

Pharmacovigilance of Nephrotoxic Herbal Medicine Used World wide

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Abstract: - Introduction Around the world, the usage of herbal remedies is expanding. Particularly in individuals with long-term conditions like kidney illness, where a significant incidence has been found in many studies. However, there are worries regarding the potential negative consequences of herbal remedies. The relationship between the usage of herbs and renal illness has been amply demonstrated by examples from the literature. The necessity to keep an eye on the safety of herbal remedies has grown as their use has increased. Therefore, the World Health Organisation (WHO) advised using natural treatments in the country's current pharmacovigilance programmes. Phytovigilance, also known as pharmacovigilance of medicinal plants, included weighing the advantages and disadvantages of phytotherapy. Protecting patients from herbal harm is the ultimate goal.

Creating trustworthy data on the safety of herbal remedies is crucial. Phytovigilance is also required by law when it comes to interactions between multiple related plants and hazards of toxicity (acute or chronic) or drug interactions (pharmacokinetic or pharmacodynamics). There are a number of problems with the naming, perception, acquisition, and application of herbal medications. The WHO released guidelines on pharmacovigilance of herbal medicines on a global scale. However, in most African nations, it is still a relatively young activity. With the exception of Morocco, where a phytotherapy pharmacovigilance program was established in 2000. Including the development of Phytotoxic and Botanicals. Understanding, identifying, and keeping an eye on adverse reactions through pharmacovigilance of herbal medicine activities is necessary in this case. There are a number of problems with the naming, perception, acquisition, and application of herbal medications. The WHO released guidelines on pharmacovigilance of herbal medicines on a global scale. However, in most African nations, it is still a relatively young activity. With the exception of Morocco, where a phytotherapy pharmacovigilance program was established in 2000. Including the development of Phytotoxic and Botanicals. Understanding, identifying,

and keeping an eye on adverse reactions through pharmacovigilance of herbal medicine activities is necessary in this case. Systematic study was done on Pub Med, Science Direct, and Scopus to demonstrate the adverse consequences of using herbal medications on the kidneys and the present global requirement to maintain Phytovigilance. Additionally, a few readily available databases on Phytovigilance or pharmacovigilance of herbal medication were explored. Aristolochic acid nephropathy, which is linked to the abuse of some traditional Chinese herbal remedies, is the most well-known herb-induced kidney damage. There is a dearth of information regarding the nephrotoxicity of European plant species. Here, we critically examine important facts about the nephrotoxicity of a number of plants utilised in European phytotherapy, such as Aloe, Euphorbia paralias, Glycyrrhiza glabra, and Artemisia herba-alba. There is discussion of the causes and risk factors for herbal intoxications. Improving pharmacovigilance of herbal medicine, particularly in patients with chronic renal disease, is the main goal of this review.

Keywords - Herbal products, Nephrotoxicity, pharmacovigilance.

I. INTRODUCTION

Herbal medicine makes use of medicinal plants that have been purified and chemically standardised using suitable pharmacological preparations and modified extraction techniques. There are potential adverse effects, contraindications, and pharmaceutical interactions, just like with any type of treatment. A fundamental understanding of the pharmacological aspects of herbal therapy is seen to be essential to the standard medical curriculum. Because of their inherent characteristics, plant extracts may be harmful to the kidneys. Similar to what is already done for nephrotoxic pharmacological drugs, choices about

their continued availability can be made if they show any degree of toxicity by weighing the risks against the benefits. Crucially, plant-drug combinations, mistakes in dosage and identification, and pollutants in the mixture are all potential causes of kidney issues related to plants, in addition to the inherent qualities of the herb. To protect users of medicinal plants, strict regulations regarding the presence of adulterants in herbal medicines, dose and contraindication labelling, and production methods must be upheld. Globally, the usage of herbal remedies is expanding. Particularly in individuals with long-term conditions like kidney illness, where a significant incidence has been found in multiple studies. However, there are worries regarding the potential negative consequences of herbal remedies. The relationship between the usage of herbs and renal illness has been amply demonstrated by examples from the literature. The necessity to keep an eye on the safety of herbal remedies has grown as their use has increased. Therefore, the World Health Organisation (WHO) suggested incorporating herbal medications into the current national pharmacovigilance systems. Phytovigilance, also known as pharmacovigilance of medicinal plants, examined the advantages and disadvantages of phytotherapy. Protecting patients from herbal harm is the ultimate goal. It is crucial to create dependable. Phytovigilance is also required by law because of the hazards of acute or chronic toxicity, pharmacokinetic or pharmacodynamics medication interactions, and interactions between many related plants. There are a number of problems with the naming, perception, acquisition, and application of herbal medications. The WHO released guidelines on pharmacovigilance of herbal medicines on a global scale. However, in most African nations, it is still a relatively young activity. With the exception of Morocco, where a phytotherapy pharmacovigilance program was established in 2000. Including the development of Phytotoxic and Botanicus. In this case, pharmacovigilance of herbal medications activities is necessary for understanding, identifying, and tracking adverse effects. Systematic study was done on Pub Med, Science Direct, and Scopus to demonstrate the renal side effects of using herbal medicines and the present requirement to monitor Phytovigilance globally. Additionally, certain readily available databases on Phytovigilance or pharmacovigilance of herbal medication were explored. This article's goal

was to give a general review of nephrotoxicity related to medication use. According to the World Health Organisation, up to 75%–80% of people worldwide, primarily in developing nations, either use traditional medicine as their primary form of therapy or as a supplement. For thousands of years, traditional medicine—including traditional Chinese medicine—has been used to prevent, treat, and cure a wide range of illnesses. Chinese herbal medicine is a significant part of traditional Chinese medicine and has gained popularity as an alternative treatment option worldwide. According to the information that is currently accessible, traditional Chinese medicine has a sizable market, and Chinese herbs have been sold to more than 175 nations and territories, including Germany, South Korea, Japan, and India. In 2012, it was projected that the overall market value of Chinese material medica in the United States was \$83.1 billion, up 20% from the year before. Because of the potential risks associated with using supplements that are not approved by the Food and Drug Administration (FDA), it is crucial to raise awareness about herbal medicine throughout the world. The majority of the natural substances used in Chinese herbal medicine are complex active molecules that might cause a range of adverse effects. Due to the misconception that herbal remedies are harmless, doctors and patients frequently ignore the fact that some of these herbal remedies can also result in nephrotoxicity. It is challenging to determine the prevalence of kidney damage caused by Chinese herbal remedies. However, it has been estimated that around 26% of hospital-acquired AKI cases and 18% of community-acquired AKI cases worldwide are caused by drug-related nephrotoxicity. RRT is typically required for critically ill patients with drug-induced AKI; it is unclear how Chinese herbal medication contributes to these numbers. Toxicity has been recorded through patient reports and series (interestingly, the majority of which are not from China), and adverse event reporting is typically optional. This lack of information frequently gives people the misleading impression that nephrotoxicity is uncommon when, in reality, there is a dearth of information. The renal toxicity of Chinese herbal remedies will be the main topic of this paper. This does not cover nephrotoxicity from other traditional medications, which are not commonly used in China. In Europe today, interest in natural preparations is

growing despite numerous advancements in synthetic medicine production technology. Eighty percent of people worldwide use traditional medications to address their healthcare needs, according to data from the World Health Organisation (WHO). In many nations, herbal remedies are widely used. They make up a sizable portion of medications in a number of therapeutic categories, including rheumatology, chronic inflammation, and infectious illnesses. The belief that they are safe because they are natural is one of the reasons for their widespread use. Additionally, there are therapeutic areas where effective treatment options have temporarily run out, leading the public to believe that plant chemicals may be a viable remedy. A number of drug-resistant bacterial infections, the uneven battle against viral diseases, and numerous other conditions for which there is now no effective treatment might all be targets of this challenge. Herbal medicines do, however, include pharmacologically active substances, some of which have been linked to negative side effects. Toxins and medications can especially harm the kidneys. Kidney damage is caused by various mechanisms that are still poorly understood. However, acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) were the most frequent pathologic findings in cases with nephrotoxic exposure. The number of papers on nephrotoxicity has significantly increased during the past 20 years. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, diuretics, paracetamol, contrast media, and chemotherapy are among the pharmaceuticals that have primarily affected them. Chinese herbs have received special attention among the plants that can be nephrotoxic. It is now permissible to refer to "Chinese herb nephropathy" as Aristolochic acid nephropathy (AAN). Nine comparable cases of quickly progressing fibrosing interstitial nephritis in young women were reported in Belgium in the early 1990s.

II. LITERATURE REVIEW

1) Noufissa Touiti, Sanae Achou et.al (2019)

To investigate the prevalence of nephrotoxicity linked to plant usage at the nephrology division of Hospital University Hassan II Fez, Morocco. The use of plants by kidney disease patients was the subject of this prospective investigation. Medical records of renal disease patients who ate potentially nephrotoxic plants

were examined. Age, sex, aetiology, and biological information were gathered. Of all patients with nephropathy who visited the department throughout the study period, 3% (18/600) had nephrotoxicity linked to plant usage. The study found that Aristolochic longa, Herniation hirsute, Artemisia herba alba, and Cassia Senna were the most implicated plants in nephrotoxicity.

2) Anna Wiela-Hojeńska et.al (2021)

In Europe today, interest in natural herbal remedies is growing despite numerous advancements in synthetic drug production technology. The belief that natural equals safe is one of the factors contributing to their widespread use. However, several of the pharmacologically active substances found in herbal medications have been linked to negative side effects. Toxins, including toxic components of therapeutic plants, can cause damage to the kidneys in particular.

3) Touiti N., Sqalli Houssaini et.al (2021).

Herbal remedies are becoming more and more popular around the world, particularly among people with long-term conditions like kidney disease. However, because many herbal remedies can have adverse effects on the kidneys, their safety is in doubt. An overview of nephrotoxicity (kidney toxicity) linked to herbal medicines is given in this article from the standpoint of pharmacovigilance (safety-monitoring). The case reports of nephrotoxicity associated with herbs that were published between 2000 and 2020 were thoroughly examined by the authors. Numerous kidney injury conditions, such as stones, nephritis, acute renal injury, chronic kidney disease, etc., were present in these instances.

4) Corinne Isnard Bagnis et.al (2004)

One intrinsic side effect of some anticancer medications is nephrotoxicity. Antineoplastic medications have a limited therapeutic index, and the dosage required to significantly lower the tumour burden typically results in substantial nephrotoxicity. The maximum tolerated doses found during phase I evaluation are frequently the same as the amount utilized in clinical trials. Compared to palliative

therapy, greater toxicity is acceptable in curative therapy. On the other hand, excretory organ function is frequently diminished in cancer patients.

5) Skalli S, Bencheikh RS et.al.(2015)

A survey questionnaire was issued to the national centers and national drug regulatory agencies of African nations that participate in the WHO International Programme for Drug Monitoring in order to characterize and assess Herbal Medicine (HM) pharmacovigilance. The period of data collection was October 1–December 31, 2014.

➤ Aim and objectives

○ Aim:

To improve patient safety and guide regulatory choices by reviewing, monitoring, and improving the worldwide pharmacovigilance systems for identifying, evaluating, and preventing drug-induced nephrotoxicity.

○ Objectives

1. To discover medicines typically associated with nephrotoxic effects through global adverse drug reaction (ADR) reporting databases.
2. To examine the prevalence, trends, and severity of nephrotoxicity that have been documented in various areas and demographics.
3. To assess the limitations and efficacy of current worldwide pharmacovigilance systems for nephrotoxicity detection.
4. To evaluate the clinical, medication-related, and patient-related risk variables that increase the probability of nephrotoxic adverse drug reactions.
5. To assess how different nations and regulatory bodies report nephrotoxicity.
6. To create suggestions for enhancing nephrotoxic event reporting, early detection, and worldwide monitoring.
7. To raise awareness of the dangers of nephrotoxicity and the significance of pharmacovigilance among legislators and medical professionals.

➤ Plan of work

i. Preparation & System Setup

○ Task

- a) Form a nephrotoxicity-pharmacovigilance team consisting of a data analyst, clinical pharmacist, nephrologist, and PV officer.
- b) Create uniform definitions (AKI KDIGO criterion).
- c) Make forms for reporting renal adverse events (eGFR, urine output, and serum creatinine).
- d) Configure data sources, such as lab alerts, spontaneous reports, and hospital HER.

• Deliverables

- SOP for PV-Nephrotoxicity.
- standard template for gathering data.
- instructional resources.

ii. Data collection

• Task

1. Regularly checking serum creatinine and other kidney indicators.
 - eGFR.
 - Urine production.
 - Electrolytes.
 - Proteinuria.
2. Every day, screen patients and high-risk drugs
3. Gather reports of adverse drug reactions (ADRs) that occur on their own.
4. Use automatic lab-trigger warnings (≥ 0.3 mg/dL rise in creatinine or $\geq 50\%$ decline in eGFR) to identify suspicious instances.

iii. Causality Assessment.

• Task

1. Examine further kidney injury causes, such as infection, dehydration, hypotension, and blockage.
2. Determine the severity (mild, moderate, severe, dialysis-required).
3. Assess preventability.

• Deliverable

- Assessment papers for causality.
- An overview of verified nephrotoxic adverse drug reactions.

iv. Data Analysis and signal detection.

• Task

1. Analyse renal adverse events on a monthly basis.
2. Identify:
 - High-risk drugs

- Dose-related risks Nephrotoxicity associated with interactions
- 3. If using big datasets, do a disproportionality analysis.
- 4. Examine results against international safety databases and literature.
- Deliverable
 - Early warning signs for possible drug use.
 - The monthly report on nephrotoxicity surveillance

v. Risk minimisation and clinical intervention

- Task
 1. Create risk-reduction techniques like:
 - Dose-adjustment recommendations based on eGFR Keeping an eye on high-risk medication regimes Contrast media hydration guidelines
 - Steer clear of nephrotoxic medication combinations
 2. Put clinical decision support technologies into practice (pop-up notifications for patients who are at risk).
 3. Inform medical professionals about the warning indications of renal damage.
- Deliverable
 - Updated drug protocols and renal monitoring charts
 - Hospital-wide advisory notices
 - Training sessions for clinicians and nurses.

vi. Communication and report's

- Task
 1. Send the national pharmacovigilance authority any confirmed nephrotoxic adverse drug reactions.
 2. Send out information about internal safety.
 3. Inform clinical departments about new signals.
 4. Report serious cases (fatal, life-threatening, requiring dialysis) right away.
- Deliverable
 - ADR submissions.
 - PV reports on nephrotoxicity every three months;
 - Safety alerts and circulars.

vii. Evaluation and Quality improvement

- Task

- Detection time
- Data completeness
- Decrease in avoidable AKI cases
- 1. Audit the nephrotoxicity PV program every year.
- 2. Revise SOPs and guidelines in light of the results.
- Deliverable
 - Revised improvement plan.
 - Annual assessment report.
 - Timeline (usually one year).

Month Activity

- 1–2 Setup, training, finalisation of SOP
- 3–4 Start active data collection and reporting
- 5–6 First data analysis, initial risk assessment
- 7–9 Risk reduction protocol implementation
- 10–11 Review trends and modify methods
- 12 Final evaluation & yearly report.

➤ Method and Materials

- Search strategy

In May 2020, electronic literature searches were carried out to find case reports of nephrotoxicity linked to the usage of herbal medications throughout the previous 20 years. Key phrases including "case report," "renal side effect," "adverse effects," "nephrotoxicity," "risk," "herbal medicine," and "kidney disease" were used to search the scientific resources, including PubMed, Scopus, and Science Direct. renal stones, nephritis, nephrotic syndrome, necrosis, acute renal injury, chronic kidney disease, and death were among the spectrum of kidney problems caused by herbal remedies. Although certain stories in other languages were taken into consideration, English articles were the main focus.

- Inclusion and exclusion criteria.

The following requirements had to be met for studies to be eligible: Case reports of nephrotoxicity linked to the use of herbs globally between 2000 and 2020 were included in the investigations. Criteria for exclusion: Case reports involving mushrooms, toxic plants, self-harm, excessive dosages (apart from vitamins and minerals), drug-herbal interactions, and commercial dietary supplements were not included.

- Study selection and data extraction.

One reviewer and a sample of the excluded titles evaluated the study titles that were found through the search for inclusion. Was examined by a second reviewer, and no inconsistencies were discovered. Two reviewers evaluated potentially pertinent abstracts and full texts, and any disagreements were settled through conversation. One reviewer extracted the data, and another verified it. The Naranjo causality assessment scale, which we modified and detailed in our most recent paper, was used to determine the causality.

• Result

An explanation of the included studies Over 15,303 citations were found during the thorough search, and 47 of them Eighty-five percent of the research was

eliminated. This led to the inclusion of 27 relevant papers. The most important information from these papers is compiled.

- Herbal medication side effects and the necessity of Phytovigilance Worldwide case reports of renal adverse effects linked to the use of herbs.

Twenty-seven case reports of nephrotoxicity associated with herb ingestion from Southeast Asia, Korea, South and North Africa, Turkey, Tunisia, and Belgium were found during our search. Males between the ages of 22 and 68 made up the majority of those with renal responses (18/27 = 66%). The traits of instances are Acute tubular necrosis is one of the renal disorders that have been linked to the usage of medicinal herbs.

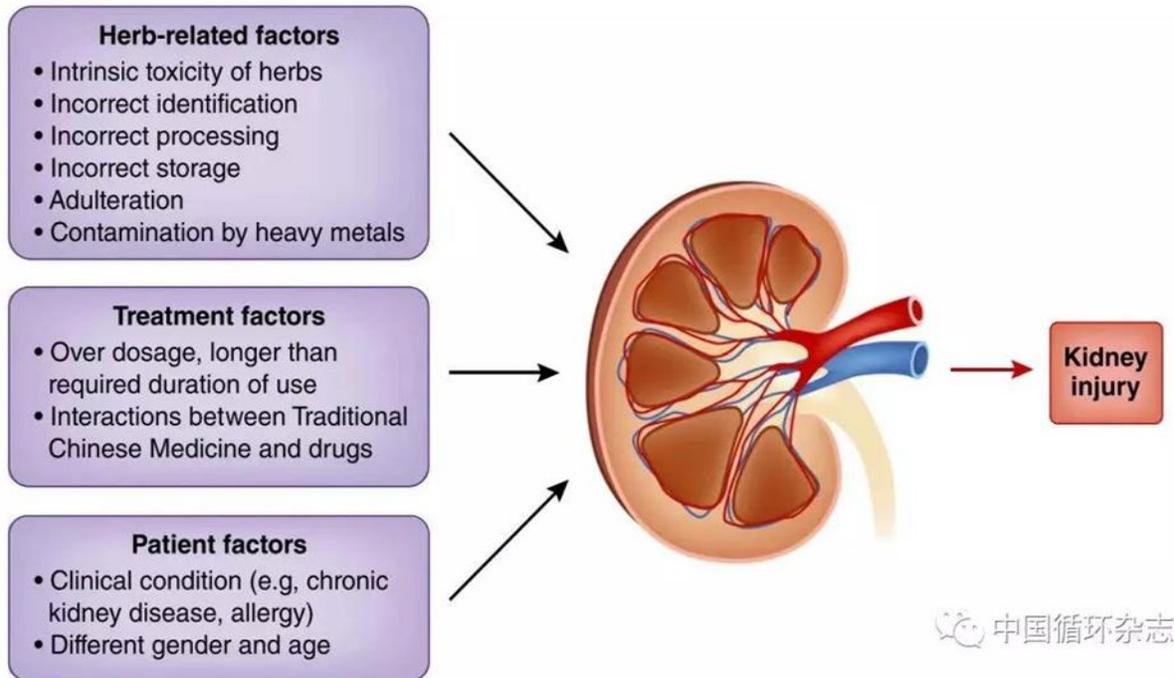


Figure: Factors affecting development of kidney disease associated with herbal medicine

III. CONCLUSION

Adverse effects, which patients may not always report, including self-medication and contacting community networks for many herbal medicines tend to reduce treatment adherence monitoring in both developed and developing nations. More precisely, the reality in Africa makes it abundantly evident that people view natural products as safe and secure, with herbal treatments being reasonably priced. AHM products

typically have some potential side effects (dose-related, time-related, or therapy failure) that can harm an organ’s basic structural, functional, and biological unit, such as a cell (cytotoxicity) or an organ like the liver (hepatotoxicity) or heart (cardiotoxicity). In particular, certain bodily systems (such as the neurological system, digestive system, and cardiovascular system) may be affected by the investigated medicinal plants.

Therefore, we have observed some adverse drug reactions with multiple clinical manifestations of toxic effects of plants that cause gastrointestinal, respiratory, cardiovascular, and neurological disorders with our research sample (Pygeum africanum, wild wisteria, Madagascar rosy periwinkle, round leaf Buchu, South African geranium, Hoodia cactus, red spinach, bird flower, Impila, ox-eye daisy, khat leaf, and liquorice). Even though they don't understand physiopathology and physiomolecular processes, practitioners of traditional medicine frequently have knowledge and expertise that isn't yet publicly or generally recognised and isn't employed enough. Nonetheless, these professionals must to have sufficient understanding of the pharmacological characteristics of therapeutic plants so that they may act as a guide and quickly recognise the data required for the interpretation of negative health consequences and patient counselling. Alkaloids, cardiac glycosides, phorbol esters, lectins, and cyanogenic glycosides are some of the active principles in these medicinal plants that are highly toxic, even though many significant African plants with ethnopharmacological uses may have potential biological activities. Lastly, in order to provide patients in the field of integrative medicine with high-quality products and safe services (the physical, mental, and social benefits of traditional medicine in the development of both preventative and therapeutic health care services), medicinal substances in the African traditional pharmacopoeia must adhere to the international pharmacopoeia and WHO recommendations. The accurate, prompt, and comprehensive dissemination of new risk information is a crucial component of pharmacovigilance in herbal medicine and has the potential to enhance patient safety and well-being. This necessitates better cooperation between contemporary medical professionals, researchers, and drug regulatory bodies and traditional practitioners.

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