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# Nephropathy induced by Aristolochic Acid. A narrative review.

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## Abstract

**Introduction:** Aristolochic acids contain a carboxylic nitro phenanthrene group and can be found in medicinal herbs of the genus Aristolochia. Their nephrotoxicity has been confirmed in endemic geographic areas such as the Balkans of Europe and the Central American region. The clinical findings consist of tubulointerstitial nephropathy and generally go unnoticed until the advanced stages of chronic kidney disease.

**Objective of the review:** The aim is to describe the main pathophysiological aspects and establish diagnosis and treatment criteria in patients with Aristolochic Acid Nephropathy.

**Essential points of the review**: Approximately 180 types of aristolochic acids (AAs) have been discovered, the most critical types AAI, AAII, AAIIIa (AA C) and AAIVa (AA D), which are differentiated according to the position of their hydroxyl radical (OH), hydrogen (H) and methoxyl (OCH3). AA-induced nephropathy occurs through at least five pathways that associate the depletion of intracellular glutathione, cellular damage due to induction of cell apoptosis, direct damage to the endoplasmic reticulum, and mitochondrial damage. This produces atrophic tubular injury and interstitial fibrosis; the metabolite has a bladder neoplastic effect.

**Conclusion:** The incidence of aristolochic acid nephropathy is probably much higher than initially thought, and its existence should be considered in patients who present with chronic kidney disease with a tubulo-interstitial clinical pattern.

## Keywords:

Aristolochic acid nephropathy, Tubulointerstitial nephropathy, Chronic renal failure.

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Aristolochic acids contain a carboxylic nitro phenanthrene group and can be found in medicinal herbs of the genera *Aristolochia* and Asarum, which are members of the Aristolochiaceae family [1].

The Euglypha and Holostylis subfamilies, which are specific to and characteristic of South America, and the Aristolochioideae subfamily, which is composed of more than 400 species of Aristolochia from tropical and temperate zones, are essential [2].

In our country, this Aristolochiaceae family is mainly found in the liana or Saragoza plant (*Aristolochia elegans*) in the coastal and eastern regions. It was traditionally used primarily to treat diarrheal syndrome; however, other types, such as *A. constricta*, are used empirically as antispasmodics and anthelmintics and for snake bites, and A. grandiflora, another popular specimen, is used as a uterus tensor [3, 4].

Approximately 180 types of aristolochic acids (AAs) have been discovered; the most important types in this genus are AAI, AAII, AAIIIa (AA C), and AAIVa (AA D), which are differentiated according to the position of their hydroxyl radical (OH), hydrogen (H), and methoxyl (OCH3) [1].

Another AA type that is especially important in European and Asian countries is aristo lactam acid (AL). This type differs from AA by its chemical structure, which contains a nitrogen hydride (NH) group. In turn, the AL types are also differentiated according to the position of their hydroxyl radical (OH) and methoxyl radical (OCH3) [1].

Type I aristolochic acids are the most toxic and produce more nephrotoxicity than others, while types I and II produce genotoxicity [1].

# Kinetics of aristolochic acid

Experimental studies in rats determined the presence of DNA adducts in various organs, including the kidneys, after oral administration of AA [5]. These studies have elucidated the pharmacokinetics of aristolochic acid and its pathophysiology in AA nephropathy [5].

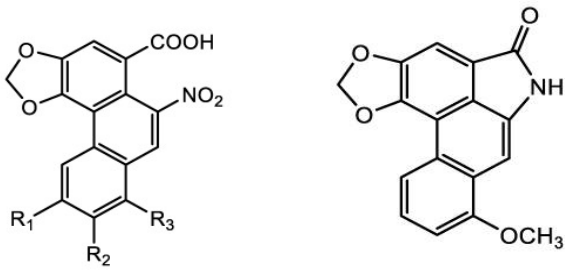
### Absorption

After AA is released in experimental rats, it is absorbed from the rodent's digestive system, from the stomach to the intestine, and subsequently to the blood [5].

### Distribution

Using molecular techniques, AA and DNA adducts (unions of AA to genetic material) can be detected in various organs, such as the kidney, stomach, liver, intestine, spleen, and lung [5].

**Figure 1.** Chemical structures of different types of aristolochic acid and aristolactamic acid.




AA I $R_1$=H, $R_2$=H, $R_3$=$OCH_3$
AA II $R_1$=H, $R_2$=H, $R_3$=H
AA IIIa (AA C) $R_1$=OH, $R_2$=H, $R_3$=H
AA IVa (AA D) $R_1$=OH, $R_2$=H, $R_3$=$OCH_3$

AL I

AAI: Aristolochic acid type 1; AAII: Aristolochic acid type 2; AAIIIa: Aristolochic acid type 3a; AA IVa: Aristolochic acid type 4a; R1: Radical 1; NH: Nitrogen hydride; OH: Oxydryl radical; OCH3: Methoxyl; NO2: Nitrogen dioxide; COOH: Carboxyl group.

Taken from Zhang SH et al. Comparative Analysis of Aristolochic Acids in Aristolochia Medicinal Herbs and Evaluation of Their Toxicities. Toxins (Basel). 2022 Dec 16;14(12):879. doi:10.3390/toxins14120879.

### Metabolism

Several enzymatic processes are involved in metabolism at the liver level to bioactivate AA. Among the most important are cytosolic nicotinamide adenine dinucleotide phosphate (NADPH), quinone oxidoreductase 1 (NQO1), microsomal cytochrome P450 (CYP), CYP1A1, CYP1A2, renal microsomal NADPH: CYP oxidoreductase (POR), and prostaglandin H synthase [5].

The nitroreduction of AAI and AAII leads to the formation of N-hydroxyaristolactam, which can be transformed into aristolactam nitrenium ions. These reactive species react with the exocyclic amino groups of the purine bases of DNA to generate DNA adducts (DNA AA) [5]. These adducts include 7-(deoxyadenosine-N6-yl) aristolactam I or II (dA-AAI or dA-AAII) and 7-(deoxyguanosine-N2-yl) aristolactam I or II (dG-AAI or dG-AAII) [5, 6].

### Elimination

Finally, the detoxification process of aristolochic acid is generated by its oxidation in the liver via the catalytic enzymes CYP1A1, CYP1A2, and CYP2C, which results in elimination products such as aristolochic acid Ia [5].

Another elimination product that allows detoxification is the formation of Aristo Lactam (AL I) at the liver level by the enzymes NQO1 and CYP1A1/CYP1A2, which is subsequently excreted [5].

Finally, through N-hydroxyristolactam I at the liver level, a Bamberger rearrangement reaction can occur, which is an organic hydrogen ion rearrangement reaction that generates 7-hydroxy aristolactam I, another elimination product [5, 6].

These DNA adducts can produce transversions of purines and pyrimidines in genes, demonstrating this type of mutation at the p53 tumor suppressor gene level. This is why aristolochic acid is linked to the development of some types of cancer, especially in areas where it accumulates, such as bladder tissue [1, 5].

It has also been shown that there may be adducts of aristolochic acid with RNA (RNA-AA), which increases the mutagenic power of aristolochic acid and its nephrotoxicity [7].

**Pathophysiology of aristolochic acid-induced nephrotoxicity.**

Nephrotoxicity induced by aristolochic acid (NiAA) occurs in the first instance as a result of the hepatic metabolism of the AAI mentioned above through nitroreducing enzymes (NQO1 and CYP1A1/CYP1A2) with the consequent generation of N-Hydroxyristolactam I and from this to Ion Arstolactam Nitrenium I, the precursor of DNA adducts (dA-AAI or dA-AAII) and (dG-AAI or dG-AAII) that cause damage not only in the kidney tissue but also at the bladder level [8].

However, experimental studies in rats have allowed us to elucidate the existence of other types of liver enzymes that also generate these DNA adducts and other metabolic components that are directly more nephrotoxic [5, 8].

These enzymes are sulfotransferases (SULTs) that act after the nitro reduction reaction of AAI to N-hydroxyristolactam I in the liver. These enzymes use this substrate to generate N-Aristo lactam sulfate (AL-NOSO3H), which causes direct nephrotoxicity [8].

AL-NOSO3H is transported out of the liver by the protein transporter associated with multidrug resistance (PMR) and enters the kidney through organic anion transporters (TAOs) [5, 8].

Type 1, 3, and 4 TAOs are directly involved in the transport of nephrotoxic AL-NOSO3H toward the proximal convoluted tubule, as they are found in the basolateral pole of these cells and type 4 TAOs in the apical pole [8]. In this way, an increase in reactive oxygen and reactive nitrogen species (ROS/RNS) occurs in the proximal tubule and, in general, generates oxidative stress at the cellular level with consequent DNA damage and, as a final result, activation. of cell apoptosis through the activation of five pathways:

**The first pathway** involves mitogen-activated protein kinase-kinase/extracellular signal-regulated kinase 1/2 (MEK/ERK1/2) signaling and intracellular glutathione depletion. (GSH), with consequent cell damage due to the induction of cell apoptosis [9].

**Second pathway:** According to several experimental studies in animals and cell cultures, this pathway is produced by direct damage to the endoplasmic reticulum (ER), which leads to an increase in intracellular Ca2+. This, in turn, affects the mitochondria, activating apoptosis via the mitochondrial pathway (release of cytochrome C (Cyt C), which activates caspase-3) [5].

**In the third pathway**, direct damage to the ER also increases the protein complex called eukaryotic initiation factor-2α (eIF2a), a protein homologous to the CCAAT enhancer binding protein (CHOP) and X box binding protein 1; OGG1 (XBP1), which can also induce cell apoptosis [5].

**In the fourth pathway,** AAI also activates mitogen-activated protein kinase (MAPK), which in turn activates p38, which induces apoptosis through mitochondrial activation, and p53, which induces apoptosis through activation of the BAX pathway [9].

**In the fifth pathway**, direct mitochondrial damage causes mitochondria to release cytochrome C (Cyt C), which activates caspase-3, inducing cell apoptosis through this pathway [5].

In addition to this entire apoptosis process, inflammation and fibrosis develop in kidney tissue, and experimental studies such as Debelle et al. performed in rats demonstrated the presence of polymorphonuclear cells in the kidney lesions of those exposed to aristolochic acid [10].

A similar study demonstrated that the accumulation of monocytes/macrophages and CD8+ T cells at the peritubular level was progressively linked to the primary process of the development of necrosis and transient tubular atrophy, thus establishing aristolochic acid as responsible for the tubulointerstitial fibrosis phase [11].

Experimental studies carried out in zebrafish further demonstrated the presence of interleukins in the kidney tissue of rats, showing positive regulation of the expression of proinflammatory genes, including tumor necrosis factor-alpha (TNFα) and cyclooxygenase (COX-2). Similarly, myeloperoxidase (MPO) and interleukin 1 beta (IL-1β) increase renal mRNA expression of proinflammatory cytokines, including IL-6, IL-1β, and TNFα, in mouse studies [12,13].

The NLRP3 inflammasome, a multimeric protein complex that initiates an inflammatory form of cell death, has been reported to be involved in aristolochic acid-mediated nephrotoxicity [14].

**Histology of aristolochic acid-induced nephrotoxicity**

In a cross-sectional study, DNA was extracted from the renal cortex and urothelial tumor tissue of 67 patients who underwent nephroureterectomy for upper urinary tract carcinomas and who resided in regions where aristolochic acid-induced nephrotoxicity was endemic (nephropathy endemic to the Balkans). The following histological changes were determined [15] (Table 1).

Aristolactamic acid-DNA adducts are concentrated in the renal cortex and could serve as biomarkers of aristolochic acid exposure [15].

In the case of tumors, the most prevalent were at the level of the renal pelvis, followed by the ureter, renal pelvis, and ureter, and finally, the ureter and bladder [15].

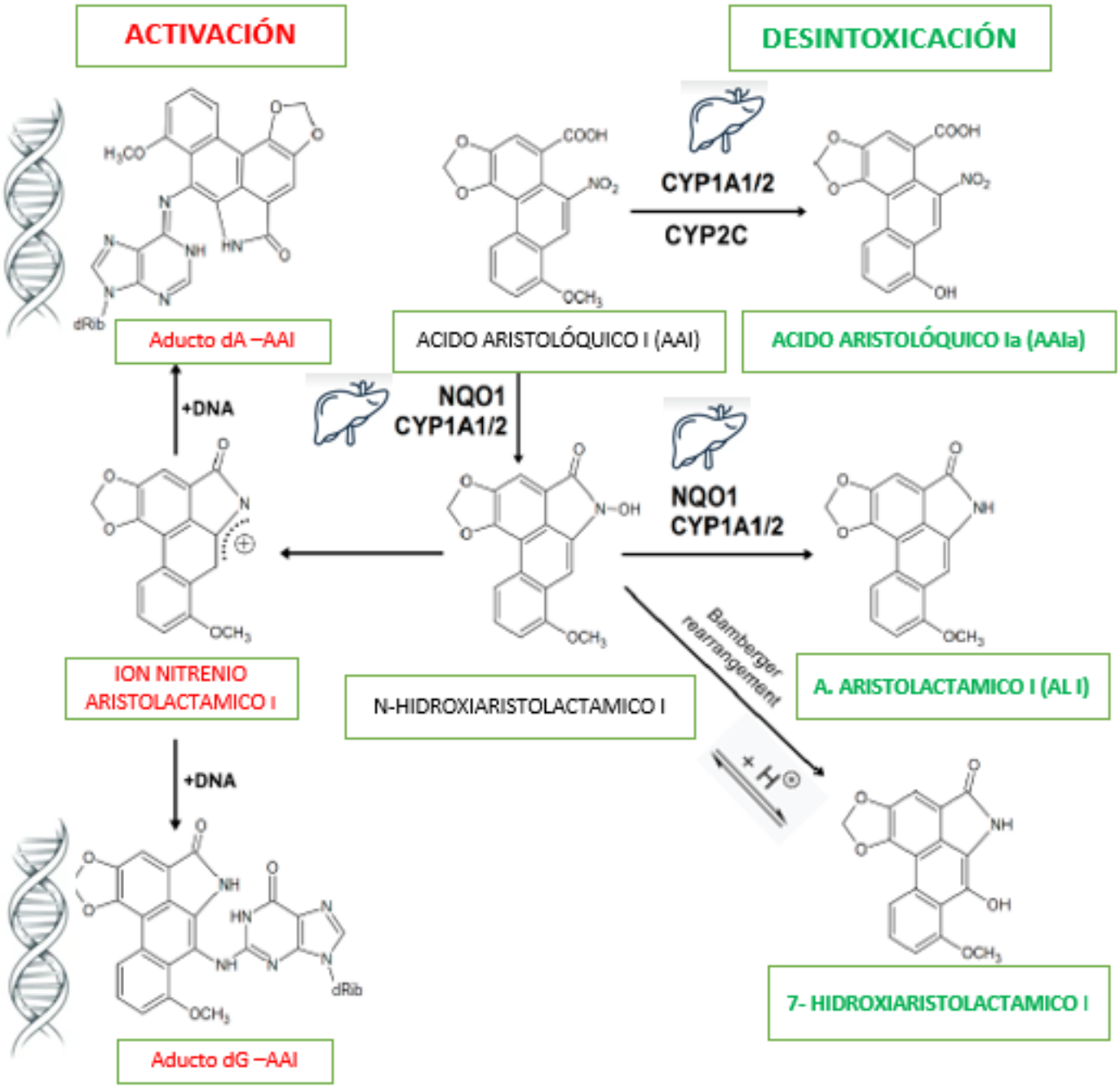



**Figure 2.** Pharmacokinetics of aristolochic acid

Retrieved from: Anger EE, Yu F, Li J. Aristolochic Acid-Induced Nephrotoxicity: Molecular Mechanisms and Potential Protective Approaches. Int J Mol Sci. 2020 Feb 10;21(3):1157. doi: 10.3390/ijms21031157. PMID: 32050524; PMCID: PMC7043226

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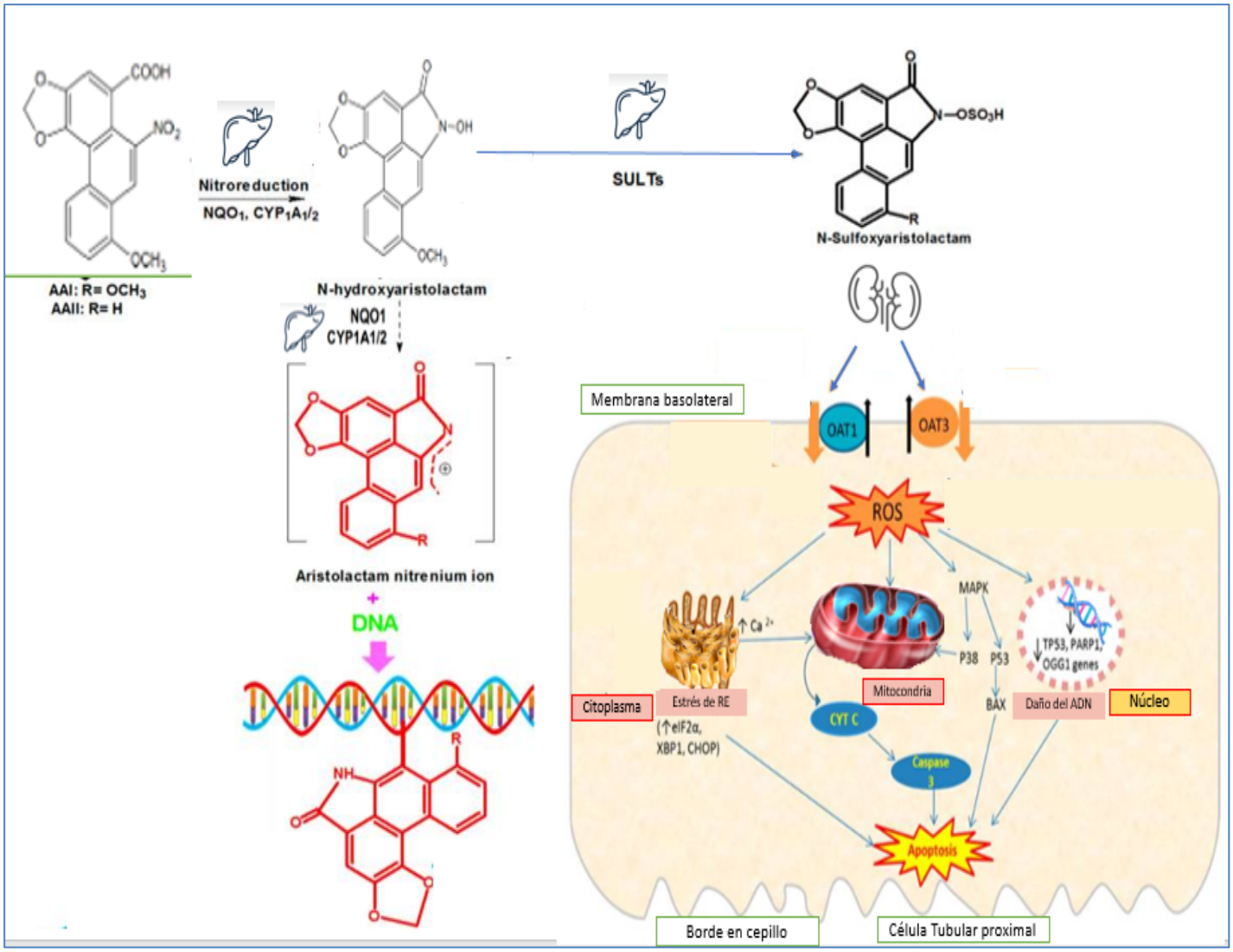
**Figure 3.** Induction pathways of nephrotoxicity induced by aristolochic acid.




Taken and modified from Anger EE, Yu F, Li J. Aristolochic Acid-Induced Nephrotoxicity: Molecular Mechanisms and Potential Protective Approaches. Int J Mol Sci. 2020 Feb 10;21(3):1157. doi: 10.3390/ijms21031157. PMID: 32050524; PMCID: PMC7043226.

**Diagnostic methods for aristolochic acid (NAA) nephropathy**

The diagnosis of Aristolochic acid nephropathy is based on the clinical suspicion of using herbal substances that may contain aristolochic acid among their compounds. The manner of presentation of nephropathy associated with aristolochic acid depends on the time of exposure to AA (Table 2).

The clinical presentation of NAA is not specific, and most of the time, elevated creatinine is evident in routine evaluations. During its progression, some patients may develop arterial hypertension, anemia as it progresses to CKD, and a decreased glomerular filtration rate; proximal tubule dysfunction can be evidenced by glycosuria with average blood glucose and mild proteinuria on urinalysis. The urinary sediment may demonstrate sterile pyuria and leukocyte casts. In 50% of cases, kidney ultrasound reveals a decreased kidney size with irregular contours (Figure 1) [17].

A renal biopsy was performed to confirm the diagnosis of NAA. Studies have shown significant involvement of the renal tubule accompanied by fibrosis and cellular degeneration, as well as effacement of the tubular basement membrane, causing progressive interstitial fibrosis of the glomeruli in the acute phases of the disease. They may be respected. However, endocapillary collapse and basement membrane involvement have been reported in the advanced stages of this disease [18].

Phytochemical analysis of herbal compounds suspected of containing aristolochic acid, as well as the identification of DNA adducts in kidney tissue, can be performed by methods including mass spectrometry and high-performance liquid chromatography since DNA adducts can persist for up to 20 years after exposure to AA. It is essential to make an accurate diagnosis of NAA since prolonged exposure can cause high rates of malignancy and complicate future kidney transplantation [19].

The incidence of aristolochic acid nephropathy is likely much more significant than initially thought, especially in regions of Asia [20]. It was first reported in a court of more than 100 patients in Belgium who took slimming pills that contained Chinese herbs (*Aristoloquia Ranchi*) [21]. Diagnostic criteria for NAA have been established and presented in Table 3 [22 ].

**Table 1.** Histology of Nephrotoxicity induced by aristolochic acid .

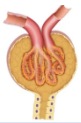
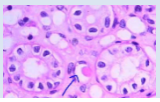
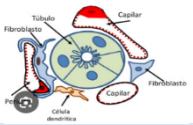
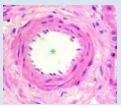
| Tissue | | Disturbance |
|---|---|---|
| **Glomeruli** |  | Mild ischemic changes (condensation and simplification) |
| **Tubules** |  | Tubular atrophy especially proximal T. |
| **Interstice** |   | Interstitial fibrosis |
| **Blood vessels** |  | Nonspecific sclerotic changes |

**Table 2.** Kidney damage associated with exposure to Aristolochic Acid .

| Syndrome | Exposure to AA | AA Dose | Progression to CKD | Malignancy |
|---|---|---|---|---|
| **CKD** | Chronicle | Low doses per day | < 2 years | High prevalence |
| **LRA** | Acute | High doses per day | 1 to 7 years | Moderate Prevalence |
| **tubular dysfunction** | Acute | Low doses per day | It is unknown | It is unknown |

CKD: Chronic Kidney Disease. AKI: Acute Kidney Injury, AA: Aristolochic Acid .

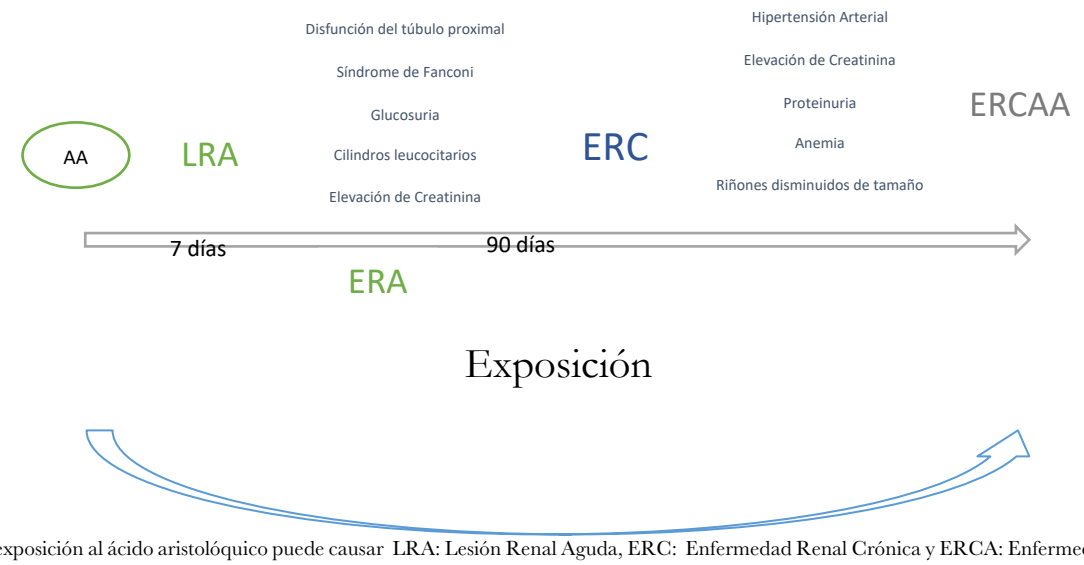



**Figura 1.** La exposición al ácido aristolóquico puede causar LRA: Lesión Renal Aguda, ERC: Enfermedad Renal Crónica y ERCA: Enfermedad Renal Crónica Avanzada, con necesidad de terapia de reemplazo renal, y su evolución sigue la clasificación por tiempo clásica de lesión renal aguda, ERA: Enfermedad renal aguda y Enfermedad Renal Crónica.

**Table 3 .** Diagnostic criteria for Aristolochic Acid Nephropathy

| **eGFR < 60 ml/min/1,732** |
|---|
| Two of the following criteria: |
| • Fibrosis of the interstitial tubule with reduction of the renal cortex |
| • Known ingestion of compounds with AA identified by phytochemical analysis |
| • Presence of AA DNA adducts in renal and ureteral tissue. |

AA: Aristolochic acid . eGFR : Estimated glomerular filtration rate, DNA adducts: chemical modifications of DNA that prevent DNA replication and can cause abnormal replications and mutations.

# Treatment

Treatment is carried out according to the clinical stage of chronic kidney disease because it presents with the clinical form of tubulointerstitial nephropathy. Diuresis remains constant, arterial hypertension does not occur due to volume control through water loss, and the patient remains asymptomatic until the most advanced stage of kidney disease. Patients who present with urea and creatinine values have higher averages than any patient who presents with glomerular nephropathy. There are no antidotes available for aristolochic acid.

The use of steroids seems advisable in the initial stages of chronic kidney disease, in stages 1 to 3. If the intake of aristolochic acid is identified, the sample should be obtained for biochemical analysis. There is no specific treatment; if the patient needs replacement therapy, it should be performed conventionally. Psychological treatment is required to reach acceptance of dialysis therapy and achieve patient education [23].

# Conclusion

The incidence of aristolochic acid nephropathy is probably much more significant than initially thought, and its existence should be considered in patients who present with chronic kidney disease with a tubulo-interstitial clinical pattern.

## Abbreviations

NAA: Aristolochic acid nephropathy.

### Supplementary information

This narrative review has no supplementary materials.

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Does not apply.

## Contributions of authors

Wilmer Stalin Sanango Reinoso: Data Curation, Formal Analysis, Funding Acquisition, Research
Washington Xavier Osorio Chuquitarco: Methodology, Project administration, Resources, Software, Writing – original draft.
Santiago David Silva Tobar: Methodology, Project administration, Resources, Software, Writing – original draft.
Octavio José Salgado Ordoñez: Conceptualization, supervision, validation, visualization, writing: review and editing.
All the authors have read and approved the final version of the manuscript.

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The study was self-financed by the authors.

**Availability of data or materials**
The datasets generated and analyzed during the current study are not publicly available but can be shared upon academic request.

# Statements

## Ethics committee approval and consent to participate
Narrative reviews are not needed.

**Consent for publication**
Patients who did not publish patient photographs, tomography scans, or X-ray studies were not needed.

**Conflicts of interest**
The authors declare no conflicts of interest.

**Author information**
Does not apply.

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