance has diminished their effectiveness. Sometimes the resistance levels were so high that they were almost worthless [89]. Even tiny dosages of gentamicin have been documented by several authors to nephrotoxicity in humans and animals, making it an "obligatory nephrotoxin." The crucial stage in the development of nephrotoxicity may involve drug accumulation in certain target organelles in the renal cortex [90]. By causing tubular necrosis, glomerular congestion and inflammation, epithelial oedema of proximal tubules, perivascular oedema and tubular fibrosis, gentamicin produces nephrotoxicity, which in tum causes renal failure [91, 92]. Biomarkers of drug induced kidney injury are involved, albuminuria, proteinuria, blood urea, c-reactive protein serum creatinine and blood urea nitrogen [93].

2.5.1. Epidemiology of drug-induced nephrotoxicity:

In Indian research, 20% of all instances of acute renal failure were due to drug-induced acute kidney damage. According to prospective cohort studies, 14%–16% of adults develop renal toxicity associated with drugs [94,95]. Nephrotoxicity associated with aminoglycoside antibiotics increased from 3% in 1969 to 10–20% in 2010 [54,96]. According to another study,

chronic kidney disease affects 27 million people worldwide. Over the past 10 years, a sharp rise in drug-related nephrotoxicity (about 30%) has been noted [97].

Approximately 16% of hospitalized acute renal failure episodes are thought to be drug-related renal damage, a prevalent illness that can affect children as well [98].

2.5.2. Mechanism of drug-induced nephrotoxicity:

While some medications cause toxicity directly or through accumulation in the renal tubules, the majority of drugs cause nephrotoxicity through many pathogenic mechanisms [99]. Because the renal cortex has 90% of the total renal blood flow, it has a larger concentration of blood-borne toxins than either the renal medulla (6–10%) or the renal papillae (1-2%). Mechanisms related to the production of urine and the nephron's reabsorption process also 3soluble compounds. The proximal tubule of the kidney has a higher chance of drug accumulation than the distal tubular region due to its high permeability and active transport [100, 101]. As a result, the majority of research on drug-induced kidney damage focuses mostly on the kidney's proximal tubular region [102]. Protoxicants can occasionally become nephron-toxicants due to renal metabolic conversion [103]. The general mechanisms causing renal impairment after exposure to nephrotoxins include changes in glomerutubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis and thrombotic microangiopathy [102,104]. By modifying intraglomerular pressure and controlling blood flow in afferent and efferent arteries, kidneys maintain a steady glomerular filtration rate (120 mL per minute) and urine output. Long-term use of nonsteroid anti-inflammatory medications (anti-prostaglandin medications), angiotensin receptor blockers and angiotensin-converting enzyme inhibitors may alter glomerular hemodynamics and cause glomerular toxicity [105]. Proximal tubular cell toxicity is linked to oxidative stress caused by free radical production, disruption of the tubular transport system, and damage to the mitochondria [106]. Common medications that cause tubular cell toxicity include gentamicin (an aminoglycoside antibiotic), cisplatin and foscarnet (anticancer medicines), amphotericin B (an antifungal agent), and adefovir (an anti-retroviral) [102,106]. Some nephrotoxic drugs frequently cause inflammation in the kidney tissue, which can lead to glomerulonephritis, acute interstitial nephritis, or chronic interstitial nephritis. Certain medications, such as gold, penicillin, and phenytoin, can cause inflammation in the glomerulus (glomerulonephritis).

Acute interstitial nephritis can be caused by long-term use of non-steroid anti-inflammatory medications and rifampicin, while chronic interstitial nephritis is caused by the administration of calcineurin inhibitors, lithium, anticancer medications or analgesics [107,108].

Crystal nephropathy is the formation of stones in human urine due to the administration of certain medications, such as antibiotics like ampicillin, antiviral medicines like acyclovir, or chemicals like ethylene glycol [102,106]. Use of heroin, methadone, methamphetamine and statins, along with alcoholism, can cause rhabdomyolysis or the disintegration of kidney muscle cells, which releases myoglobin and serum creatine kinase into the bloodstream [109]. Some medications, such as quinine, cyclosporin and mitomycin-C, can directly damage renal epithelial cells or cause inflammation that could lead to drug-induced thrombotic microangiopathy [110].

2.5.3. Gentamicin-induced nephrotoxicity:

Nephropathy is a significant clinical consequence of genetically modified organisms (GMs) that has been documented in patients getting preventive doses of gentamicin as well as therapeutic dosages; in certain cases, nephropathy has also occurred in patients receiving meticulous monitoring from the antibiotic stewardship programme [111,112]. About 15% of cases of acute renal damage that were related to GM used [113]. Larger doses of gentamicin (40 mg/kg or more) are required to quickly cause extensive cortical necrosis, although clinical dosages of gentamicin given to people or 10-20 mg/kg given to rats for a few days were sufficient to cause certain tubular alterations that could lead to kidney failure [57]. According to reports, nephrotoxicity is evident in 30% of patients who get gentamicin treatment for longer than seven days [59].

Aged patients, those with a history of renal impairment, hypothyroidism, dehydration, pregnancy, liver dysfunction, hyponatremia, metabolic acidosis, longer treatment times, higher dosages, and multiple daily dosing regimens are among the many factors that raise the risk of nephrotoxicity. Moreover, the coadministration of additional nephrotoxic medications, such as diuretics, amphotericin B, cisplatin, cyclosporin, vancomycin, cephalosporins, iodide-based contrast media, and non-steroidal anti-inflammatory medicines (NSAIDs), can raise the risk of GM-induced kidney damage [60,61]. Serum trough levels greater than 2 µg/ml were associated with nephrotoxicity [62]. The precise processes responsible for genetically modified nephrotoxicity remain unclear. The primary alteration seen was the death of tubular epithelial

cells, mostly those in the proximal tubules, as a result of gentamicin buildup in these cells [61]. There are two basic mechanisms known for gentamicin uptake into cells: endocytosis and diffusion. Non-selective cation channels facilitate diffusion [63,64]. The megalin and cubulin complex, which is a transport molecule for cations and proteins, is involved in endocytosis [104]. The GM in endosomes is released into the cytoplasm once it reaches a specific threshold [65]. GM produces oxidative stress and mitochondrial dysfunction when it enters the cytoplasm by producing too many hydroxyl radicals and apoptotic pathways [66,67]. Damaged cells have the potential to block the lumen, increasing hydrostatic pressure in the tubules and capsule that lower glomerular filtration [68]. In order to prevent excessive loss of fluids and solutes, GM interferes with the reabsorption of cations, which activates the tubule glomerular feedback loop and decreases glomerular filtration [69,70]. Gentamicin reduces glomerular filtration rate (GFR) by contracting mesangial cells, which is followed by their proliferation and eventual apoptosis [71].

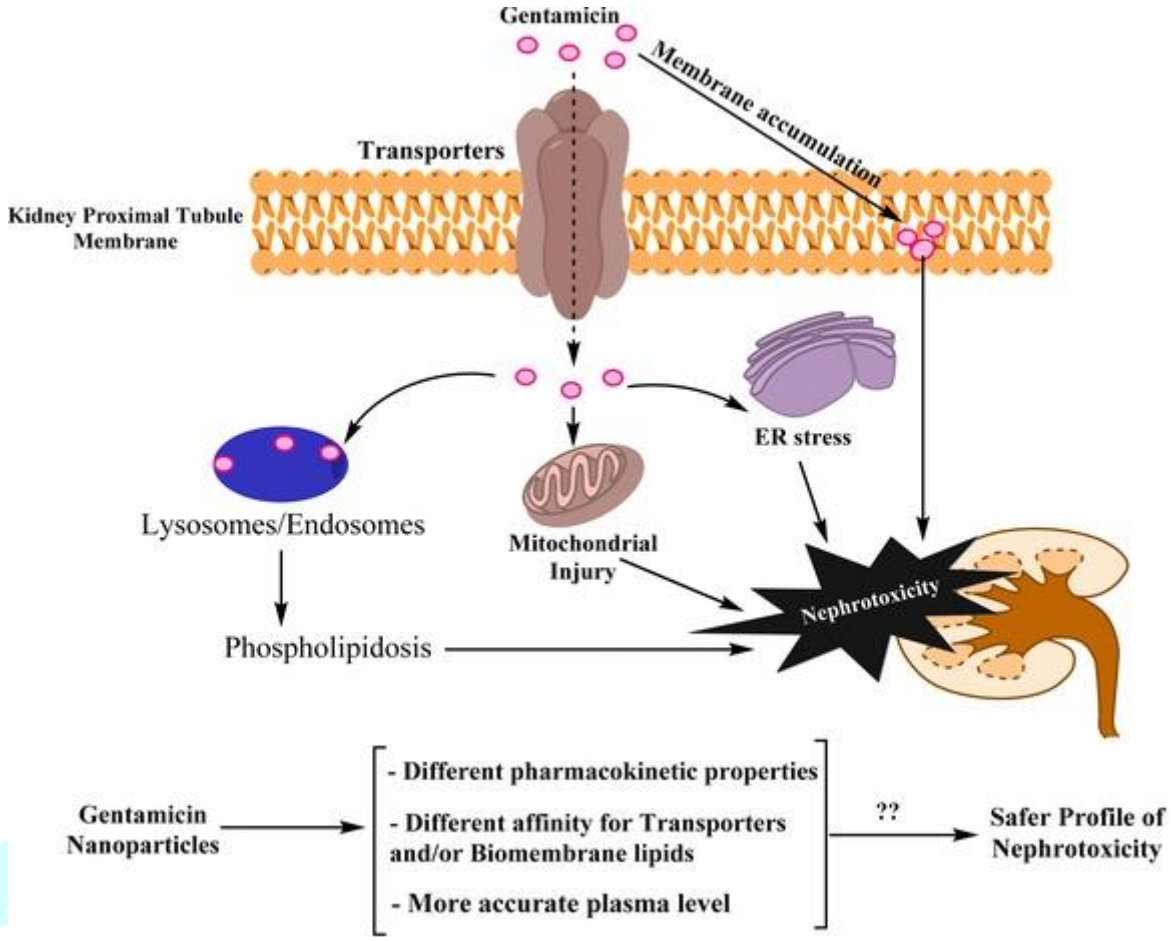

Figure 4: Mechanism involved in GM nephrotoxicity [71]

The overproduction of reactive oxygen species, endothelin-1, angiotensin-II, thromboxane A2 and platelet activating factor release may be the mechanisms mediating the mesangial contraction [72,73]. In addition, mesangial cells undergo apoptosis due to oxidative stress [74]. Additionally, GM can cause interstitial nephritis [75]. Renal perfusion decreases after gentamicin treatment due to elevated vascular resistance [75]. Increased serum levels of creatinine and urea, along with elevated serum cystatin C and a decrease in GFR, are linked to gentamicin-induced kidney damage [76]. The production of casts, glomerular injury, infiltration of inflammatory cells, and tubular epithelial cell apoptosis and necrosis are among the histopathological alterations linked to GM-induced renal damage [77].

2.6. Pathogenesis

Nephrotoxicity is a significant side effect of using these medications and accounts for 10% to 15% of all occurrences of acute renal failure [115]. Therefore, renal toxicity is a clinical issue that increases morbidity both during and after gentamicin therapy and causes acute kidney damage (AKI). Following membrane rupturing, gentamicin is released into the cytoplasm along with calpains and cathepsins, which activate proapoptotic proteins that immediately harm the mitochondria, initiating apoptosis, the formation of reactive oxygen species (ROS), and an inflammatory response. These discoveries all lead to the escalation and intensification of kidney injury [116].

2.6.1. Role of oxidative stress and inflammation in gentamicin induced nephrotoxicity

Gentamicin induces formation of free radicals like Reactive nitrogen species (RNS) and reactive oxygen species (ROS), thus driving to oxidative stress resulting in inflammatory process [92]. Several mechanisms, such as the peroxidation of membrane lipids, DNA damage, and protein denaturation, can macromolecules to be damaged by ROS, leading to cellular injury and necrosis [117]. Tubular necrosis, glomerular, vascular stimulation and contraction, which also contribute to tubular damage, are connected by inflammation and oxidative stress. It is well recognized that ROS is involved in the initiation and signaling of inflammation [118]. Hydrogen peroxide and superoxide anion activate nuclear factor-kß (NF-kB), which has an important role in initiation of the inflammatory cascade [119].

NF-kß activates nitric oxide synthase and proinflammatory cytokines, both of which cause cell damage by producing peroxynitrites when they combine with superoxide ions [120].

Nitric oxide, the most prevalent RNS, is needed to maintain normal renal function, but too much of it causes tissue damage and oxidative stress, which are key pathophysiological features of acute renal failure [121].

Antioxidant enzymes and ROS scavengers can stop gentamicin induced nephrotoxicity, Delivery of trans resveratrol, which has significant antioxidant action and inhibits both lipid peroxidation and ROS generation [122], lowered the renal blood flow and rate of glomerular filtration reduction brought on by a nephrotoxic dosage of gentamicin in rats noticeably [123].

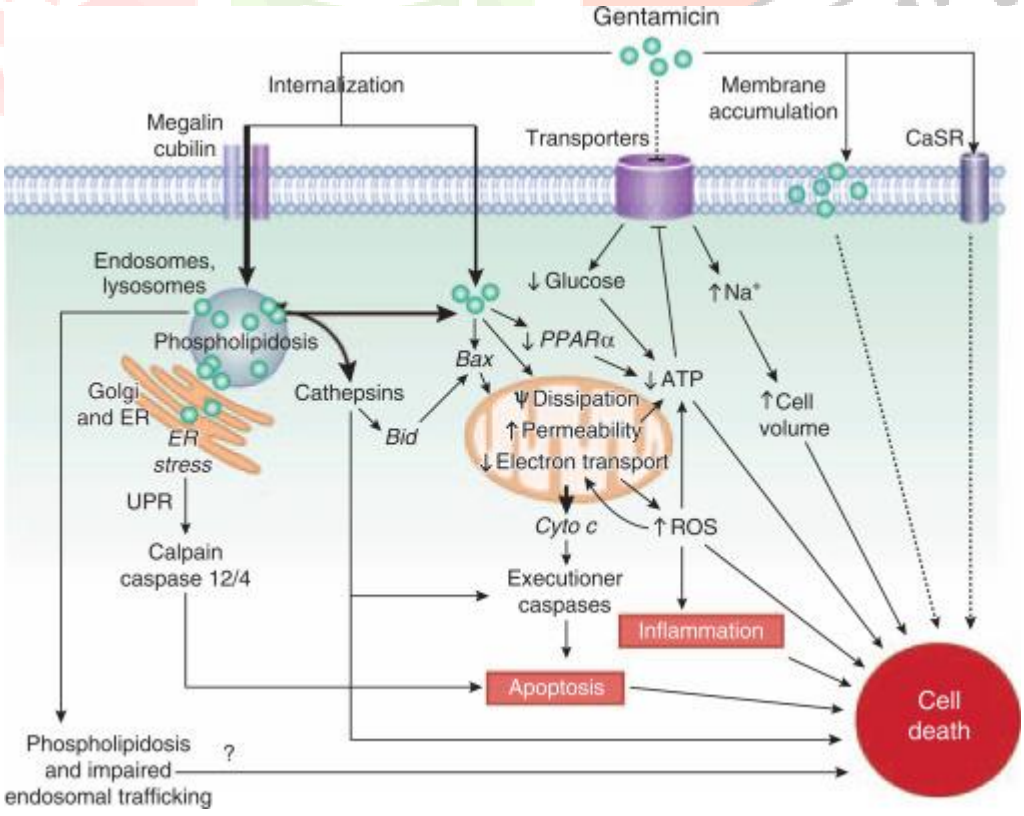

Figure 4: Role of Oxidative stress and Inflammation in nephrotoxicity **[123].**

Nitric oxide synthase is induced by GM, which increases NO production and causes the synthesis of per-oxy nitrite, a hazardous by product [124]. The lipid membranes of renal tubular cells undergo alterations due to lipid peroxidation (LPO) caused by gentamicin induced free radicals [125].

In the chain of events leading to gentamicin induced nephrotoxicity. LPO is a critical first step. Malondialdehyde (MDA) & measure of lipid peroxidation, 3 enhanced in the gentamicin-induced nephrotoxicity, which suggests increased free radical formation [126]. Gentamicin stimulates phospholipases and modifies the lysosomal membrane in addition to producing oxidative stress [127].

2.6.2. Signalling pathways involved in gentamicin induced nephrotoxicity

According to recent research, GM-induced nephrotoxicity is mediated by redox-sensitive transcription factors, including nuclear factor-kappa B (NPkB) and mitogen activated protein kinase (MAPK) [128]. It is well known that the NF-Ks pathway controls the expression of many genes involved in cell growth and inflammation. Since it controls the gene expression of cytokines, chemokines, and adhesion molecules, it is believed to be a crucial transcription factor that can drive acute and chronic inflammation, resulting in interstitial fibrosis and apoptosis in long- term renal disease [129].

2.6.3. p38-mitogen activated protein kinase (p38 MAPK) Signalling

As per the research done by *Volpini et al*. in 2006, p38MAPK expression rises during the onset of gentamicin-induced interstitial nephritis, This change is linked to inflammation in the renal cortex and increased NF-kß expression indicating that this signalling pathway is responsible for the renal lesions brought on by gentamicin [130]. The p38MAPK pathway is a crucial intracellular signal transduction system involved in the synthesis of pro-fibrotic and pro-inflammatory mediators, Numerous stimuli, such as lipopolysaccharide, UV radiation, interleukin-1 (IL-), TNF-α, and TGFB-1, activate the p38MAPK pathway. When these stimuli are activated, a number of upstream kinases are sequentially phosphorylated and activated, which leads to the activation and phosphorylation of p38MAPK [131,135]. P38 MAPK activation has been linked to the synthesis and release of TGFB- 1 and extracellular matrix proteins, TGFB-1 is a significant profibrotic mediator crucial for matrix and collagen deposition [136]. TGF has a significant role in the development of renal fibrosis in a number of chronic kidney disorders [137]. It has been established that the c-jun N- terminal kinase (JNK), a mitogen-activated protein kinase (MAPK), is a key player in the apoptotic signalling cascade. TGFB-I has also been linked to glomerulonephritis- related apoptosis [135].

2.6.3.1. Extracellular signal-regulated kinase (ERK) Signalling

The majority of immune cell functions, such as chemoattraction, apoptosis, survival, differentiation, and generation of inflammatory mediators, are fundamentally regulated by MAPKs. They employ three independent signalling pathways, including c-jun NH2-terminal kinase, p38, and ERK A Signal transduction pathway called extracellular signal-regulated kinase (ERK) conveys messages from external stimuli such as hormones, neurotransmitters, growth factors, and others. ERK is made up of a

wide range of receptor tyrosine kinases, G-protein coupled receptors, and ion channels that are important for cell growth and differentiation [136-137]. Additionally, ERK signaling is crucial for the response of renal cells to a variety of stimuli and contributes to pathogenic and hypertrophic kidney disorders such tubulointerstitial and glomerular disease [138]. In the injured kidney, ERK signaling is crucial for the proliferation of tubular epithelial cells [139]. Transient ERK activation promotes cell proliferation, but chronic ERK activation promotes differentiation [140]. Increases in angiotensin-2, endothelin, and TGFB-1 levels were related with fibrogenic and inflammatory responses to gentamicin, suggesting their participation in the development of tubulointerstitial nephritis [141]. In the CS54 cells, TGF-1 elevates MEK and ERK phosphorylation. Within 5 minutes of the TGF-1 therapy, MEK and ERK phosphorylation also increased quickly [142]. Additionally, it was discovered that TGFB-1 stimulates ERK signaling in mesangial cells. Tubular epithelium and myofibroblast-like cells proliferate when the ERK pathway is activated [143]. ERK expression is one of those mechanisms that can both directly and indirectly involve the regulation of genes by TGFB-1 that are involved in endocytosis, cell matrix interactions and cell motility [144]. Infiltrating macrophages and lymphocytes into inflamed cells may be facilitated by the ERK pathway [145]. Nephrotoxicity induced by gentamicin, cells that resemble tubular epithelium and myofibroblasts proliferate in large part due to the ERK pathway [146]. *Sang Heon Shu et al*. showed the renoprotective effect of paricalcitol by suppression of p-JNK in gentamicin induced nephropathy [147].

Gentamicin accumulates in some types of cells, where it causes cytotoxicity. These cells make up the epithelial cells in the cortex of the kidneys, mostly in the proximal tubule of animals and people, as well as in the collecting ducts and distal tubules. The expression of a protein and cation transporter, the giant endocytic complex formed by the proteins megalin and cubilin, which is only found in the proximal tubule, interrupts the respiratory chain, reduces ATP production, and causes oxidative stress by raising superoxide anions and hydroxy radicals, all of which contribute to cell death, is consistent with a higher accumulation of gentamicin in these cells [148].

2.6.3.2. p53 signalling

Nuclear protein transcription of genes and encoding are significantly regulated by the tumour protector genes (p53), sometimes known as the "Guardian of the Genome" [149]. Numerous studies have proven the contribution of TGF-B1/p53 signalling to the development of renal fibrosis. Furthermore, TGFß promotes the activation of the p53 and Smad complexes, both of which play important roles in renal fibro genesis [150]. The latter function causes concerns about the use of TGF beta in treating progressive renal failure [151]. Apoptotic indicators like caspase-9, Bcl-2- associated X-proteins (BAX-2) caspase-3, and p53 were assessed in a study by *Sahu et al*., and it was discovered that naringin improved the amount of cleaved Bax-2, caspase-3, and p53 expressions [130]. Apoptosis is crucial to renal health, drug-induced nephrotoxicity, and renal illness in addition to its need for normal kidney function [149]. The proximal convoluted tubules exhibit apoptosis and necrosis, which contribute to gentamicin-induced nephrotoxicity. Analysis of the kidney damage induced by gentamicin has improved with the use of p53 as an indicator of renal damage [152]. DNA transcription, cellular growth, and apoptosis are all governed by the nuclear

phosphoprotein p53 [153]. A significant transcriptional component in the activation of apoptosis is p53. Micro RNAS, transcriptional- independent processes, and target gene activation or repression are all involved in p$3 cell death and apoptosis, and p53 malfunction leads to dysregulated levels of apoptosis [154].

2.7. Effective Antioxidants Against Gentamicin Nephrotoxicity

One of the main reasons of gentamicin nephrotoxicity is the production of ROS, which damages DNA, peroxides lipid membranes, and causes protein denaturation and cellular injury and necrosis [155]. Kidney antioxidant enzymes such GSH. SOD, Glutathione peroxidase (GPX), MDA, and CAT are decreased by gentamicin [156]. Some of the herbal and synthetic antioxidants which decrease the changes induced by the gentamicin in preclinical studies.

2.7.1. Herbal antioxidants

Herbs are defined as plants which are used for flavouring, food, medicine or perfume. Herbs are "potentially beneficial to the kidneys if they possess specific and potent renal antioxidant effects or if there is strong evidence of their renal protection from toxic substances. Herbal remedies are considered for usage in kidney dysfunction and are effective when used in conjunction with other therapies to prevent and treat renal disorders.

- The ability of ***Moringa Oleifera*** seed oil newly developed functional food oil to reduce GM-induced nephrotoxicity through mechanisms that are antioxidant, anti-inflammatory and anti-apoptotic [157].
- Phytochemicals with potential for nephroprotection, ***Coriandrum sativum's*** flavonoids and polyphenols are the most significant ingredients. A rise in serum levels of urea, creatinine, and blood urea nitrogen was inhibited by **Coriandrum sativum** extract [158].
- ***Naringin,*** a bioflavonoid, reduces oxidative stress, inflammatory, and apoptotic indicators, which improves renal failure in rats with gentamicin- induced nephrotoxicity [155].
- ***Tephrosia purpurea*** prevents oxidative stress and toxicity brought on by benzoyl peroxide in the skin. It is unknown whether *Tephrosia purpurea* has anticancer activity in mouse skin, but the main explanation for this appears to be its capacity to capture free radicals and shield cellular macromolecules from harm caused by oxidative stress. *Tephrosia purpurea* contains a variety of well-known antioxidants, which may be responsible for the plant's free radical quenching properties [156]. Using *Tephrosia purpura's* ethanol extract, gentamicin-induced kidney image was repaired. The ethanolic extract demonstrated considerable in vivo antioxidant activity as well as strong, DPPH scavenging, Superoxide radical scavenging and overall antioxidant activity [157].

- **Rutin** and the ***Cardiospermum hieracium*** aqueous extract have also been shown to have nephroprotective qualities, and the capacity to reduce oxidative stress is thought to be the reason behind this [158].
- ***Poyalthia longifolia*** extracts in both ethanolic and aqueous form demonstrated superoxide radical scavenging action. When compared to Poyalthia water extracts, ethanolic extracts were found to have higher antioxidant activity [159).
- **Rutin** and **quercetin** have also been reported to be antioxidants and nephroprotective, according to *Singh et al*., who also conducted a thorough assessment of the function of antioxidants in avoiding the development of renal disorders [160].
- **Wild nutshell** extracts in methanol have been shown to have antioxidant and antiradical activity, which may vary among species. This phenolic extract may be helpful in

delaying or preventing the onset of many oxidative disorders associated with stress [161].

- By increasing renal glutathione levels, decreasing lipid peroxidation, and boosting the activity of antioxidant enzymes, Houttuynia cordata Thunb defends against the nephrotoxicity that Gentamicin sulphate (GS) causes [162].
- Olive leaf extract reduces the kidney damage caused by gentamicin by increasing renal glutathione levels and the activity of antioxidant enzymes, with the exception of glutathione peroxidase [59].
- Ursolic is the plant extract of ***Osmium sanctum*** which blocked the lipid peroxidation and prevents gentamicin nephrotoxicity induced by free radicals. Ursolic acid inhibited the gentamicin-induced rise in blood urea nitrogen serum urea, uric acid, and creatinine [163].
- The gentamicin nephrotoxic effects can be mitigated in vivo by ***Adhatoda zeylanica***, according to recent study by other scientists. *A. zeylanica* mitigate the nephrotoxic effect of gentamicin by scavenging the gentamicin induced free radicals [97].
- **Kabab chini** *(Piper cubeba*) works equally well as a preventative an therapeutic agent, In terms of impacts, there was no distinction between post-and pre-treatment. The curative effect of drug is action of kabab chini [98].
- Gentamicin induced Endogenous free radical generation was effectively stopped or decreased by the aqueous-ethanolic extract of the fungus mycelium Morchella. Without causing any negative side effects, this mushroom can act as a nephroprotective agent [99].
- Ethanol extract of ***Momordica dioica*** fruit may have therapeutic are nephroprotective properties because they have antioxidant properties that protect the body from reactive Oxygen species, which are created when cisplatin is used medically [100].
- Isolated Oleanolic acid from ***Viscum articulatum Burm. f****. (Viscaceae)* has significant protective action on gentamicin induced nephrotoxic effects on rats. The increased levels of albumin, urea, and creatinine in both urine and serum were dramatically lowered by oleanolic acid [117].

- Gentamicin-induced increases in BUN and serum creatinine were avoided in rats treated with curcumin concurrently and before the antibiotic. Since it has been

discovered that ROS may be responsible for the degradation of glomerular filtration rate, this effect might be linked to the antioxidant capabilities of curcumin [168].

- Defatted phenolic extract of **soybean** may therefore be able to prevent GM- induced tubular necrosis or microsomal damage by stabilizing the cell membrane and/or other essential cellular macromolecules at a reasonably low and effective dose. The antioxidant polyphenolic content present in soybeans appears to be connected to the protective benefits of the extracts [169].
- It has been established that ROS plays a role in gentamicin-induced kidney damage, and that Resveratrol therapy lowers lipid peroxidation and boosts antioxidant status. Its capacity to scavenge free radicals accounts for the reduced parietal cell hyperplasia, tubular vacuolization, and tubular necrosis observed in gentamicin-treated rats [170].
- The protective action of leaf and seed aqueous extract of ***Phyllanthus amarus*** against gentamicin induced nephrotoxicity due to its free radicals-scavenging and antioxidant properties [171].
- Gentamicin induced acute renal failure is prevented by Thymoquinone supplementation by its power to control the oxidative stress and to secure the properties of antioxidant enzyme, with its power to prevent the declamation energy in kidney tissue [172].
- At both biological and histological levels, caffeic acid phenethyl ester (CAPE) functions in the renal system as a strong free radical scavenger to halt the harmful effects of gentamicin [173].
- When combined with GM, Lycopene can have a significant protective impact on gentamicin-induced oxidative damage and renal toxicity. Lycopene has gained special attention due to its excellent antioxidant activity, which includes singlet-oxygen and free radical scavenging [174].
- ***Cassia auriculata*** is a huge brilliant yellow flowering shrub native to central and western India. The antioxidant and free-radical-scavenging properties of ethanolic extract of **C. auriculata** roots may have a role in nephroprotection.
- This plant has the potential to be useful for the management of acute renal failure caused by nephrotoxins such as cisplatin and gentamicin [175]. In vitro and in vivo, Aged Garlic Extract is a powerful antioxidant. AGE has a protective role against gentamicin induced nephrotoxicity. The capacity of AGE to minimize GM-nephrotoxicity in patients is still being investigated [176].

Table No. 1 List of herbal drugs and their mechanism and its uses [40-56]

Herbal Drug	Mechanism of Action	Uses
Ginseng (Panax ginseng)	Antioxidant, reduces oxidative stress, inhibits inflammation.	Drug-induced nephrotoxicity
Curcumin (Curcuma longa)	Inhibits NF-κB signaling, reduces cytokines (IL-6, TNF-α).	Diabetic nephropathy, ischemia-reperfusion injury
Silymarin (Silybum marianum)	Reduces lipid peroxidation, enhances glutathione, anti-inflammatory.	Cisplatin, aminoglycoside nephrotoxicity
Ashwagandha (Withania somnifera)	Reduces oxidative stress, inflammation, enhances antioxidants.	Nephrotoxicity, renal function
Green Tea (Camellia sinensis)	Contains EGCG, scavenges free radicals, anti-inflammatory.	Diabetic nephropathy, ischemia-reperfusion
Nigella sativa (Black seed)	Contains thymoquinone, reduces oxidative stress, inflammation.	Cisplatin, methotrexate nephrotoxicity
Tribulus terrestris	Increases antioxidant activity, reduces inflammation.	Protects from ischemia-reperfusion injury
Garlic (Allium sativum)	Inhibits lipid peroxidation, enhances antioxidant enzyme activities.	Diabetic nephropathy
Ginger (Zingiber officinale)	Antioxidant, anti-inflammatory, modulates pro-inflammatory cytokines.	Cisplatin nephrotoxicity, diabetic nephropathy
Licorice (Glycyrrhiza glabra)	Reduces oxidative stress, modulates inflammatory cytokines.	Chronic kidney disease (CKD)
Punica granatum (Pomegranate)	Reduces oxidative stress, anti-inflammatory effects.	Ischemia-reperfusion injury, nephrotoxicity
Aloe vera	Reduces oxidative damage, enhances antioxidant enzymes.	Nephroprotective in gentamicin-induced toxicity
Cinnamon (Cinnamomum zeylanicum)	Inhibits oxidative stress, anti-inflammatory.	Diabetic nephropathy

Cranberry (Vaccinium macrocarpon)	Prevents bacterial adherence, anti-inflammatory.	Prevents urinary tract infections (UTIs)
Moringa oleifera	Rich in antioxidants, reduces oxidative stress.	Nephrotoxicity in drug-induced injuries
Basil (Ocimum sanctum)	Antioxidant, anti-inflammatory, modulates cytokines.	Nephroprotective in ischemic conditions
Phyllanthus amarus	Reduces oxidative stress, modulates pro-inflammatory cytokines.	Hepatorenal syndrome
Amla (Emblica officinalis)	High vitamin C content, antioxidant, reduces inflammation.	Diabetic nephropathy
Baicalin (Scutellaria baicalensis)	Anti-inflammatory, reduces oxidative stress, inhibits fibrosis.	Chronic kidney disease
Hibiscus sabdariffa	Antioxidant, reduces oxidative stress, lowers blood pressure.	Diabetic nephropathy, hypertensive nephropathy
Bupleurum chinense	Anti-inflammatory, inhibits TNF-α and IL-6.	Renal fibrosis, CKD
Salvia miltiorrhiza (Danshen)	Antioxidant, reduces inflammation, prevents fibrosis.	Diabetic nephropathy, CKD
Berberine (Berberis vulgaris)	Anti-inflammatory, antioxidant, reduces oxidative stress.	Diabetic nephropathy, CKD
Quercetin (from various plants)	Potent antioxidant, inhibits NF-κB, reduces oxidative stress.	Diabetic nephropathy, drug-induced nephrotoxicity
Resveratrol (from grapes)	Activates SIRT1, reduces oxidative stress, anti-inflammatory.	Diabetic nephropathy, CKD
Centella asiatica	Reduces oxidative stress, enhances antioxidant enzymes.	Nephrotoxicity in drug-induced models
Terminalia chebula	Potent antioxidant, anti-inflammatory.	Diabetic nephropathy, CKD

Urtica dioica (Stinging nettle)	Reduces oxidative stress, anti-inflammatory properties.	Renal failure, CKD
Picrorhiza kurroa	Reduces oxidative stress, enhances glutathione.	Drug-induced nephrotoxicity
Erythrina variegata	Antioxidant, anti-inflammatory.	Nephroprotective in ischemia-reperfusion injury

Conclusion

Gentamicin, a widely used aminoglycoside antibiotic, is associated with significant nephrotoxicity, primarily due to oxidative stress, mitochondrial dysfunction, and tubular cell damage. The search for effective nephroprotective agents has led to increasing interest in herbal drugs, which offer renoprotective benefits through antioxidant, anti-inflammatory, and cytoprotective mechanisms. Various medicinal plants and their bioactive constituents, such as flavonoids, polyphenols, and alkaloids, have demonstrated promising potential in mitigating gentamicin-induced renal injury. Integrating these herbal remedies into clinical practice could offer a safer and more effective approach to managing drug-induced nephrotoxicity. However, further preclinical and clinical investigations are necessary to establish standardized formulations, optimal dosages, and long-term safety profiles.

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