

Herbal Nephroprotective Agents against Gentamicin-Induced Nephrotoxicity: Mechanisms, Phytoconstituents, and Therapeutic Potential

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ABSTRACT

Toxicity towards the kidneys is a common side effect of many drugs and is a major cause of acute kidney injury globally. Gentamicin, a commonly used aminoglycoside antibiotic, is an important cause of renal impairment in humans because of its tendency to accumulate in the epithelial cells of the proximal tubules. Multiple mechanisms including oxidative stress, inflammation, mitochondrial dysfunction and apoptosis contribute to the pathogenesis of gentamicin-induced nephrotoxicity, which in turn results in structural and functional deterioration of renal tissues. Medicinal plants have gained much attention in recent years as promising nephroprotective agents due to their phytochemical profile and good safety. A number of plant-derived compounds have exhibited potent antioxidant and anti-inflammatory activities which may help protect against renal injury, and these include flavonoids, phenolic acids, carotenoids, and terpenoids. *Tagetes erecta* L. (African marigold) is a medicinal plant that belongs to family Asteraceae and is known for the various pharmacologic properties. It possesses several phytochemical constituents such as flavonoids, carotenoids, phenolics, essential oils and terpenoids, which help explain some of its antioxidant, anti-inflammatory, antimicrobial, hepatoprotective and cytoprotective properties. This review aims to summarise the current knowledge about the nephrotoxicity induced by gentamicin, emphasise the mechanisms proposed for promoting renal damage by oxidative stress, inflammation and apoptosis and to discuss the nephroprotective potential of medicinal plants with special reference to *Tagetes erecta*. Evidence indicates that the phytoconstituents of *T. erecta* could reduce renal damage by acting as a scavenger of ROS, boosting endogenous antioxidant defense, regulating inflammatory mediators, maintaining mitochondrial function, and blocking apoptotic pathway. There is yet insufficient direct evidence of the nephroprotective effects of *T. erecta*, but the pharmacological profile of this plant suggests it as an attractive natural therapeutic agent for gentamicin induced renal damage prevention and management. It needs further experimental and clinical studies to prove its efficacy and to better understand its molecular mechanism.

Keywords: Gentamicin, Nephrotoxicity, Nephroprotection, Renal Injury, Oxidative Stress.

INTRODUCTION

The kidneys are specialised organs that function in the regulation of fluid balance, electrolyte concentration, acid–base balance and excretion of metabolic waste products as a fundamental way of maintaining physiological homeostasis. The kidneys also play an important role in the endocrine system, synthesizing hormones regulating erythropoiesis, blood pressure, and calcium metabolism. The kidneys are highly susceptible to injury by xenobiotics, environmental toxicants and therapeutic drugs, due to their high

blood flow and active transport systems. Drug-induced nephrotoxicity is a major clinical problem and has been identified as a significant proportion of the cases of acute kidney injury in hospitalized and outpatient patients. Gentamicin is one of the most thoroughly researched and utilized of the nephrotoxic antibiotics, the aminoglycosides. Gentamicin is also a broad-spectrum antibiotic with a low cost and is used extensively to treat severe Gram-negative bacterial infections. Although clinically effective, gentamicin is often found to be neurotoxic when administered for a long period of time or at high doses. The drug is

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concentrated in the epithelial cells of the proximal tubules of the kidneys and causes structural and functional changes in the kidneys. Experimental and clinical studies have shown that gentamicin nephrotoxicity is associated with increased level of serum creatinine and blood urea nitrogen, tubular degeneration, inflammatory responses and oxidative damage. Oxidative stress has been suggested as one of the main mechanisms in gentamicin-induced renal damage. Overproduction of ROS leads to cellular antioxidant defence failure, lipid peroxidation, protein oxidation, mitochondrial dysfunction and DNA damage. Furthermore, oxidative stress triggers several inflammatory signaling pathways which further damage tissues. Eventually, the interaction of oxidative stress, inflammation and apoptosis leads to the pathogenesis of renal dysfunction. Therapeutic approaches that can dampen the inflammatory responses and oxidative damage have thus received much attention as possible nephroprotective strategies. There is a growing interest in bioactive molecules obtained from natural products or medicinal plants for their renal protection properties. Various phytochemicals such as flavonoids, phenolic acids, terpenoids, alkaloids and carotenoids have shown antioxidant, anti-inflammatory and cytoprotective effects in experimental nephrotoxicity models. This increasing popularity of herbal medicine can be attributed to the demand for alternative treatment methods that are both safer and more cost effective, which are able to reduce harmful side effects of conventional medicine. Preliminary research has demonstrated the nephroprotective properties of several medicinal plants, which have the potential to be used in the prevention and treatment of renal diseases. *Tagetes erecta* L. is an ornamental and medicinal plant of the family Asteraceae or Compositae, also called as African marigold. Traditionally, the plant has been used for treating inflammatory diseases, skin diseases, gastrointestinal upset and infectious diseases in a variety of health care systems. The phytochemical studies have identified various bioactive compounds like flavonoids, carotenoids, phenolic compounds, triterpenes, and essential oils. Various constituents exhibit a wide range of pharmacological properties like antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, wound-healing and anticancer properties. The antioxidant activity of *Tagetes erecta*

is particularly notable, and the extract may thus have great nephroprotective activity against oxidative stress-induced renal damage. *Tagetes erecta* is pharmacologically important, yet there has been no exhaustive review of the potential protection role of *T. erecta* against drug induced renal toxicity. The ability of the plant and its bioactive compounds to potentially inhibit oxidative stress, inflammation, and cell damage may offer significant insight for future therapeutic interventions. Hence, the aim of the present review is to summarize the current knowledge of gentamicin-induced nephrotoxicity, the molecular mechanisms involved in renal injury, the medicinal plants used for nephroprotection and the emerging therapeutic potential of *Tagetes erecta* in renal protection. It also points out the gaps in existing research and future directions in developing plant-based nephroprotective interventions.

1. KIDNEY STRUCTURE AND FUNCTION

The two kidneys are bean shaped with the perinephric (behind the kidney) position, located side by side on either side of the vertebral column. Each kidney is 120 – 170 g in healthy adults and receives about 20 – 25% of the total cardiac output, making it important in maintaining systemic homeostasis. The main role of kidneys is to filter blood, to remove those metabolic wastes, to help maintain fluid and electrolyte balance, to help maintain acid–base balance, and to play endocrine function in controlling blood pressure and making red blood cells. The kidney has two regions, an outer cortex and an inner medulla. The cortex is composed of renal corpuscles and parts of renal tubules, the medulla is composed of renal pyramids containing loops of Henle and collecting duct. They combine together to make the nephron is the functional unit of the kidney. The kidneys of humans consist of about one million nephrons that together are responsible for the formation of urine and the maintenance of physiological balance. The nephron consists of two main parts, the renal corpuscle and the renal tubule. The renal corpuscle is made up of a glomerulus surrounded by the Bowman's capsule. The blood enters the glomerulus via the afferent arteriole and water and small solutes are filtered out of the blood into the tubule under the influence of hydrostatic pressure. The filtrate formed fills Bowman's space and then flows through the tubular



portions of the nephron. The filtration barrier is a highly specialized one, consisting of fenestrated endothelial cells, the glomerular basement membrane and podocytes. These structures together allow the passage of water and low-molecular weight substances to pass through, while excluding blood cells and plasma proteins from passing through. The filtered water and sodium are reabsorbed by the proximal convoluted tubule and two thirds of the filtered water and sodium is reabsorbed. This segment also absorbs glucose, amino acids, bicarbonate ions and other essential nutrients. The proximal tubule is very metabolically active and has a lot of transport activity, making it very vulnerable to toxic injury. Gentamicin is a nephrotoxic drug which concentrates in the proximal tubular cells, so that the region is a first target for the kidney damage. The filtrate is then passed through the loop of Henle (DLH) which has two limbs, descending and ascending. The ascending limb actively pumps sodium, potassium and chloride ions while the descending limb is permeable to water. This set-up creates the medullary osmotic gradient that allows the kidneys to concentrate urine and conserve water. Hormones like antidiuretic hormone (ADH) and aldosterone further control electrolyte balance and water reabsorption in the distal convoluted tubule and collecting duct. These regulation mechanisms enable the kidneys to adjust to fluctuations in fluid intake, electrolyte intake, and physiological needs. The elimination of metabolic waste products is one of the most important functions of the kidneys. Other compounds like urea, uric acid, creatinine and xenobiotics are filtered and excreted in urine. Eliminating them efficiently means that they stay out of the blood stream and avoid toxic effects. If renal function is impaired the urea and other waste products can accumulate, causing metabolic disturbances and eventual organ failure. The kidneys also are very important in electrolyte homeostasis. The ions which are continuously controlled are Na^+ , K^+ , Ca^{2+} , Mg^{2+} , phosphate and chloride ions. Changes in electrolyte balance, even if they are small, can have a significant impact on the function of the nervous system, the heart and cell metabolism. Thus,

accurate renal regulation is vital for normal physiological functions. Kidneys not only participate in excretory functions but also play an important role in maintaining acid–base balance. Hydrogen ions are released in the tubular lumen and bicarbonate ions are reabsorbed and produced to keep the blood pH close to a physiologic range. Renal acid–base disturbance can lead to either metabolic acidosis or metabolic alkalosis, which could have serious clinical implications. The kidneys also have significant endocrine activities. Juxtaglomerular cells synthesize and secrete the enzyme renin, which is involved in the renin–angiotensin–aldosterone system, which controls blood pressure and fluid balance. Also, the kidneys generate a glycoprotein hormone called "erythropoietin," which encourages red blood cell manufacture in the bone marrow. In addition, renal tissues play a role in the activation of vitamin D which is key to calcium absorption and bone health. The kidneys are very sensitive to toxic effects due to their great blood supply and large exposure to chemicals in the blood. Renal tissues can be damaged by drugs, heavy metals, environmental pollutants and reactive metabolites, which have been shown to cause oxidative stress, inflammation, mitochondrial dysfunction and apoptosis. The proximal tubular epithelium is especially vulnerable because of its ability to actively transport and its energy needs. Therefore, drug induced nephrotoxicity is still a great problem in clinical medicine and pharmaceutical research. The structure and physiological functions of the kidneys are important to grasp in order to appreciate the mechanisms of renal injury and the therapeutic ability of nephroprotective agents. Maintenance of integrity of nephrons and normal renal function are important goals in the prevention and management of renal diseases. Thus, finding strategies that will help to protect renal tissues from toxic insults has become an important area of study, especially in the context of gentamicin-induced nephrotoxicity and the development of plant-based nephroprotective therapies.



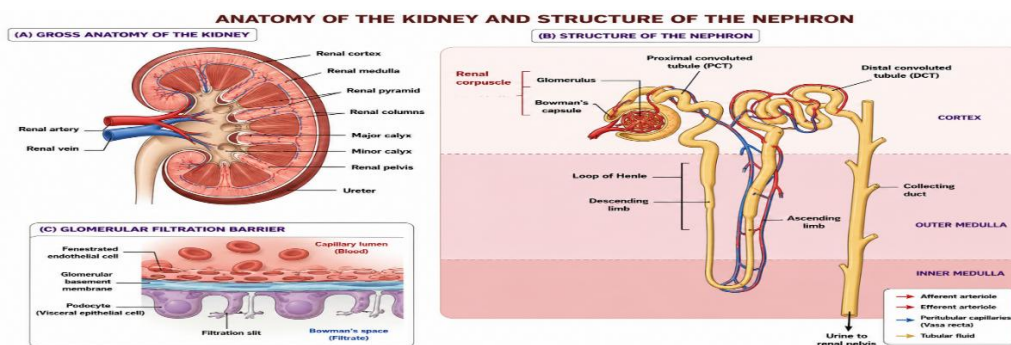


Table no. 1

Renal Structure	Primary Function
Glomerulus	Blood filtration
Bowman's capsule	Collection of filtrate
Proximal tubule	Reabsorption of nutrients and water
Loop of Henle	Urine concentration
Distal tubule	Electrolyte regulation
Collecting duct	Final urine formation

2. Nephrotoxicity: Definition, Causes, And Clinical Significance

Nephrotoxicity is the injury or damage of the kidney(s) caused by an endogenous or exogenous toxic agent that impairs renal function and structure. The kidneys are one of the most sensitive organs in the body to toxic effects because they are receiving a great percentage of cardiac output and continuously filtering the blood at great rates. In this process, many chemicals, drugs, metabolites and environmental toxins are introduced into renal tissues and can become trapped in the nephron and cause damage to the cells. Drug exposure-induced nephrotoxicity is a significant contributor to morbidity, mortality, longer hospital stay, and higher healthcare expenses globally and is one of the leading causes of acute kidney injury (AKI). There has been a significant rise in the prevalence of nephrotoxicity with the use of therapeutic agents such as antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anti-cancer drugs, immunosuppressive agents, and radiologic contrast media. These agents have significant clinical value but there has been a concern for high dose or chronic use potentially to have a negative impact on renal function. Many factors contribute to the severity of renal injury such as nature of toxic agent, dosage,

duration of exposure, patient age, genetic susceptibility, underlying kidney disease and use of other nephrotoxic drugs. The nephrotoxic manifestations may be: acute kidney injury, chronic kidney disease, glomerular dysfunction, tubular dysfunction, interstitial nephritis and electrolyte disturbance. Acute kidney injury involves rapid reduction in glomerular filtration rate (GFR), and buildup of nitrogenous waste products (urea and creatinine) in the blood. Renal changes associated with chronic exposure to nephrotoxic agents can include progressive renal fibrosis and irreversible loss of nephron function, ultimately resulting in chronic kidney disease. There are many types of medications associated with nephrotoxic effects. Nephrotoxicity is the most widely studied toxicity of the aminoglycoside antibiotics, especially gentamicin. Gentamicin enters cells of the proximal tubular epithelial cells and causes oxidative stress, mitochondrial dysfunction and apoptosis of these cells. Likewise, cisplatin, a chemotherapeutic agent commonly used, causes severe tubular damage by generation of ROS and inflammatory responses. NSAIDs have been shown to decrease blood flow to the kidneys by inhibiting prostaglandin generation, while calcineurin inhibitors like cyclosporine and tacrolimus can lead to a decrease in blood flow and chronic kidney injury. Further, it is well established that the use of radiographic contrast agents can cause contrast-associated nephropathy by ischemic and oxidative mechanisms. Nephrotoxicity is a complex phenomenon with several interconnected molecular pathways involved in its pathogenesis. Renal injury is thought to be mediated by one of the most significant mechanisms of oxidative stress. The over-production of reactive oxygen species (ROS) exceeds the capacity of the endogenous antioxidant defenses, leading to initiation of lipid peroxidation, protein oxidation and DNA damage. It is these events that

disrupt the integrity of the cells and the normal functioning of the kidneys. Mitochondria are very vulnerable to oxidative damage and consequently suffer from decreased ATP production and depletion in tubular cells. Inflammation also has a pivotal role in the development of nephrotoxic injury. Nephrotoxic agents trigger the release of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF- α), Interleukin-1 beta (IL-1 β) and Interleukin-6 (IL-6). These mediators stimulate leukocytes to infiltrate and cause additional damage to tissues and vascular dysfunction. Chronic inflammation leads to fibrosis and progressive renal architecture changes. Other mechanisms of nephrotoxicity include apoptosis and necrosis. The activation of both intrinsic and extrinsic apoptotic pathways initiates programmed cell death and in case of very severe damage, necrosis and inflammatory tissue destruction can occur. Finally, the consequences of oxidative stress, inflammation, apoptosis and mitochondrial dysfunction lead to a loss of integrity and function of the nephrons. Clinical signs of nephrotoxicity include symptoms depending on the severity and type of damage. Patients may have elevated serum creatinine, elevated blood urea nitrogen, decreased urine output, electrolyte abnormalities, hypertension and edema. Nephrotoxicity can become more severe and progress to renal failure which may be treated with dialysis or kidney transplantation. Therefore early detection and intervention are essential to avoiding irreversible renal damage. There are several biomarkers that are routinely used to assess renal injury/nephrotoxicity. As well as the most commonly used markers, serum creatinine and blood urea nitrogen, these markers may increase only after significant renal damage has been present. There has been recent interest in novel biomarkers like kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and N-acetyl- β -D-glucosaminidase (NAG) that may allow for more timely and sensitive detection of renal injury. Nephrotoxicity is an important side effect and due to the lack of effective prevention measures, efforts have been focused on the development of nephroprotective agents. The antioxidant, anti-inflammatory and cytoprotective properties of natural products and medicinal plants have led to their being evaluated as therapeutic candidates. Many phytochemicals such as flavonoids,

phenolic acids, carotenoids and terpenoids have been shown to have protective properties against experimental renal damage. The discovery has stimulated a wide-ranging search for plant-based treatments for kidney disease. The knowledge of the causes, mechanisms and implications of nephrotoxicity is vital for the development of effective prevention and therapeutic measures. This knowledge will form a basis to assess the nephroprotective effect of medicinal plants like *Tagetes erecta* against drug induced renal injury. Moreover, it emphasizes the need to find natural antioxidant strategies to reduce the harmful effects on the kidneys of drugs like gentamicin that are known to be nephrotoxic.

Table no.2

Category	Examples	Major Mechanism
Aminoglycosides	Gentamicin, Amikacin	Oxidative stress
NSAIDs	Ibuprofen, Diclofenac	Reduced renal perfusion
Anticancer drugs	Cisplatin, Methotrexate	Tubular toxicity
Contrast agents	Iohexol	Renal ischemia
Heavy metals	Lead, Cadmium	ROS generation
Environmental toxins	Pesticides	Cellular damage

3. Gentamicin-Induced Nephrotoxicity

Gentamicin is a broad spectrum aminoglycoside antibiotic which is widely used to treat serious infections caused by Gram-negative bacteria. Gentamicin is an important therapeutic agent in clinical practice because of its potency, low cost and availability. Although useful, gentamicin has a marked nephrotoxic effect that prevents its clinical use. Some patients who are treated with gentamicin for longer than the usual course of 14 days will develop renal impairment to varying extents. Thus, gentamicin nephrotoxicity is now one of the most studied models for the study of acute renal failure and testing of nephroprotective agents.



Gentamicin is mainly nephrotoxic to the proximal convoluted tubules of the kidney. Systemically, gentamicin is freely filtered across the glomerulus and is found in the tubular lumen. Megalin and cubilin receptors are responsible for the receptor-mediated endocytosis of a large percentage of the filtered drug by epithelial cells of the proximal tubules. When gentamicin is taken continuously it accumulates in the cell, especially in the lysosomes, mitochondria, and endoplasmic reticulum. This build-up of the drug triggers a chain of pathological events culminating in renal dysfunction. Oxidative stress is one of the key mechanisms responsible for gentamicin induced nephrotoxicity. Gentamicin causes the overproduction of Reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals and hydrogen peroxide. In normal physiology, antioxidant systems within the cells, including endogenous enzymes like superoxide dismutase, catalase and glutathione, act as cellular defence systems. Gentamicin, however, can disrupt the balance between oxidants and antioxidants leading to oxidative stress. Increased ROS damages membrane lipids, proteins, and nucleic acids resulting in dysfunction and structural damage to the cells. Gentamicin nephrotoxicity is characterized by the presence of lipid peroxidation. ROS combine with the polyunsaturated fatty acids, which are present in the cellular membranes, and form lipid peroxides and secondary toxic products like malondialdehyde (MDA). An increased lipid peroxidation leads to damage to membrane integrity, changes in membrane permeability and disruption of normal cellular functions. Experimental studies always show an increase in MDA level in gentamicin treated animals, showing significant renal tissue damage from oxidation. Another important event in gentamicin nephrotoxicity is mitochondrial dysfunction. Mitochondria are the main producers of energy for the cells, and are particularly vulnerable to oxidative stress. The generation of ROS by gentamicin causes damage to the mitochondrial membranes, impairs the activity of the electron transport chain and decreases ATP production. Depleted energy leads to reduced ability of tubular epithelial cells to actively transport and causes cellular injury. In addition, damaged mitochondria release proapoptotic factors that trigger the cell death pathways. Gentamicin-induced renal injury is associated with significant inflammation.

Various inflammatory signaling pathways such as nuclear factor-kappa B (NF- κ B) become activated with oxidative stress. These pathways activate and stimulate the release of pro-inflammatory cytokines including tumour necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6). These inflammatory mediators attract immune cells to the injury site and make it worse. Prolonged inflammation can lead to tubular degeneration, vascular dysfunction and gradual loss of kidney function. Another important mechanism involved in gentamicin induced nephrotoxicity is called 'apoptosis'. Increase in anti apoptotic proteins like Bcl-2 and decrease in pro apoptotic proteins like Bax and caspases in oxidative stress and mitochondrial damage are hallmarks of intrinsic apoptotic pathways. The imbalance leads to apoptosis or programmed cell death in tubular epithelial cells. When apoptosis occurs in the kidney in large quantities, it leads to loss of nephrons and kidney dysfunction. Gentamicin may also cause necrosis of renal tubular cells, apart from the apoptosis. Necrosis differs from apoptosis in that it causes swelling and rupture of the cell membranes and leakage of intracellular contents into the surrounding tissues. This inflammation perpetuates further injury to the kidneys. In kidneys of gentamicin-treated animals, tubular necrosis, desquamation of the epithelial cells, glomerular congestion and infiltration of inflammatory cells are common features, as identified by histopathological examination. There are several biochemical markers that are used to evaluate gentamicin-induced nephrotoxicity. Raised serum creatinine and blood urea nitrogen (BUN) levels are typical post-gentamicin and are associated with decreased glomerular filtration. Other signs are elevated protein in the urine, decreased creatinine clearance, and changes in electrolyte levels. Other laboratory tests, like oxidative stress markers like malondialdehyde, reduced glutathione, superoxide dismutase, and catalase that show the degree of renal damage is also measured in experimental studies. Histopathological examination is important for information on histological lesions of gentamicin nephrotoxicity. The microscopic findings usually show degeneration of the epithelium of the proximal tubules, tubular dilation, cast formation, alteration of the glomeruli, interstitial edema, and inflammatory infiltration. The severity of these changes is generally proportional to



the length of time and the dose of gentamicin therapy. Since oxidative stress is thought to be the main mechanism involved in the gentamicin nephrotoxicity, antioxidants have been the focus of much interest as possible nephroprotective agents. Many natural products and medicinal plants extracts have been shown to have protective effects, through their ability to block the production of ROS, boost endogenous antioxidant systems, suppress inflammatory responses and prevent the onset of apoptosis. Flavonoids, phenolic compounds, carotenoids and terpenoids from plants have yielded especially promising results in the experimental models of gentamicin-induced renal injury. Herbal medicines have been the focus of recent research as alternative medicines that do not cause nephrotoxicity. Different medicinal plants have shown a remarkable protective effect against kidney damage induced by gentamicin by acting as antioxidants and anti-inflammatory. The results indicate that natural products could be important therapeutic agents to reduce renal injury without compromising the anti-bacterial effects of gentamicin. In this group of medicinal plants, *Tagetes erecta* has consequently gained increasing scientific interest because of its high phytochemical content and a variety of pharmacological activities. The flavonoids, carotenoids, phenolic compounds, terpenoids and essential oils found in the plant have strong antioxidant and anti-inflammatory activity. The anti-oxidative activity and anti-inflammatory action of these bioactive components can reverse the gentamicin induced nephrotoxicity. Thus, the study of nephroprotective effect of *Tagetes erecta* against gentamicin-induced renal damage is an area that may have therapeutic relevance. To summarize, the nephrotoxicity of gentamicin is a complex phenomenon that includes oxidative stress, lipid peroxidation, mitochondrial dysfunction, inflammation, apoptosis and necrosis. All these mechanisms together result in renal structural and functional damage. The knowledge of these pathological mechanisms offers a solid scientific platform for testing the natural nephroprotective agents and continues to be a basis for further research on the therapeutic potential of medicinal plants like *Tagetes erecta* in the prevention of kidney injury caused by drugs.

Table no. 3

Parameter	Effect of Gentamicin
Serum Creatinine	Increased
Blood Urea Nitrogen (BUN)	Increased
Creatinine Clearance	Decreased
Malondialdehyde (MDA)	Increased
Reduced Glutathione (GSH)	Decreased
Superoxide Dismutase (SOD)	Decreased
Catalase (CAT)	Decreased
TNF- α	Increased
IL-1 β	Increased
IL-6	Increased

4. Role Of Oxidative Stress, Inflammation, And Apoptosis In Renal Injury

Renal injury is a complex pathological state with multiple molecular and cellular mechanisms involved in the process. Of these, oxidative stress, inflammation, and apoptosis are well known as the most important factors in the initiation and progression of kidney damage. These processes are closely interrelated and tend to reinforce each other and lead to structural and functional changes of renal tissues. Oxidative stress is the initial event that triggers inflammatory and apoptotic pathways in different types of nephrotoxicity such as that elicited by gentamicin. These mechanisms should be understood to develop effective nephroprotective drugs and also to develop scientific bases for the use of medicinal plants like *Tagetes erecta* which contain antioxidants.

Oxidative Stress in Renal Injury

Oxidative stress is the state that occurs when the biosynthesis of reactive oxygen species (ROS) is greater than the ability of the endogenous antioxidant defense systems. In the normal state of physiological function, ROS are produced in the normal course of cellular metabolism and are essential to cell signaling and immune defense. But too much ROS production can be harmful and may cause dysfunction of cells and damage to tissues.



Superoxide anions, hydroxyl radicals, hydrogen peroxide and peroxynitrite are the major reactive oxygen species that contribute to renal injury. These very reactive molecules are responsible for damaging lipids, proteins and other macromolecules of cells. The kidneys are especially vulnerable to the effects of oxidative damage, due to high metabolic activity, high content of mitochondria and great blood supply. Nephrotoxic agents, like gentamicin, cause a massive increase in the generation of ROS in the cells. Hyperproduction of ROS leads to unbalanced redox state of cells and triggers lipid peroxidation of membrane phospholipids. Lipid peroxidation results in the generation of toxic aldehyde metabolites such as malondialdehyde (MDA) that continue to cause damage to cell structures and disrupt membrane integrity. As a result, the cells in the renal tubules can be more easily damaged and become dysfunctional. Proteins are also susceptible of oxidative damage. Protein oxidation due to ROS may impact on enzyme function, receptor sensitivity and cellular signaling pathways. Likewise, oxidative damage to DNA can lead to mutations, dysfunction in gene expression and the triggering of cell death pathways. Cumulative effects play an important role in the development of renal injury. The body has multiple enzymatic and non-enzymatic antioxidant defense systems to help protect against oxidative stress. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are key antioxidant enzymes. Reduced glutathione (GSH) is a prominent intracellular antioxidant that helps in scavenging ROS and regulating cellular redox status. During nephrotoxic conditions, the reduction of these antioxidants adds to the oxidative damage and promotes renal deterioration.

Mitochondrial Dysfunction and Oxidative Damage

The mitochondria are essential to the production of energy and the survival of the cell. They are also important sources of Reactive Oxygen Species. Mitochondrial structure and function will be disrupted by excess oxidative stress, resulting in decreased ATP production and depletion of energy. The kidney tubular cells demand high energy for active transport, which makes the mitochondrial dysfunction have wide repercussions on kidney function. Mitochondrial membrane damage results in increased permeability

of the membrane and the release of pro-apoptotic proteins into the cytoplasm, like cytochrome c. This event brings about apoptotic pathways that play a role in renal cell death. Furthermore, mitochondrial dysfunction leads to further production of ROS, establishing an "oxide vicious cycle" and mitochondrial cell damage.

Inflammation in Renal Injury

The inflammatory component is a key element in renal injury process. While inflammation is a useful mechanism of defence to combat harmful stimuli and repair tissues, there can be severe tissue damage if inflammation is excessive or prolonged. Oxidative stress is a powerful trigger of inflammatory signaling pathways. Reactive oxygen species activate transcription factors, like nuclear factor-kappa B (NF- κ B) that control the expression of multiple pro-inflammatory genes. NF- κ B activation leads to an upregulation of inflammatory mediators such as tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6) and several chemokines. These cytokines attract and activate immune cells, including macrophages and neutrophils, to the kidney. Further production of activated immune cells releases further rOS, proteolytic enzymes and inflammatory mediators, which cause further damage to renal structures. This means that inflammation increases oxidative stress and accelerates the continuously worsening kidney function. Inflammatory responses also influence renal hemodynamics by changing the permeability and blood flow of blood vessels. The endothelial dysfunction may occur, resulting in inadequate oxygen transfer and hypoxia of tissues. Oxygen deficit is further aggravated by oxidative stress, leading to renal injury. Renal fibrosis, a process involving excess accumulation of extracellular matrix proteins, is closely related to persistent inflammation. As fibrosis progresses, normal functional tissue is replaced and this leads to irreversible loss of kidney function. Thus, anti-inflammatory therapy is regarded as one of the therapeutic approaches to prevent the progression of chronic kidney disease.

Apoptosis in Renal Injury

Apoptosis, or programmed cell death, is a highly regulated process that eliminates damaged or



dysfunctional cells while maintaining tissue integrity. Although apoptosis is essential for normal physiological homeostasis, excessive activation of apoptotic pathways contributes significantly to renal injury. Oxidative stress and inflammation are major triggers of apoptosis in kidney cells. Increased ROS production damages mitochondrial membranes and promotes the release of cytochrome c into the cytoplasm. This event activates caspases, a family of proteolytic enzymes that execute the apoptotic program. The intrinsic apoptotic pathway is regulated by members of the Bcl-2 protein family. Pro-apoptotic proteins such as Bax and Bak promote cell death, whereas anti-apoptotic proteins such as Bcl-2 and Bcl-xL support cell survival. During nephrotoxic injury, oxidative stress shifts this balance toward apoptosis by increasing pro-apoptotic protein expression and reducing anti-apoptotic protein levels. Activation of apoptotic pathways results in characteristic cellular changes, including chromatin condensation, DNA fragmentation, membrane blebbing, and formation of apoptotic bodies. Excessive apoptosis of tubular epithelial cells contributes to nephron loss and impaired renal function.

Interrelationship between Oxidative Stress, Inflammation, and Apoptosis

Oxidative stress, inflammation, and apoptosis do not occur independently. Instead, they form a highly interconnected network that drives renal injury progression. Oxidative stress activates inflammatory pathways, while inflammatory mediators further enhance ROS generation. Both oxidative stress and inflammation stimulate apoptotic signaling, leading to cell death and tissue damage. This positive feedback loop creates a self-perpetuating cycle that amplifies renal injury. Consequently, therapeutic interventions targeting only one pathway may provide limited protection. Agents possessing antioxidant, anti-inflammatory, and anti-apoptotic activities simultaneously are therefore considered particularly valuable for nephroprotection.

Therapeutic Implications

Growing evidence suggests that natural products rich in bioactive phytochemicals can effectively interrupt the pathological cycle of oxidative stress,

inflammation, and apoptosis. Flavonoids, phenolic acids, carotenoids, and terpenoids have demonstrated potent antioxidant and cytoprotective properties in various experimental models of nephrotoxicity. These compounds may reduce ROS generation, enhance endogenous antioxidant defenses, suppress inflammatory cytokine production, and inhibit apoptotic pathways. As a result, medicinal plants containing these phytochemicals have attracted considerable attention as potential nephroprotective agents. *Tagetes erecta* is particularly noteworthy because it contains abundant flavonoids, carotenoids, phenolic compounds, and other antioxidant constituents. These phytochemicals may protect renal tissues by scavenging free radicals, reducing inflammatory responses, preserving mitochondrial function, and preventing apoptosis. Therefore, understanding the relationship between oxidative stress, inflammation, and apoptosis provides a strong mechanistic basis for investigating the nephroprotective potential of *Tagetes erecta* against gentamicin-induced kidney injury.

Table no. 4

Biomarker	Significance
MDA	Indicator of lipid peroxidation
GSH	Cellular antioxidant defense
SOD	Superoxide scavenging enzyme
CAT	Hydrogen peroxide detoxification
TNF- α	Pro-inflammatory cytokine
IL-1 β	Inflammatory mediator
IL-6	Marker of inflammation
Caspase-3	Apoptosis marker
Bax	Pro-apoptotic protein
Bcl-2	Anti-apoptotic protein

5. Medicinal Plants With Reported Nephroprotective Activity

Increased kidney disease and the rising number of drug-induced nephrotoxicity have sparked a great deal of interest in the development of effective nephroprotective therapies. While the main objective of conventional treatment approaches is to control symptoms and to stop further damage to the kidneys, many of the treatments available have limitations, including side effects, cost and effectiveness. Thus, medicinal plants are gaining attention as potential



alternatives because of their long history of traditional use, favorable safety profiles and high content of bioactive phytochemicals. The secondary metabolites of medicinal plants are of different classes such as flavonoids, phenolic acids, alkaloids, terpenoids, saponins, tannins and carotenoids. These compounds exhibit antioxidant, anti-inflammatory, anti-apoptotic and cytoprotective effects which could be responsible for renal protection. A large number of experimental studies have shown that plant extracts can help alleviate renal damage, which is currently attributed to attenuation of oxidative stress, antioxidant enzyme activity, inflammatory responses and renal function markers.

Curcuma longa (Turmeric)

Curcuma longa, popularly referred to as turmeric, is one of the most widely studied medicinal herbs with nephroprotective properties. Curcumin is the principal active compound found in turmeric, it is a polyphenolic compound with powerful antioxidant and anti-inflammatory properties. In several experimental models of renal injury, curcumin has been found to exert antioxidant effects by decreasing lipid peroxidation, increasing the levels of endogenous antioxidants, and inhibiting the production of pro-inflammatory cytokines. Several studies have shown that including curcumin in the diet of gentamicin-induced nephrotoxicity models resulted in a significant reduction in serum creatinine and blood urea nitrogen. On the histopathological level, curcumin treatment has also been shown to have a beneficial effect on the degree of tubular degeneration, inflammatory infiltration and oxidative damage. Based on these results, it appears that turmeric offers significant defense against kidney damage caused by drugs.

Moringa oleifera

Moringa oleifera is a well known medicinal plant with nutritional and medicinal properties. Leaves are rich in flavonoids, phenolic compounds, vitamins and minerals which give its antioxidant properties. In experimental studies, *Moringa* extracts have been shown to ameliorate renal oxidative stress and renal function in nephrotoxic animal models. The primary nephroprotective properties of *Moringa* include its ability to scavenge the reactive oxygen species, bring

back antioxidant enzyme activity and inhibit inflammatory pathways. Dietary supplementation with *Moringa* extracts has been linked to a decrease in serum creatinine, urea and oxidative damage markers. Moreover, histological evaluations have shown the preservation of renal architecture and reduced tubular injuries.

Azadirachta indica (Neem)

Neem (*Azadirachta indica*) is a tree that has been used for centuries in traditional medicine systems. Antioxidant, anti-inflammatory, antimicrobial and immunomodulatory effects of various parts of the plant. The flavonoids, limonoids, polyphenols and other bioactive compounds found in the leaves of neem are responsible for its renal protection properties. Experimental investigations have demonstrated that neem extracts have beneficial effects on renal function and oxidative stress in nephrotoxic induced animals. The protective effects are attributed to reduction of lipid peroxidation, elevation of glutathione levels, and an elevation of antioxidant enzymes like catalase and superoxide dismutase. These mechanisms contribute to the maintenance of cell integrity and to the prevention of progression of renal injury.

Camellia sinensis (Green Tea)

Catechins are abundant in green tea and epigallocatechin gallate (EGCG) in particular has potent anti-inflammatory and antioxidant effects. The protective effects of green tea polyphenols against oxidative stress induced diseases, such as renal diseases, have been shown in numerous studies. Green tea extracts have been demonstrated to have renal functions markers improving properties, to lower the production of inflammatory cytokines and to prevent histopathological changes in nephrotoxicity models. Catechins' potent antioxidant and protective effects on mitochondria are thought to play a significant role in their nephroprotective benefits.

Zingiber officinale (Ginger)

Ginger is a medicinal plant which is commonly used and contain the bioactive compounds gingerol, shogaols, and zingerone. The phytochemicals in these



herbs have strong antioxidant and anti-inflammatory effects, which could help prevent damage to renal tissues. In experimental nephrotoxicity studies, ginger extract was reported to have antioxidant activity, suppress the release of inflammatory mediators and enhance the renal biochemical parameters. Improvements in histological parameters after ginger treatment further suggests its nephroprotective effects.

Phyllanthus niruri

Phyllanthus niruri has traditionally been used to treat kidney stones, liver disorders and urinary tract diseases. The chemical constituents of the plant include lignans, flavonoids, tannins, polyphenolic compounds which has pharmacologic properties. The results suggest that *Phyllanthus* extracts have anti-oxidative and anti-inflammatory properties in renal tissues. These effects are correlated with the improvement of antioxidant status, reduction of lipid peroxidation and the improvement of the preservation of the kidney morphology. Thus, the plant has been found to be a potential nephroprotective plant.

Terminalia chebula

The *terminalia chebula* is the plant of great medicinal value in traditional ayurvedic medicine. It is enriched with tannins, phenolics and flavonoids with high free radical scavenging activity. Experimental studies have proven that extracts of *Terminalia chebula* can effectively decrease the nephrotoxic effects of different chemical agents. Restoration of antioxidant enzyme activity, reduction in inflammatory markers and preservation of renal histoarchitecture are examples of protective effects. The results confirm the therapeutic potential of the plant in renal diseases.

Mechanisms of Herbal Nephroprotection

While there are differences in the phytochemical composition of medicinal plants, there are some common mechanisms that explain their nephroprotective effects. Antioxidant activity is the most crucial mechanism. Antioxidants derived from plants can scavenge ROS and lessen the damage to cell macromolecules mediated by ROS. These compounds restore redox balance, thus protecting renal tissue from lipoperoxidation and mitochondrial

dysfunction. Another major mechanism is to dampen inflammation. Numerous phytochemicals can block activation of NF- κ B as well as other inflammatory pathways, which in turn decreases the production of cytokines and infiltration of immune cells. This anti-inflammatory effect prevents tissue damage and promotes recovery of renal function. Medicinal plants also have anti-apoptotic properties which affect the expression of proteins related to programmed cell death. Up-regulation of anti-apoptotic proteins and blockade of caspase activation increases the survival of cells and maintains their nephron integrity. Moreover, some phytochemicals play a role in improving mitochondrial function, energy production within the cell and in stabilizing membrane structures. Overall nephroprotective activity of medicinal plants is due to these combined effects.

Relevance of Medicinal Plants in Gentamicin-Induced Nephrotoxicity

Most experimental nephroprotective studies have been undertaken with models of renal injury caused by gentamicin. Medicinal plants with antioxidant and anti-inflammatory activity are especially effective in this model because oxidative stress and inflammation are the key mechanisms involved in gentamicin nephrotoxicity. Many plant extracts have shown marked decrease in serum creatinine, blood urea nitrogen, lipid peroxidation and histopathological damage after gentamicin administration. The results of the present study make scientific basis for the use of medicinal plants as nephroprotective agents and they spurred further research of medicinal plants with unexplored renal protective activity.

Transition to *Tagetes erecta*

Among the various medicinal plants investigated for pharmacological applications, *Tagetes erecta* has gained increasing attention because of its diverse bioactive constituents and wide range of therapeutic activities. The plant contains flavonoids, carotenoids, phenolic compounds, triterpenoids, and essential oils known for their antioxidant and anti-inflammatory effects. Given that oxidative stress, inflammation, and apoptosis play crucial roles in gentamicin-induced renal injury, the phytochemical composition of *Tagetes erecta* suggests significant potential for nephroprotection.



Although studies have extensively documented the antioxidant, hepatoprotective, antimicrobial, wound-healing, and anti-inflammatory properties of *Tagetes erecta*, its nephroprotective potential remains relatively underexplored. Therefore, a comprehensive

evaluation of its phytochemistry and pharmacological activities is necessary to understand its possible role in preventing gentamicin-induced kidney damage and to support future experimental and clinical investigations.

Table no.5

Plant	Major Phytoconstituents	Reported Mechanism
<i>Curcuma longa</i>	Curcumin	Antioxidant, anti-inflammatory
<i>Moringa oleifera</i>	Flavonoids, phenolics	ROS scavenging
<i>Azadirachta indica</i>	Limonoids, flavonoids	Antioxidant protection
<i>Camellia sinensis</i>	Catechins	Anti-inflammatory
<i>Zingiber officinale</i>	Gingerols, shogaols	Antioxidant activity
<i>Phyllanthus niruri</i>	Lignans, polyphenols	Cytoprotection
<i>Terminalia chebula</i>	Tannins, flavonoids	Anti-apoptotic effects
<i>Tagetes erecta</i>	Flavonoids, carotenoids	Potential nephroprotection

6. Phytochemistry And Pharmacological Activities Of *Tagetes Erecta*

Tagetes erecta L., commonly known as African marigold or Aztec marigold, is an annual flowering plant belonging to the family Asteraceae. The plant is widely cultivated throughout tropical and subtropical regions for ornamental, medicinal, agricultural, and industrial purposes. Native to Mexico and Central America, *T. erecta* has been traditionally used in folk medicine for the treatment of inflammatory disorders, wounds, gastrointestinal disturbances, respiratory ailments, skin infections, and fever. In recent decades, scientific investigations have validated many of its traditional uses and revealed a wide range of biological activities. These pharmacological effects are largely attributed to the presence of diverse bioactive phytochemicals distributed throughout different parts of the plant, including flowers, leaves, stems, and roots. The leaves of *T. erecta*, in particular, contain numerous antioxidant and anti-inflammatory constituents that may contribute to nephroprotective activity.

Botanical Description

Tagetes erecta is an erect, aromatic herb that typically grows between 30 cm and 120 cm in height. The plant possesses branched stems, pinnately divided leaves, and large yellow to orange flower heads. The leaves

are opposite in arrangement, lanceolate in shape, and characterized by serrated margins. The entire plant emits a characteristic odor due to the presence of volatile essential oils.

Taxonomical Classification

Table no. 6

Taxonomic Rank	Classification
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Asterales
Family	Asteraceae
Genus	<i>Tagetes</i>
Species	<i>Tagetes erecta</i> L.

Phytochemical Composition of *Tagetes erecta*

The therapeutic importance of *Tagetes erecta* is primarily associated with its rich phytochemical profile. Various phytochemical investigations have identified numerous secondary metabolites with significant biological activities.

Flavonoids

Flavonoids represent one of the most important classes of bioactive compounds present in *T. erecta*.



These compounds are well known for their potent antioxidant and anti-inflammatory activities.

Major flavonoids reported from *T. erecta* include:

- Quercetin
- Kaempferol
- Quercetagenin
- Patuletin
- Isorhamnetin

Flavonoids protect biological systems by scavenging free radicals, chelating metal ions, and enhancing endogenous antioxidant defenses. Their ability to inhibit oxidative stress makes them particularly relevant in the prevention of nephrotoxicity.

Carotenoids

The flowers and leaves of *T. erecta* contain significant quantities of carotenoids, which are responsible for the characteristic yellow-orange coloration of the plant.

Major carotenoids include:

- Lutein
- Zeaxanthin
- β -Carotene
- Cryptoxanthin

Among these compounds, lutein is considered the most abundant and commercially important carotenoid. Carotenoids function as powerful antioxidants and protect cells from oxidative damage caused by reactive oxygen species.

Phenolic Compounds

Phenolic compounds contribute substantially to the antioxidant capacity of *T. erecta*. These compounds neutralize free radicals and inhibit oxidative chain reactions.

Reported phenolic constituents include:

- Gallic acid
- Caffeic acid
- Ferulic acid
- Chlorogenic acid
- p-Coumaric acid

Phenolic acids play a significant role in reducing lipid peroxidation and inflammatory responses.

Terpenoids and Triterpenes

Terpenoids are another important class of compounds found in *Tagetes erecta*. These molecules exhibit various biological activities including anti-inflammatory, antimicrobial, and antioxidant effects.

Common terpenoids identified include:

- α -Pinene
- β -Pinene
- Limonene
- Ocimene
- Tagetone

These compounds contribute to the medicinal value of the plant and may participate in renal protective mechanisms.

Essential Oils

The leaves and flowers of *T. erecta* contain volatile oils rich in monoterpenes and sesquiterpenes. Essential oils exhibit antimicrobial, anti-inflammatory, insecticidal, and antioxidant activities.

Major components include:

- Limonene
- Linalool
- Tagetone
- Ocimenone



- Caryophyllene

These constituents have demonstrated significant biological activities in both in vitro and in vivo studies.

Antioxidant Activity

Antioxidant activity is among the most extensively studied pharmacological properties of *Tagetes erecta*. Various extracts prepared from flowers and leaves have demonstrated remarkable free radical scavenging activity in multiple experimental models. The antioxidant effects are primarily attributed to flavonoids, carotenoids, and phenolic compounds. These phytochemicals neutralize reactive oxygen species before they can damage cellular structures. In addition, they enhance the activity of endogenous antioxidant enzymes such as:

- Superoxide dismutase (SOD)
- Catalase (CAT)
- Glutathione peroxidase (GPx)

Since oxidative stress is a major mechanism involved in gentamicin-induced nephrotoxicity, the antioxidant properties of *T. erecta* suggest considerable nephroprotective potential.

Anti-inflammatory Activity

Inflammation plays a central role in the progression of renal injury. Several studies have reported significant anti-inflammatory effects of *Tagetes erecta* extracts.

The plant has been shown to:

- Suppress inflammatory cytokine production
- Reduce edema formation
- Inhibit leukocyte infiltration
- Decrease inflammatory mediator release

These effects are largely mediated through flavonoids and terpenoids, which interfere with inflammatory signaling pathways including NF- κ B activation.

By reducing inflammation, *T. erecta* may help prevent further deterioration of renal tissues following toxic injury.

Antimicrobial Activity

Numerous investigations have demonstrated the antimicrobial properties of *Tagetes erecta* against bacteria, fungi, and certain parasites.

Extracts of the plant have exhibited activity against:

- *Escherichia coli*
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Candida albicans*

The antimicrobial activity is primarily attributed to essential oils, flavonoids, and terpenoids.

Hepatoprotective Activity

Experimental studies have demonstrated hepatoprotective effects of *T. erecta* against chemically induced liver injury. These protective effects are associated with antioxidant activity and stabilization of cellular membranes.

Observed benefits include:

- Reduction of liver enzyme levels
- Prevention of lipid peroxidation
- Improvement of histological architecture
- Enhancement of antioxidant defenses

These findings support the broader organ-protective potential of the plant.

Wound Healing Activity

Traditional medicine systems have long utilized *Tagetes erecta* for wound management. Modern studies have confirmed its ability to accelerate wound healing through multiple mechanisms.

These include:



- Enhanced collagen synthesis
- Reduced inflammation
- Improved tissue regeneration
- Antimicrobial protection

Such effects indicate the capacity of the plant to support tissue repair processes.

Anticancer Activity

Recent investigations have reported cytotoxic and antiproliferative effects of *T. erecta* extracts against various cancer cell lines. The anticancer activity is believed to involve induction of apoptosis, inhibition of cell proliferation, and modulation of oxidative stress pathways. Although further studies are needed, these findings demonstrate the broad pharmacological potential of the plant.

Relevance to Nephroprotection

The phytochemical composition and pharmacological profile of *Tagetes erecta* strongly support its potential role as a nephroprotective agent. The major mechanisms involved in gentamicin-induced nephrotoxicity include oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis. Interestingly, the principal phytochemicals present in *T. erecta* possess activities capable of counteracting each of these pathological processes. Flavonoids and phenolic compounds may reduce oxidative stress through free radical scavenging. Carotenoids can protect cellular membranes from lipid peroxidation. Terpenoids and essential oils may suppress inflammatory responses and improve cellular survival. Collectively, these effects could preserve renal structure and function during exposure to nephrotoxic agents. Therefore, the pharmacological characteristics of *Tagetes erecta* provide a strong scientific rationale for investigating its nephroprotective efficacy against gentamicin-induced kidney injury. Further experimental studies are required to fully elucidate its mechanisms of action and therapeutic potential.

7. Potential Nephroprotective Mechanisms Of *Tagetes Erecta* Against Gentamicin-Induced Nephrotoxicity

Gentamicin induced nephrotoxic reaction is a multifactorial process which includes oxidative stress, inflammation, mitochondrial dysfunction, apoptosis and tubular necrosis. The combination of these processes ultimately leads to a fall in kidney function and kidney tissue damage. Currently, there are not any effective therapeutic approaches to nephrotoxicity, so much effort has gone into finding natural products that can help to prevent renal tissue damage. *Tagetes erecta* has a high phytochemical content of flavonoids, carotenoids, phenolic compounds, terpenoids, and essential oils. It has been shown in many studies that these phytoconstituents exhibit potent antioxidant, anti-inflammatory and cytoprotective activities. The nephroprotective potential of *Tagetes erecta* is limited at present; however, its pharmacological properties indicate that it has great potential to protect against gentamicin-induced renal damage.

Antioxidant-Mediated Renal Protection

It is believed that oxidative stress is the main mechanism for gentamicin nephrotoxicity. Gentamicin triggers excessive amounts of reactive oxygen species (ROS) such as superoxide radicals, hydroxyl radicals and hydrogen peroxide. These reactive molecules cause injury to lipid, protein and DNA in cells which results in impaired renal function. *Tagetes erecta* contains flavonoids and phenolics with high free radical scavenging properties. Quercetin, quercetagenin, kaempferol and phenolic acids are able to neutralize ROS prior to interaction with cellular components. This antioxidant property can significantly decrease the oxidative damage in renal tissues. Phytochemicals of *T. erecta* not only scavenge free radicals directly, but can also strengthen the antioxidant defence mechanism in the body. An increased activity of antioxidant enzymes like SOD, CAT, GPx may help increase cell resistance to oxidative stress. Replenishment of reduced glutathione (GSH) may be further protection against antioxidants and maintain renal cell integrity. In this way, the *Tagetes erecta* can inhibit lipid peroxidation, the formation of malondialdehyde and preserve the



stability of the membranes in the kidney tissues of animals treated with gentamicin.

Inhibition of Lipid Peroxidation

Lipid peroxidation is a significant effect of oxidative stress, and is a significant contributor to renal injury. Reactive oxygen species damage polyunsaturated fatty acids in cell membranes resulting in toxic aldehyde formation and compromising membrane integrity. The antioxidants lutein and zeaxanthin present in *Tagetes erecta* are very efficient antioxidants that prevent lipid peroxidation. The compounds maintain the integrity of cell membranes and help prevent oxidative damage to phospholipids. Carotenoids can decrease the damage to the membranes, which can help preserve the normal functions of intracellular membrane transport, maintain the integrity of the mitochondria, and prevent leakage of intracellular enzymes. Thus, the anti-lipid peroxidation activity could be one of the relevant mechanisms of the protective effects of *T. erecta* on renal tissue.

Anti-inflammatory Mechanisms

The significance of inflammation in increasing gentamicin-induced renal injury is undeniable. Oxidative stress leads to activation of inflammatory signaling pathways, causing the upregulation of pro-inflammatory cytokines including TNF- α , IL-1 β and IL-6. Every experimental research carried out to date has revealed that *Tagetes erecta* contains flavonoids and terpenoids with marked anti-inflammatory activity. These compounds could inhibit the activation of nuclear factor-kappa B (NF- κ B), a crucial transcription factor for the expression of inflammatory genes. Blocking the activation of NF- κ B decreases the production of cytokines and infiltration of inflammatory cells to damaged renal tissues. Minimizing inflammation may help to prevent secondary tissue injury and promote recovery of renal function. Additionally, anti-inflammatory activity can prevent chronic renal fibrosis, which is a key feature of the chronic injury of the kidney after toxic damage.

Preservation of Mitochondrial Function

Mitochondria are highly vulnerable to oxidative stress and a major role in the pathogenesis of nephrotoxicity.

Gentamicin disrupts mitochondrial function and causes decreased ATP production, decreased cell metabolism, and induction of apoptotic pathways. The antioxidant properties of *Tagetes erecta* can help to shield the mitochondrial membranes from oxidative damage and maintain the normal mitochondrial function. Renal tubular epithelial cells maintain their mitochondrial integrity and this supports ATP production and other cellular functions. *T. erecta* could do this by stopping mitochondria injury, which may disrupt the process of apoptosis and death of the cell.

Anti-apoptotic Effects

Gentamicin induced kidney injury is characterized with massive nephron loss and apoptosis plays a significant role in this loss. Over-accumulation of oxidative stress and mitochondrial dysfunction triggers apoptotic signaling pathways such as caspases and Bcl-2 family proteins. The ability of the bioactive compounds of *Tagetes erecta* to inhibit apoptosis can be mediated by various mechanisms. The antioxidant activity helps to inhibit oxidative stimuli that activate the apoptotic pathways, and the maintenance of normal mitochondrial function inhibits the release of pro-apoptotic factors like cytochrome c. Furthermore, flavonoids could modulate the expression of proteins involved in apoptosis by upregulating the expression of anti-apoptotic protein, Bcl-2, and downregulating the expression of pro-apoptotic protein, Bax. This type of modulation helps preserve the survival of cells and helps prevent excessive cell loss in renal tissues.

Protection of Renal Tubular Cells

Gentamicin only affects the proximal tubular epithelium. Gentamicin is accumulated into these cells and starts oxidative damage, inflammation and apoptosis. The antioxidant, anti-inflammatory and anti-apoptotic properties of *Tagetes erecta* might directly protect tubular epithelial cells. Maintenance of tubular integrity will enhance reabsorption processes, preserve nephron function and lessen the degree of renal injury. The benefits of such protection are expected to be histopathological, with the appearance of less tubular degeneration, necrosis, inflammatory infiltration and normal renal architecture.



Potential Effects on Renal Biomarkers

Gentamicin-induced nephrotoxicity is typically associated with elevated serum creatinine, blood urea nitrogen (BUN), uric acid, and oxidative stress markers. Administration of nephroprotective agents often results in normalization of these parameters.

Based on its pharmacological properties, *Tagetes erecta* may potentially:

- Reduce serum creatinine levels.
- Decrease blood urea nitrogen concentrations.
- Lower malondialdehyde (MDA) levels.
- Increase glutathione (GSH) content.
- Enhance SOD and CAT activity.
- Suppress inflammatory cytokines.
- Improve creatinine clearance.

These effects collectively indicate improved renal function and reduced tissue injury.

Proposed Mechanistic Pathway

The nephroprotective activity of *Tagetes erecta* can be explained through a multifactorial mechanism involving simultaneous modulation of oxidative stress, inflammation, and apoptosis.

Following administration, bioactive phytoconstituents may:

1. Scavenge reactive oxygen species.
2. Enhance antioxidant enzyme activity.
3. Reduce lipid peroxidation.
4. Suppress inflammatory cytokine production.
5. Protect mitochondrial function.
6. Inhibit apoptotic signaling pathways.
7. Preserve renal tubular architecture.
8. Improve kidney function biomarkers.

The integration of these effects may significantly reduce the severity of gentamicin-induced renal injury.

Future Perspectives

Despite strong theoretical and pharmacological support for nephroprotection, direct experimental evidence regarding the renal protective activity of *Tagetes erecta* remains limited. Future studies should focus on:

- Isolation and characterization of active nephroprotective constituents.
- Evaluation of dose-response relationships.
- Investigation of molecular signaling pathways.
- Histopathological assessment of renal protection.
- Long-term safety studies.
- Clinical translation of preclinical findings.

Such investigations will provide valuable insights into the therapeutic potential of *Tagetes erecta* as a natural nephroprotective agent.

CONCLUSION

The oxidative stress, inflammation, mitochondrial dysfunction and apoptosis induced by gentamicin are associated with renal structural and functional impairments, making gentamicin-induced nephrotoxicity a major clinical challenge. The antioxidant, anti-inflammatory, and cytoprotective properties of medicinal plants with high concentrations of bioactive phytochemicals are suggested to possess nephroprotective effects. More and more pieces of evidence have emerged suggesting medicinal plants with high concentration of bioactive phytochemicals have nephroprotective effects with antioxidant, anti-inflammatory, and cytoprotective properties. Of these, *Tagetes erecta* has received much interest due to its rich phytochemical profile including flavonoids, carotenoids, phenolic compounds, terpenoids and essential oils, which exhibit substantial pharmacological properties that can inhibit the key mechanisms responsible for kidney damage.



The findings from the literature indicated that *Tagetes erecta* might have nephroprotective effects through the inhibition of generation of ROS, boosting endogenous antioxidant activities, down-regulation of inflammatory mediators, maintaining mitochondrial activities, and inhibition of the apoptotic pathway. Though there is limited evidence of it being effective for gentamicin induced nephrotoxicity, its known antioxidant and anti-inflammatory properties offer great scientific rationale for additional study. Further experimental and clinical trials are recommended to confirm its nephroprotective activity, elucidate the active principles which mediate renal protection and evaluate its use as a safe and effective herbal therapeutic intervention for the prevention and treatment of drug-induced kidney injury.

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