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## **Herbal nephropathy – a serious condition based on the innocence of nature**

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## Abstract

**Introduction and purpose:** This study aimed to discuss herbal supplement usage in population and possible harmful effects with a strong emphasis on the kidneys health.

**Materials and methods:** A literature search was conducted in the PubMed MEADLINE database of medical publications using the following keywords: herbal nephropathy, aristolochic nephropathy, herbal supplementation, Chinese traditional medicine

**Results:** Despite the widespread use of herbs among the general public, awareness of possible side effects appears to be negligible. The herbal medicine market is often unregulated, moreover, there are problems with correct identification of the plant, variable cultivation, its processing and the lack of accurate information about its biological activity. Possible side effects include frequent contamination of preparations with heavy metals, other substances such as hormones, aflatoxins or pesticides. In addition, herbs can directly affect the metabolism of drugs taken for specific medical indications. They are able to change the level of their absorption, metabolism in the liver and secretion. The kidneys are a special organ exposed to the harmful effects of herbs due to their high blood flow, resorption from the renal tubules and high metabolic activity. Among kidney damage, aristolochic nephropathy is the one worth mentioning, induced by the herb *Aristolochia fangchi* and causing a rapidly progressing kidney disease, largely ending up with the need for dialysis or kidney transplantation.

**Conclusion:** The use of herbs as medical substances carries dangers. They should be prevented through proper education of the society, appropriate legal regulations and doctors' awareness of their occurrence.

**Key words:** nephropathy, herb, traditional medicine

## Introduction

It is estimated that over 1/3 developed countries inhabitants and 80% of the population of developing countries use herbal products for prophylactic and therapeutic purposes. <sup>1</sup> Despite such a widespread phenomenon, public awareness of the potential side effects of using herbal preparations seems to be negligible. In most countries, there are no legal regulations regarding the safe use of herbs. <sup>2</sup> The reason may be that the side effects of pharmacotherapy are widely known and described, while herbal medicine is associated with words such as “safety”, “nature” and “mildness”. <sup>3</sup> This phenomenon is also based on a greater sense of control in the area of treatment option, without relying solely on medical knowledge. The problem of

using herbal preparations is complex - they largely do not meet the requirements regarding consistency of composition and biological activity due to the lack of proper identification of a given plant, variable cultivation and processing conditions of extracts, and the lack of information on pharmacological active substances.<sup>4</sup> Such supplements are also contaminated with heavy metals, pesticides or aflatoxins.<sup>5</sup> One systematic review reported a total of 106 cases of heavy metal poisoning associated with the use of traditional Chinese medicine herbs.<sup>6</sup> As for example, in 1977, a 59-year-old patient was reported to consume 15 mg of lead daily by taking a Chinese herbal preparation prescribed by a Chinese medicine practitioner.<sup>7</sup> The literature also describes cases of acute lead-induced encephalopathy, including fatal ones, developing on the background of consumption of this type of preparations.<sup>8</sup> Drugs such as ephedrine, sildenafil, methyltestosterone, fenfluramine were found in herbal supplements sold in California, USA.<sup>4</sup> As mentioned earlier, proper preparation of the plant is sometime crucial, as illustrated by the example of the plant called *Aconitum genus*, traditionally used in Chinese medicine. Before treatment, the plant contains aconitine and other alkaloids that are highly neuro and cardiotoxic.<sup>5,9,10</sup> Only the appropriate soaking, boiling and decoction preparation causes the toxic alkaloids to hydrolyze into less dangerous compounds.<sup>5</sup> Another major concern of herbs is their potential to interact with medications prescribed by medical doctors. Herbs can change the pharmacokinetics of medicinal substances, influencing their absorption, metabolism, distribution and secretion. This is believed to be due to induction or inhibition of liver enzymes (cytochrome P450 [CYP]) that metabolize drugs and drug transporters such as P-glycoprotein (P-gp).<sup>11</sup> For example, a very famous and widely used herb called *Ginkgo biloba* interacts with warfarin (an anticoagulant drug), which can lead to increased bleeding.<sup>12</sup>

## Herbal nephropathy

The kidneys are particularly susceptible to the negative effects of substances entering the body. This is thought to be due to the high blood flow of the kidneys, their high metabolic activity and the resorption in the renal tubules.<sup>13</sup> The most common histological findings in the kidney after contact with neurotoxins are acute tubular necrosis and acute interstitial nephritis.<sup>13,14</sup> In total, herbal-induced nephropathy can manifest itself in many forms - acute kidney injury, renal tubular dysfunction, dyselectrolythemia, systemic hypertension, chronic kidney disease, renal tubular necrosis, urolithiasis, and urothelial carcinoma.<sup>15</sup> Herbs can also induce high blood pressure, cystinuria and hyperkalemia in the blood.<sup>16</sup> Regarding the incidence of such nephropathy, it is estimated that 30-35% of acute kidney damage in Africa is induced by herbal intake.<sup>17</sup> According to a Pubmed database review from 1966 to 2016, 7 herbs and 10 supplements contributed to kidney damage.<sup>18</sup> Herbs that has been mentioned are Chinese yew (*Taxus celbica*) extract, impila (*Callilepis laureola*), morning cypress (*Cupressus funebris Endl*), St. John's wort (*Hypericum perforatum*), thundergod vine (*Tripterygium wilfordii hook F*), tribulus (*Tribulus terrestris*) and wormwood (*Artemisia herba-alba*). Apart from them, the damage can be acquired by chocolate vine or mu tong (*Caulis aristolochiae*), guang fang ji (*Aristolochia fangchi*), ma huang (*Ephedra sinica*), however, they have been banned in the United States for this particular reason.<sup>18</sup> For instance, there were two published studies reporting nephrolithiasis development associated with *Ephedra sinica*.<sup>19,20</sup> The stones composed of substances such as ephedrine, norephedrine, and pseudoephedrine. Adverse effects lead to total prohibition of ephedra-containing supplements by Food and Drug Administration (FDA) in 2004.<sup>21</sup> St. John's wort, a plant known as *Hypericum perforatum*, has

been used as a natural antidepressant since ancient times.<sup>2</sup> Its sales in Germany are believed to be 4 times higher than sales of selective serotonin reuptake inhibitors. Moreover, its effectiveness has been confirmed in a fairly large meta-analysis.<sup>22</sup> As this plant induces the CYP system in liver, it may lower the concentration of other drugs, leading to serious clinical sequelae. Its use has been reported to the rejection of kidney transplants in patients, reducing levels of immunosuppressive drugs (cyclosporine and tacrolimus).<sup>23</sup>

### **Aristolochic acid nephropathy**

In 1993, two cases of women living in Belgium were described who developed rapidly progressive fibrosing interstitial nephritis after the use of the weight loss supplement.<sup>24</sup> Some time later, a total of over 100 such cases were described, of which 1/3 required dialysis, 1/3 kidney transplantation, and the remaining people struggled with progressive kidney disease.<sup>25</sup> The complications were caused by a Chinese herb called *Aristolochia fangchi*. Nephropathy, originally known as "Chinese herb nephropathy", became known as "aristolochic acid nephropathy" after the causative agent was established. This herb contains aristolochic acid which, in addition to nephrotoxicity, is a carcinogen for both animals and humans.<sup>26,27</sup> Aristolochic acid nephropathy is characterized by early, severe anaemia, mild tubular proteinuria and initially normal arterial blood pressure in half of the patients.<sup>28</sup> In addition, nearly half of the patients develops urothelial malignancy of the upper urinary tract. Progression to end-stage renal disease is rapid, with the kidney chronic disease development in two years' time.<sup>29</sup> The treatment consist of glucocorticosteroids administration and pre-emptive bilateral nephroureterectomies. Although Chinese medicine practitioners believed that these supplements were not properly prepared and administered to people from Europe in the wrong doses, in Taiwan, where more than 1/3 of the population uses *Aristolochia fangchi*, the incidence of upper urinary tract cancers is the highest in the world.<sup>30</sup> Even though products containing aristolochic acid have been banned in most countries, cases of nephropathy remain regularly reported.<sup>31</sup>

### **Summary**

To summarize, due to the widespread use of herbs in society, it is important to conduct scientific studies in order to detect potential side effects, learn about their properties and prohibit use in case of the discovery of a dangerous effect. Additional legal regulations are needed, focusing not only on pharmacotherapeutic agents. In addition, doctors should be aware of the harmful effects of taking herbs, with particular attention to nephrologists, because the kidneys are a potential site of damage by many substances. They should conduct interviews with particular care and remember about the possible effects of plants. The public should also be made aware that these substances are not neutral to the organism and that they should not be considered only as "innocent" or safe.

### **Contribution of authors:**

**Iga Dudek- study concept and design; critical revision of the manuscript for important intellectual content; study supervision**

**N. Rybak- acquisition of data; analysis and interpretation of data; technical support;**

**T. Skubel- acquisition of data; analysis and interpretation of data; technical support;**

**J. Czarnota- acquisition of data; analysis and interpretation of data; technical support;**

**M. Dobrzyński - acquisition of data; analysis and interpretation of data; technical support;**

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