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OVERALL REVIEW ON WITHANIA SOMNIFERA IN THE ARSENIC INDUCED NEPHROTOXICITY

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ABSTRACT

The current investigation was perfomed to determine the ameliorative properties of *Withania somnifera* and its active components against arsenic-induced nephrotoxicity. Renal functional markers (urea, uric acid and creatinine), mitochondrial enzymes (tricarboxyclic acid cycle and electron transport chain enzymes), and histopathology of the kidney were assessed to determine the extent of arsenic-induced toxicity. Oxidative stress (lipid peroxidation, enzymatic and non-enzymatic antioxidants) in the kidney of the studied animals was also evaluated. The *endogenous* antioxidant status in the kidney of the animals was restored by the *W.somnifera*.In addition, *W.somnifera* treatment significantly ($p < 0.05$) decreased the arsenic-induced increased levels of renal functional parameters. Furthermore, arsenic administration elicited an inflammatory response in the animals that caused induction of TNF-α and IL-1β. In addition, the imbalance in Bax/Bcl-2 expression of BB- induced animals was effectively prevented by *Withania Somnifera*. Ashwagandha work by interacting with components of the proinflammatory cell signaling pathway, such as NF-κB, signaling kinases, HSP90, Nrf2, and the inflammasome complex. These findings suggest that *W.somnifera* treatment attenuates renal dysfunction by ameliorating oxidative and mitochondrial function alterations which might be due to the presence of its active components.

KEYWORDS: *Withania somnifera*, Proteinuria, Glomerulus, Nephrotoxicity.

1. WITHANIA SOMNIFERA

1.2 INTRODUCTION

Pharmacological characteristics of *Withania somnifera* include anti-inflammatory, anti-stress, antioxidant, and immuno-modulating effects.[1] Alkaloids (isopellertierine, anferine), steroidal lactones (withanolides, withaferins), saponins with an extra acylgroup (sitoindoside VII and VIII), and withanoloides with a glucose at carbon 27 (sitonidoside XI and X) are some examples of chemical constituents that may be responsible for these characteristics.[2] The main pharmacologically active portion of *W.somnifera* (WS) is its roots, which are also known to have antioxidant and free radical scavenging properties.[3]

Fig 1: The roots of *Withania somnifera.*

Fig 2: The fruits of *Withania somnifera*.

Fig 3. The leaves of *Withania somnifera.*

Fig 4: The blooms of *Withania somnifera.*

Withania somnifera (Fig.1) is one of the most potent traditional Indian herbs used in Ayurvedic therapy is "Ashwagandha," also referred to as winter cherry.[4] Ashwagandha, which has yellow blooms (Fig.4) and oval leaves (Fig.3), is a member of the Solanaceae family. It is indigenous to the arid regions of the Middle East and India, and it yields red fruit (Fig.2).[5] High levels of protein (10.72%), ash (5.41%), crude fiber (14.58%) and total carbs (65.80%) are found in ashwagandha roots chemical makeup.[6]

1.3 Pharmacological Properties

1.3.1.Hepatoprotective and Nephroprotective Effects

It is already established that *W.somnifera* protects rats from gentamicin-induced kidney damage[8] and has restorative effects on carbendazim-induced hepatic and renal histoarchitecture changes.[7] An alcoholic extract of *W.somnifera* (100 mg/kg body weight) was found to prevent γ- irradiation-induced hepatotoxicity in a study.[9]

This was confirmed by the reformation of liver functional assessments and antioxidant status, decreased DNA fragmentation, and a significant decrease in Heme oxygenase-1 induction. Additionally, it was discovered to have hepatoprotective properties against toxicity caused by paracetamol.[10]

1.3.2. Anti-Inflammatory and Anti-Arthritic Effects

By reducing inflammation, *W.somnifera* has anti-inflammatory and anti-arthritic properties.[3] Additionally, *W.somnifera* has antipyretic qualities, and studies have shown that it has stronger anti-inflammatory and anti-arthritic effects than the common medication indomethacin. When given orally to rats an hour before the inflammatory agent, *W.somnifera* had anti-inflammatory activity comparable to that of hydrocortisone sodium succinate, a routinely recommended anti-inflammatory medication.[11]

1.3.3. Neuroprotective Effects

W. somnifera is one of the main ingredients in the well-known natural medication BR-16A which has been shown to prevent experimental catalepsy in rats. Both *W.somnifera* and BR-16A reduced catalepsy in test animals. Another study used the experimental Parkinson's effect in animals to determine the antiparkinson properties of *W.somnifera* extract.[12] *W.somnifera* exhibits strong central nervous system antidepressant effects and anticonvulsant properties in cases of severe and chronic epilepsy.[13]

1.3.4. Anti-Oxidant Effects

Animals in hypercholesteremic conditions had their antioxidant state assessed, and rats treated with *W.somnifera* showed a reduction in lipid peroxidation. Additionally, *W.somnifera* reduced lipid peroxidation levels in animals under stress.[1] Additionally, the ability of a small number of withanolide glycosides that were separated from *W.somnifera* leaves to inhibit cycloxygenases (COX) was evaluated. It was demonstrated that withanolides inhibited COX selectively and stopped lipid oxidation.[14]

1.3.5. Anti-Cancer Effects

In malignant cell lines, *W.somnifera* promotes apoptotic signaling and decreases the production of intercellular tumor necrosis factor and nuclear factor kappa B. The animal's lungs histoarchitecture modifications were lessened after seven months of pre-administration of *W. somnifera*. *W.somnifera* has the potential to be an anti-cancer agent because it also reduced the viability of various cancer cell lines, which restricted their proliferation.[15] The active ingredient in *W.somnifera*; 'withaferin A'inhibited the viability of breast cancer cells.[16] Previous research has shown that the roots of *W.somnifera* are rich in iron and contain a number of alkaloids, withanolides, reducing sugars, and a few flavonoids.[3]

1.4 Chemical Constituents of Withania Somnifera

In reaction to both internal and external stimuli, plants generate a range of phytocompounds, including propanoids, terpenoids, and alkaloids. The roots, stems, and leaves of *W. somnifera* have been found to contain a variety of sitoindosides, withanolides, and alkaloids (Fig.1, 2, 3).[17] A lactone or its byproducts are joined to a steroid support to form withanolides (WT). In the past, a significant and thorough investigation has been conducted to assess the pharmacological characteristics of the WT, specifically Withaferin A, WT E, and WT D. These substances have been shown to have notable anti-inflammatory, anti-tumor, immunosuppressive, and antioxidant qualities.[18]

The pharmacological properties of *W. somnifera* extracts have been widely studied. Numerous studies on the chemical components of *W. somnifera* using various approaches have been conducted in order to demonstrate the bioactive components of ashwagandha. The main biological components of *W. somnifera* are flavonoids, alkaloids, tannins, and steroidal lactones like WT.[10]

2. THE KIDNEY

2.1 Introduction

There are two kidneys on either side of the spine, situated in the back of the abdomen behind the peritoneum. It

controls fluid volume, preserves acid-base balance and electrolyte content, and supports metabolic and endocrine processes, including detoxification. Nephrons make up the kidney's basic structure. A rat's kidney contains about 35,000 nephrons, compared to about 1.5 million in a person. The proximal tubule is where a nephron's structure starts. The loop of Henle in the middle part comes next. The distal tubule makes up the last segment, and the nephron's ends form the Bowman's capsule around the glomerulus, a knot of capillaries.

Following the Bowman's capsule, the proximal tubule is the first segment of the nephron (Fig 5). Nephrons can be classified as cortical (having short loops of Henle) or juxtamedullary (having long loops of Henle). Rats have a 30% juxtamedullary nephron count, compared to 15% in humans. [19; 20]

Due to their metabolic activity, the kidneys are susceptible to substances that interfere with metabolism. Mammals' kidneys are complicated organs with intricate structures and functions that are crucial to preserving equilibrium. Numerous physiological processes, including excretion, osmoregulation, homeostasis maintenance, and pH and salt regulation, are carried out by the kidney. Inhibition of these vital processes and the accumulation of harmful chemicals are the results of impaired kidney function.[19; 21] Immune processes can be activated in the interstitium and renal glomeruli.

Changes in the distribution of membrane proteins are brought about by cellular damage to renal tissue. As a result, severely damaged cells slough off by necrosis or apoptosis.[22] Precipitate can occur when the sloughed cells adhere to the tubules and cling to one another. Obstruction follows, which impacts renal filteration.

These irreversible alterations eventually result in segmental glomerulosclerosis and end-stage renal failure if the damage worsens.[20] Due to the disease's high incidence, costly treatment, and recognition as a major mediator of cardiovascular failure, kidney function abnormalities have recently drawn a lot of attention from the global public health community. Acute and chronic renal dysfunctions are primarily caused by environmental causes such as xenobitics.[23]

Environmental pollutants, industrial chemicals, radio contrast agents, heavy metals (lithium, cadmium, lead, mercury), chemotherapy (cisplatin), NSAIDS, Amphothericin B, ACEs, crystals, chemicals (bromobenzene), and calcineurin inhibitors (cyclosporine, tacrolimus) are just a few of the toxicants that may contribute to the development of chronic and severe kidney disorders.[24]

Instead of acting as defensive mechanisms, the kidney's physiological functions and anatomical characteristics make it the target organ for the toxicants when they conjugate with glutathione. This could result in the bioaccumulation of these toxicants and their metabolites. This sets off many processes that lead to the suppression of renal function. In acute renal damage, both necrosis and apoptosis may contribute to cell death.[25]

2.2 Arsenic Exposure

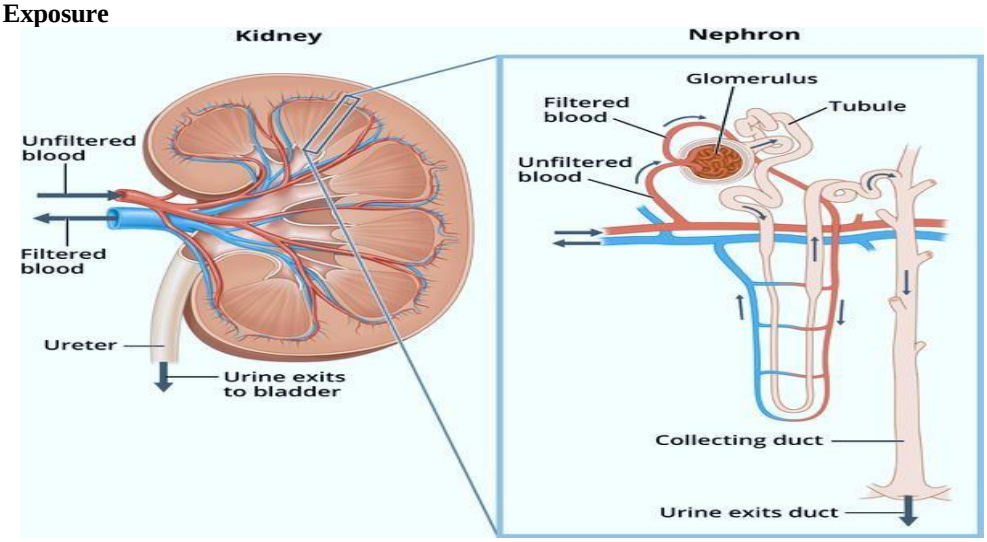

Fig 5.The structure of kidney and nephron.

Since millions of people are exposed to water levels above the limit, arsenic exposure continues to be a serious public health concern. Arsenobetaine is the most common chemical in fish and is non-toxic to humans, but arsenite is mostly found in drinking water and is extremely hazardous to humans. These compounds are found in nature as either inorganic (arsenite, arsenate) or organic (arsenobetaine, arsenocholine, and arseno sugars).[26] Skin, lung, bladder, liver, and kidney malignancies are linked to arsenic exposure.[27, 28]

Additionally, exposure to arsenic has been identified as a risk factor for diabetes mellitus, peripheral artery disease, hypertension, cardiovascular disease, and peripheral artery disease.[29, 30] Although exposure to arsenic has recently been identified as a risk factor for renal illness,

there are still few research and epidemiological data available. We searched for research on the physiopathology and epidemiology of arsenic exposure and nephrotoxicity in order to assess the involvement of arsenic in kidney disease.

2.3 Early Biomarkers to Evaluate Arsenic Exposure and Renal Injury

A "biomarker" is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, according to the US National Institutes of Health. Only when we comprehend the normal physiology of a biological process, its pathophysiology in a disease state, and the impact of an intervention on these processes will biomarkers which are objective and quantifiable features of biological processes by definition will be able to truly replace clinically relevant end-points.[33] Monitoring risk populations for early indications of exposure and toxicity has been one of the main challenges in the sciences of toxicology.

A statistically significant increase in the relative risk (odds ratio or hazard ratio) of developing progressive renal disease, CKD, and/or an increase in the morbidity associated with renal injury must be linked to a reliable biomarker of arsenic nephrotoxicity.[34]

The glomerular filtration rate (GFR), proteinuria, albuminuria, N-acetyl-b-D- glucosaminidase (NAG), b2-microglobulin, a1-microglobulin, and retinol-binding protein have all been measured as indicators of renal toxicity in epidemiological and experimental investigations assessing arsenic nephrotoxicity. The best methods for assessing kidney function are estimates of GFR; serum creatinine by itself is not a reliable indicator of GFR; instead, equations that consider serum creatinine along with certain factors including age, gender, race, and body size yield helpful estimates of GFR.[35]

Very little protein is typically excreted in the urine by healthy people, and chronically elevated protein excretion is typically indicative of kidney disease. The kind of renal illness that is present determines the excretion of particular protein types, such as albumin and/or low molecular weight proteins. While increased excretion of low molecular weight proteins is a sensitive indicator for certain forms of tubule-interstitial illness, increased excretion of albumin is a sensitive indicator for kidney disease brought on by diabetes, glomerular disease and hypertension.[36] Adults who excrete 30–300 mg/d of urine during a scheduled urine collection are said to have microalbuminuria, and those who excrete more than 300 mg/d are said to have macroalbuminuria.

The significance of isolated microalbuminuria as a risk factor for the progression of chronic kidney disease is still up for debate, but albuminuria has long been recognized as a marker for renal disease and is a well-known predictor of poor renal and cardiovascular outcomes in patients with type 2 diabetes and essential hypertension[37] albuminuria indicates glomerular and endothelial injury[38] and some studies have used this marker as a clinical subrogate of kidney disease related to arsenic exposure.[39]

The addition of albumin measurement to estimated GFR best classifies the population at risk for renal impairment[40, 41] Low molecular-weight (LMW) plasma proteins or urinary enzymes, which are often freely filtered past the glomerulus, have been employed as particular indicators of tubular damage.

Low-molecular weight proteinuria and increased excretion in urine are the outcomes of these proteins poor reabsorption through the proximal tubule. B2 microglobulin, a1-microglobulin, and retinol-binding protein are among the proteins with a molecular weight less than 40 kDa that are readily filtered through the glomerular membrane.

Their reabsorption in this segment is decreased when tubular dysfunction is present.[42–44] Because of its large molecular weight, NAG, a lysosomal enzyme that is present in many bodily tissues, is unable to pass through the glomerular membrane.

Although this protein's function as a marker of risk for the advancement of renal disease is still unknown, it is highly expressed in renal proximal tubular cells and leaks into the tubular fluid when proximal tubular cells are injured, such as in arsenic exposure. This causes an increase in urine levels, which is used as a reflection of proximal tubular cell necrosis.[45] Arsenic nephrotoxicity has not been assessed using other urine markers such as interleukin-18, NGAL (neutrophil gelatinase-associated lipoprotein), or KIM-1 (Kidney Injury Molecule-1).

2.4 Metabolism and Pathophysiology of Arsenic-Mediated Nephrotoxicity

When consumed in drinking water, inorganic arsenic is efficiently (80–90%) absorbed by the intestine. Proteins such as aquaporin-10, GLUT-5, and organic anion transporting polypeptides (OATPB) have been identified as arsenic intestinal transporters;[46] low intake of vitamin B, folic acid, and selenium, as well as nutritional deficiencies, are linked to increased absorption and toxicity of arsenic.[47, 48] Inhalation and skin exposure are two additional ways to enter the body.[49] The half-life of arsenic in blood varies noticeably between animal species, and in humans, the majority of arsenic may be quickly removed from blood with a half-life of roughly one hour.

Aqua-glyceroporins (AQ) and hexose permeases facilitate the hepatocytes' uptake of arsenite in the liver, whereas the Na–P co-transporter facilitates the entry of arsenate into the cell.[50,51] Research conducted on cell cultures has demonstrated that the intracellular

accumulation of As rises with increased cellular production of AQ3 and AQ9.[52] Glutathione (GSH) mediates the methylation and transformation of arsenate into arsenite within the cell, reducing its toxicity and facilitating its elimination in the urine and biliary system.[53] All eukaryotic and some prokaryotic cells express metallothioneins (MT), a class of cysteine-rich, metal-binding proteins, which are synthesized in response to arsenic.

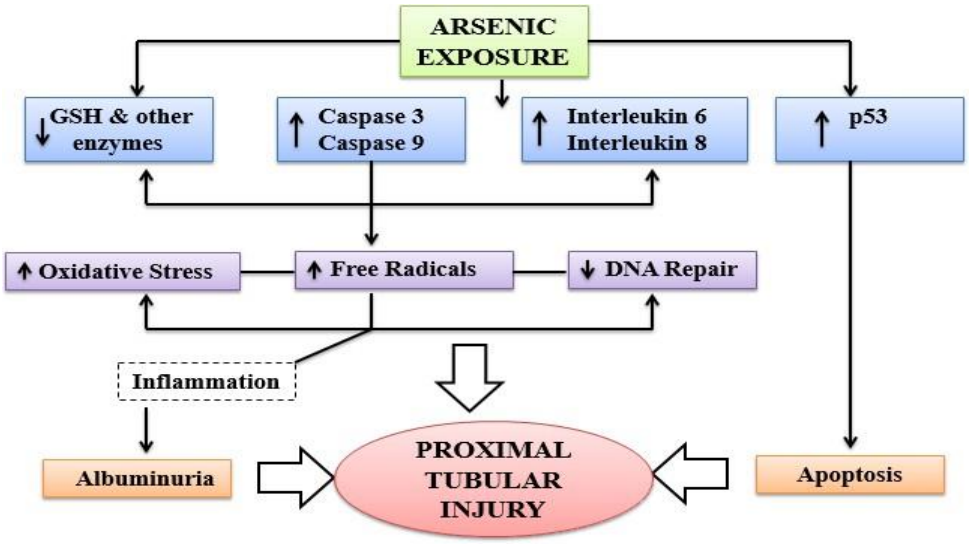

Fig 6. Pathophysiology of arsenic mediated nephrotoxicity. Mechanisms whereby arsenic exposure may lead to proximal tubular injury.

By trapping metals in protein-bound forms and acting as scavengers to squelch reactive oxygen species (ROS) and other free radicals, metallothioneins control metal homeostasis.[54] Chronic exposure to heavy metals can cause nephrotoxicity in MT knockout (MT-null) mice.[55] Through the cellular efflux of Arsenic–GSH conjugates to the bile, the ATP-binding cassette transporter proteins, multidrug resistance protein 1 (MRP1/ABCC1) and the related protein MRP2 (ABCC2) are crucial for arsenic detoxification. Proximal tubule cells (PTCs) also contain the MRP- 2 transporter, which mediates the efflux of As for excretion by urine.[56] Depletion of intracellular GSH reserves, activation of the caspase-3 and-9 signaling pathway, elevations in interleukin-6 and interleukin-8 production and activation of the p-53 apoptotic pathway are the first steps in arsenic toxicity in PTC (Fig.6).

This causes inflammation, apoptosis and an increase in the generation of ROS and other free radicals.[57–59] Fanconi syndrome (phosphaturia, glucosuria, and low-molecular weight proteinuria) is a clinical manifestation of arsenic's uncoupling of oxidative phosphorylation which results in decreases in sodium, phosphate, and glucose transport.[60] It has been demonstrated that nephrotoxicity can be linked to either direct podocyte damage[61] or endothelial dysfunction through a mechanism that increases the expression of the angiotensin type I receptor and vascular cell adhesion molecule 1 (VCAM1).[62]

Low-dose sodium arsenate (0.7 mg/kg) treatment in dogs causes modest degeneration and vacuolation of the ascending thick section of the nephron but has no effect on glomerular filtration rate or fractional reabsorption of sodium, potassium, or chloride. All nephron segments are affected by severe acute tubular necrosis and mild glomerular sclerosis at higher dosages (14.6 mg/kg).[63] Urine albumin (UAlb) excretion is not affected by drinking water containing arsenic (22.5 mg/L), however urine NAG is. Mice given both cadmium in diet and arsenic in drinking water in this model show significantly larger increases in urine protein and NAG excretion than mice given either cadmium or arsenic alone.[64]

2.5 Epidemiological Studies in Humans

Since ancient times, arsenic has been used as a poison and as a therapeutic. Clinical signs of acute As toxicity have been documented since then, but only 50 years ago was arsenic nephrotoxicity identified, when industrial workers exposed to the metal developed hemolysis and acute renal failure; renal biopsies of these patients revealed acute tubular necrosis, renal cortical necrosis,diffuse interstitial fibrosis,and subsequent progression to chronic kidney disease.[65,66] Since some studies have discovered a direct link between drinking water arsenic concentrations and negative health outcomes, there has been a lot of interest in evaluating the health risks associated with exposure to low to moderately elevated levels of arsenic in drinking water.

Higher As exposure in men but not in women, was linked to a higher mortality ratio for renal disease, according to a study on ecological mortality based on historical data[67, 68] discovered that increased death rates for diabetes mellitus, cerebrovascular illness, and kidney disease were linked to drinking water containing arsenic at levels above 200–300 mg/L in both males and females. Nevertheless, there are currently few epidemiological

studies that connect long-term exposure to arsenic with indicators of renal damage, and it is uncertain if arsenic is a risk factor for developing chronic kidney disease.

In Taiwan, Hsuehetal[69] examined 125 individuals with GFR 60 mL/min and 229 individuals with normal renal function. They discovered a weak correlation between urinary arsenic levels and reduced renal function (r2¼0.04, p 0.001). Higher arsenic excretion was associated with lower plasma lycopene levels, indicating that increased oxidative stress is the mechanism causing kidney damage.[70] The prevalence of proteinuria was found to be higher in subjects with higher exposure and higher urinary arsenic excretion in Bangladesh where 10,160 men and women were tested for proteinuria using the urinary dipsticks test. However, incident proteinuria during follow-up visits was not linked to either baseline well arsenic or baseline urinary arsenic. According to this population's follow-up, the risk of proteinuria increased with a 469 mg/L increase in urine arsenic excretion.

Zheng assessed the relationship between albuminuria and inorganic arsenic in American-Indian individuals who lived in rural U.S. locations and had low to moderate exposure to arsenic.[39] An open non-diabetic population study conducted in central Mexico found an increase in the urinary excretion of a1-microglobulin, a marker of tubular injury associated with higher urinary arsenic excretion.[71]

However, this association disappeared when data were adjusted for age, body mass index, systolic blood pressure, glucose, and uric acid levels. This population had a high burden of diabetes (49.7%), obesity, and albuminuria (30%).

They also found a higher prevalence ratio of albuminuria in subjects with higher urinary excretion of arsenic after statistical adjustments for diabetes, urinary Cd excretion, hypertensive medication, and systolic blood pressure. The consequences of arsenic exposure and renal injury in children are not well understood, and in the one study that has been published,They found no rise in renal injury indicators in 800 children with modest exposure levels in Europe.[72] According to some animal research, exposure to both inorganic arsenic (As) and cadmium (Cd) together causes more severe kidney damage than exposure to either element alone[64], and some human epidemiological investigations have supported this conclusion.[73]

The levels of Ub2MG, UAlb, and UNAG in the subjects living in a polluted area were significantly higher than those in the non-polluted area, according to study of 245 subjects in China who were co-exposed to arsenic and cadmium[74], 122 of whom lived in an area that was polluted with arsenic and cadmium, and 123 of whom lived in a non-polluted area. Assessments of Ub2MG, UNAG, URBP (urinary retinol binding protein), and UAlb were employed as indicators of renal impairment in study of 619 individuals living in two metal-contaminated regions of China.[75]

The incidence of albuminuria and LMW proteinuria was higher in individuals exposed to higher levels of both As and Cd than in those exposed to either element alone, indicating a synergistic impact between the two elements. Huang assessed the impact of co-exposure to low levels of Cd and As in the environment on oxidative stress and urine biomarkers.[76] Both Cd and As were favorably connected with urinary excretion of NAG and the oxidative stress indicators (urinary malondialdehyde and 8 hydroxy-2-deoxyguanosine) and the effects were stronger when both Cd and As were co-exposed.

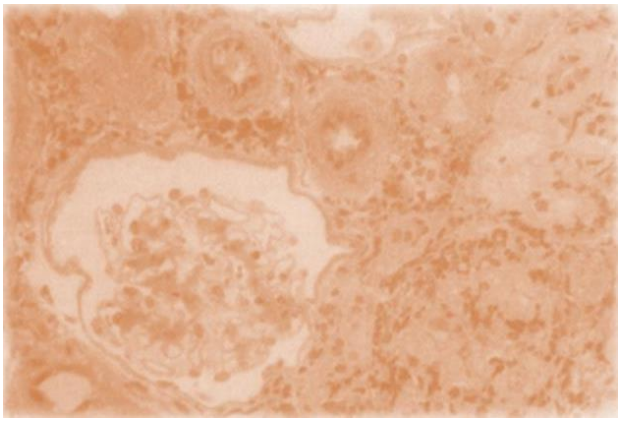

Fig 7. Renal biopsy done in a woman with arsenic poisoning and tubulointerstitial nephritis. Biopsy specimen showing a normal glomerulus, extensive interstitial fibrosis with tubular atrophy, and a cellular infiltrate consisting mainly of lymphocytes.[77]

2.6 Clinical Manifestations of Arsenic-Induced Renal Disease

Individuals with systemic toxicity from severe acute arsenic poisoning have been known to develop acute tubular necrosis with acute renal failure; some of these individuals also advance to chronic kidney disease (CKD) and develop cortical necrosis. Proteinuria may be the outcome of glomerular damage, hemoglobinuric or myoglobinuric tubular injury, direct effects of arsenic on tubule cells, or hypotensive shock as the precipitating cause of renal injury.

Another clinical sign of acute arsenic poisoning has been identified as acute tubular interstitial nephritis (Figure 7),[77] Clinical features linked to long-term exposure include low molecular weight proteinuria, aminoaciduria, glycosuria, and phosphaturia as well as a progressive decline in renal function.

While numerous therapies and functional diets have been tested in animals to avoid arsenic nephrotoxicity, there are currently no proven treatments to lower arsenic levels in the blood or prevent toxicity in humans. Resveratrol's effects on arsenic nephrotoxicity were assessed in

Chinese Dragon- Li cats that were treated to arsenic trioxide to cause renal damage. Resveratrol dramatically reduces oxidative stress indicators, tubular necrosis, morphologic damage and the buildup of arsenic in renal tissues.[78] Additional substances like silibinin, a naturally occurring plant bioflavonoid present in the milk thistle species Silybum marianum, Pleurotus floridalectin, and naringenin, a naturally occurring citrus flavanone,Green tea extract[81], flaxseed oil[85], taurine[84], and Curcuma aromatica leaf extract[83] have demonstrated promising results in shielding the kidney from arsenic nephrotoxicity.

Numerous studies have indicated that arsenic mitigation eventually lowers arsenic -related morbidity but this effect may be seen years after arsenic -free water is made available. The general public is not well informed of the health risks connected with arsenic exposure.[86] In summary, a variety of pathophysiological mechanisms account for the renal effects associated with exposure to arsenic; however, the evidence relating to exposure to arsenic and chronic kidney disease is still limited to certain populations, and further research is required to determine the effects of low to moderate levels of arsenic on chronic renal disease.

CONCLUSION

Withania somnifera decreased the inflammation caused by nephrotoxicity by interacting with components of the proinflammatory cell signaling pathway, such as NF-κB, signaling kinases, HSP90, Nrf2, and the inflammasome complex.It also reduced oxidative stress and decreased proximal tubular injury. Withania somnifera will show promising results if it's used in the treatmemt of arsenic induced nephrotoxicity. Withania Somnifera have most of the active components which showed positive effects against arsenic induced nephrotoxicity.

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