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Evaluating the safety of common herbal supplements in chronic kidney disease, dialysis, and kidney transplant patients

By Nathaniel Lee and Marisa Battistella

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LEARNING OBJECTIVES

1. Describe the use and safety concerns of common herbal supplements in chronic kidney disease (CKD), dialysis, and kidney transplant patients.
2. List and discuss potential drug-herb interactions.
3. Identify tools and available resources to evaluate herbal supplement safety profiles in CKD.

BACKGROUND

Herbal supplements are widely used and remain a popular complementary alternative medicine (KDIGO, 2013; Hassen et al., 2022). A 2017 study that evaluated the prevalence of herbal supplement use in a large population of US adults demonstrated that more than a third of the study participants used at least one herbal medicine (Rashrash et al., 2017). Herbal supplement use in chronic kidney disease (CKD), dialysis, or transplant patients is also prevalent. One study found that 18.6% of CKD and post-transplant patients in several nephrology clinics in Isafahan, Iran, were using herbal supplements (Mohammadi et al., 2020). Another study in three outpatient nephrology clinics and dialysis centres in Egypt demonstrated that greater than 40% of patients with CKD and dialysis, or transplant recipients, used herbal and

natural products (Osman et al., 2015). Multiple studies have proposed that patients with CKD or receiving dialysis may be more concerned about their health due to their generally poor quality of life and seek alternative medical approaches at a higher rate (Rashrash et al., 2017; Mohammadi et al., 2020).

Despite the prevalence of herbal supplement use, health-care providers are generally unaware of alternative treatment modalities that could be impacting patients' health (Mohammadi et al., 2020). A Turkish study revealed that only 12.5% of patients with CKD reported herbal consumption to their physicians (Mohammadi et al., 2020; Kara, 2009). One reason for the lack of transparency may be due to disapproval for complementary alternative medicine (Mohammadi et al., 2020; Birdee et al., 2013; Blackmer & Jefromova, 2002).

Herbal supplements as a whole do not have good quality safety or efficacy data, and some are known to adversely affect CKD and kidney transplant patients through electrolyte changes, pharmacokinetic interactions, effects on the immune system or production of toxic metabolites (KDIGO, 2013; Rashrash et al., 2017; Hassen et al., 2022; Mohammadi et al., 2020; Dahl, 2001). Herbal supplements that contain aristolochic acid, for example, are known to be nephrotoxic through several mechanisms including apoptosis, oxidative stress, and inflammation (KDIGO, 2013; Anger et al., 2020; Ji et al., 2021). Common supplements that contain aristolochic acid include *guang fang ji* (*Aristolochia fangchi*), chocolate vine, *mu tong* (*Akebia*), *xi xin* (*Asarum*), *chuan mu tong* (*Clematis*), *wei ling xian* (*Clematis chinensis*), and *han fang ji* (*Stephania*) (Brown, 2017). Aristolochic acid may often be found as an additive in other typically unregulated herbal supplements, which poses an added risk when herbal supplements are taken and are not rigorously tested before they are distributed (Audimoolam & Bhandari, 2006; Brown, 2017). Noni is another herbal supplement that is used commonly by patients and can be potentially dangerous for patients with kidney impairment. Juice made of noni contains a significant amount of potassium: about 6 mEq per 100 mL of juice according to one case report (Mueller et al., 2000). It can, thereby, cause large shifts of

AUTHOR NOTES

Nathaniel Lee, PharmD(c), Albany College of Pharmacy and Health Sciences, Albany, NY

Marisa Battistella, PharmD, ACPR, Clinician Scientist, Assistant Professor, Leslie Dan Faculty of Pharmacy, University of Toronto, Pharmacy Clinician Scientist, Clinical Pharmacist – Nephrology, University Health Network, Toronto, ON

Correspondence should be addressed to: Marisa Battistella, University Health Network, 200 Elizabeth Street, EB 214, Toronto, ON M5G 2C4

Email: marisa.battistella@uhn.ca

potassium and increase the risk of hyperkalemia (Mueller et al., 2000; Natural Medicines, 2022a).

Herbal supplements may also have serious drug interactions leading to adverse health outcomes. Since many patients with CKD, on dialysis, or who have had a kidney transplant often take multiple prescription medications for several different conditions, herbal supplements may pose a potential threat to a patient's health, either through direct effects or interactions with prescription medications (Mohammadi et al., 2020; Markell, 2005; Akyol et al., 2011; Nowack et al., 2009). As such, herbal remedies are not recommended to be used in people with CKD (KDIGO, 2013).

All of these issues highlight the importance of considering the potential impact of herbal supplements in the health and management of patients, especially those who may be more vulnerable such as those with CKD, receiving dialysis, or have had kidney transplant, or in patients who express a strong desire to use herbal supplements. The healthcare team therefore plays a pivotal role in assessing if herbal supplement use is safe and appropriate as well as promoting an open and welcoming discussion with patients to ensure all facets of healthcare are considered. Common herbal supplements used in the community will be discussed in the context of their current safety profile in CKD, dialysis, and kidney transplant patients, which will provide a framework for how to evaluate and assess their safety in these patients.

ST. JOHN'S WORT

St. John's wort is a popular herbal supplement that is commonly made into oral or topical formulations. It may be used by patients for a variety of conditions or reasons, although it has been only shown to be likely effective for depression and possibly effective in reducing menopausal symptoms or symptoms of somatization disorder (Natural Medicines, 2022b). Although oral St. John's wort is generally well tolerated, its concerns for use in patients with kidney dysfunction stem from a limited number of case reports, its elimination pathway, and its numerous drug interactions. In one case, a 46-year-old female developed acute kidney injury (AKI) after ingesting a tea made with St. John's wort. She subsequently had acute kidney failure and required three hemodialysis sessions to recover (Natural Medicines, 2022b; Adibelli et al., 2021). Some of the active ingredients of St. John's wort are primarily eliminated by the kidneys, which also raises concerns for its use in patients with kidney impairment, as impaired renal elimination could lead to accumulation and adverse effects (Burrowes & Van Houten, 2006; Duncan, 1999). There are no current data that demonstrate St. John's wort is safe to use in dialysis patients.

Last, St. John's wort has a plethora of drug interactions that would further merit a strong advisory against using it, especially since patients with CKD, receiving dialysis, and who have had a kidney transplant typically use multiple medications that have a high probability of interacting with St. John's wort. Notable common medications prescribed in CKD and dialysis that can interact with St. John's wort include clopidogrel, digoxin, HMG-CoA reductase inhibitors (statins), omeprazole, oxycodone, rivaroxaban, tramadol, and

warfarin (Natural Medicines, 2022b). Of note, in regard to kidney transplant patients, St. John's wort is known to interact with immunosuppressant medications. Organ transplant rejection occurred in numerous case reports and clinical trials when St. John's wort was combined with cyclosporine, as St. John's wort increased cyclosporine clearance through induction of CYP3A4 and P-glycoprotein/MDR-1 (Borrelli & Izzo, 2009; Mandelbaum et al., 2000; Mai et al., 2000; Barone et al., 2000; Bauer et al., 2003; Brown, 2017). This led to acute transplant rejection in patients with heart, liver, or kidney transplants (Barone et al., 2000; Bauer et al., 2003; Breidenbach et al., 2000; Brown, 2017). Similarly, St. John's wort interacts and decreases serum levels of the immunosuppressive drug tacrolimus, which can pose a risk of organ rejection (Mai et al., 2003). These drug interactions are evidence for kidney transplant patients to clearly avoid using St. John's wort.

ECHINACEA

Echinacea is a common herbal supplement that is possibly effective when used to prevent and manage symptoms of the common cold (Burrowes & Van Houten, 2006; Natural Medicines, 2022c). It is generally well tolerated when taken orally and at recommended doses (Natural Medicines, 2022c). In CKD and dialysis patients, safety evidence about echinacea is limited. In one case report, a 36-year-old female who took a mix of supplements including echinacea, St. John's wort, and kava for two weeks, subsequently developed muscle weakness, hypocalcemia, hypophosphatemia, critical hypokalemia ($K^+ 1.3$), renal tubular acidosis, fatigue, and dry mouth and eyes. This particular patient was diagnosed with Sjogren's syndrome, an autoimmune disease thought to have been triggered by echinacea's immunostimulant effects, and this ultimately resulted in her kidney complications (Logan & Ahmed, 2003; Brown, 2017; Natural Medicines, 2022c). Additionally, there was one case of acute kidney failure out of 51 adverse reaction reports linked to echinacea use in Australia in a single year (Mullins & Heddle, 2002). An important conclusion from these case reports is that echinacea's nephrotoxic adverse events, although rare, is probable in a large population of patients who take echinacea in unsupervised and non-standardized formulations (Mullins & Heddle, 2002). There are also no data that supports safe echinacea use in patients receiving dialysis. In this way, the potential benefits of echinacea use in CKD or dialysis patients should be heavily scrutinized and weighed against its potential risks, or it should be avoided altogether if possible.

For kidney transplant patients, echinacea should absolutely be avoided, despite a lack of evidence. It is theorized by various studies that echinacea can interfere with immunosuppressant therapy such as cyclosporine and mycophenolate through the various mechanisms it can stimulate the immune system (Mohammadi et al., 2020; Natural Medicines, 2022c; Barrett, 2003; Shi & Klotz, 2012; Staines, 2011). In turn, this could lead to kidney graft rejection (Mohammadi et al., 2020). This is a serious potential adverse health outcome that can easily be prevented by avoiding echinacea herbal supplements in kidney transplant patients.

GINKGO BILOBA

Ginkgo biloba, which comes from ginkgo leaf extracts of large trees with fan-shaped leaves native to Asia, but can be seen in many other parts of the world including Canada now, is a popular supplement used for a variety of conditions. It is noted to have possible effectiveness for reducing anxiety, symptoms of schizophrenia, severity of tardive dyskinesia, and improving hearing loss, recovery from stroke, symptoms of premenstrual syndrome, and vertigo. Ginkgo is available as a variety of formulations, including intravenous, intramuscular, topical, ophthalmic, and oral, although the oral formulation is much more common and is mostly well tolerated when used at recommended doses (Natural Medicines, 2022d). There is limited and conflicting evidence for ginkgo's safety in patients with any kidney impairment. Li and colleagues (2019) examined the *in vitro* and *in vivo* effects of the bioflavonoids from ginkgo biloba. The *in vitro* human kidney tubular epithelial cells demonstrated reduced cell viability in a dose-dependent manner from the bioflavonoids, indicating potential kidney toxicity. *In vivo* experiments in mice showed that bioflavonoid administration of 20 mg/kg/day for seven days resulted in significantly increased alkaline phosphatase activity and acute kidney injury. In this study, ginkgo bioflavonoids also cause hepatic toxicity, suggesting the other potential health risks of using this herbal supplement. Various other researchers have investigated ginkgo's use in improving a variety of complications associated with CKD. These have included a potential to alleviate vascular calcification, slow down progression of hypertensive nephropathy and improve kidney in these patients, as well as reduce tubular damage in diabetic kidney disease (Wang et al., 2019; Jialiken et al., 2021; Han et al., 2021; Yu et al., 2021; Welt et al., 2007; Wang et al., 2020). Jialiken et al.'s study was focused on humans; however, ginkgo therapy was combined with conventional anti-hypertensive therapy and thus ginkgo's effect on hypertensive nephropathy remains still uncertain. Interestingly, ginkgo has been studied to show a potential to protect against nephrotoxicity from various medications such as gentamicin and methotrexate in rats (Naidu et al., 2000; Sherif et al., 2019). Thus, in CKD patients, ginkgo should be avoided to prevent possible nephrotoxicity.

In peritoneal dialysis patients, ginkgo was being safely used at 160 mg/day for 8 weeks (Kim et al., 2005). Another study used ginkgo in hemodialysis patients; however, no safety outcomes were reported from it (Huang et al., 2008). There is also conflicting evidence that ginkgo can increase bleeding risk in patients who take antiplatelets, anticoagulants, or ibuprofen as it may have antiplatelet effects itself (Natural Medicines, 2022d). This may pose a problem in dialysis patients who are at an increased risk of bleeding due to platelet dysfunction. It therefore may be safe to use ginkgo in dialysis patients, although data is limited, and any use should be monitored with extreme caution and evaluated in terms of dosing, formulation, bleed risks and patient-specific factors. Additionally, Hauser and colleagues (2002) described a patient with a case of subphrenic hematoma occurring one week after a second liver transplantation due

to postoperative ginkgo use. There were no further bleeding episodes after the ginkgo supplement use was discontinued. Aside from this evidence that suggests ginkgo should be avoided around the time of surgery due to its potential to increase bleeding, there are few pieces of evidence to demonstrate explicitly that ginkgo is unsafe in kidney transplant patients. Unlike the other herbal supplements, ginkgo has not been reported to interact with immunosuppressants. Given the paucity of data, however, it would be safest to avoid ginkgo supplement use in these patients.

GLUCOSAMINE

Glucosamine is a widely used supplement for osteoarthritis, although there are conflicting viewpoints and evidence as to whether it is effective. Glucosamine is generally made using the chitin in the shells of shellfish, which may already pose a risk to those with shellfish allergies (Murray, 2012; Heller, 2008; Natural Medicines, 2022e). However, there are glucosamine products made from fungus or corn (Heller, 2008; Natural Medicines, 2022e). It is generally combined with other supplements such as chondroitin and methylsulfonylmethane (MSM), both of which are also used for osteoarthritis and joint health. Some glucosamine capsules contain potassium chloride to stabilize the product, which can additionally raise problems in patients with potassium-restricted diets, such as those with CKD or receiving dialysis (Wangroongsub et al., 2010; Natural Medicines, 2022e).

One major drug interaction of glucosamine is warfarin. It is thought that glucosamine has weak antiplatelet activity, and it has been shown in multiple case reports that concomitant use leads to increased INR and bleeding risk (Knudsen & Sokol, 2008; Yue et al., 2006; Rozenfeld et al., 2004; Danao-Camara, 2000; Natural Medicines, 2022e). At recommended oral doses, glucosamine is usually well tolerated. Similar to St. John's wort, the major pathway of elimination for glucosamine is through the kidneys. This means its elimination may be delayed in CKD patients (Natural Medicines, 2022e). Clinical trial data in healthy, non-CKD patients have suggested no nephrotoxic effects of glucosamine (Reginster et al., 2001; Pavelka et al., 2002; Natural Medicines, 2022e). Other case reports have indicated potential nephrotoxicity with glucosamine use. In one study, out of 200 patients with osteoarthritic pain who took combination glucosamine and chondroitin, there were four cases of 1+ to 2+ proteinuria, and three patients with elevated creatinine phosphokinase level that was reversible (Danao-Camara, 2000). In another case, a 79-year-old patient taking glucosamine for several months had elevated blood urea nitrogen and creatinine levels without proteinuria that gradually returned to normal once the patient discontinued glucosamine. This patient was also noted to take cyclosporine concurrently, which may have had an additive nephrotoxic effect (Guillaume & Peretz, 2001). There have been cases of acute tubulointerstitial nephritis reported as well (Audimoolam & Bhandari, 2006; Gueye et al., 2016). Gueye and colleagues observed a reduction in glomerular filtration rate (GFR) from 86 to 47 mL/min/1.73m² within three months with non-inflammatory

fibrosis of the renal cortex in a patient who took glucosamine 1,200 mg daily for three years. The patient's kidney function improved from 47.5 to 60 mL/min/1.73m² after glucosamine was discontinued. However, after the patient restarted glucosamine, there was repeated loss in kidney function from 60 to 53 mL/min/1.73m² after three weeks (Gueye et al., 2016). Due to the potential for nephrotoxic effects and delayed elimination, glucosamine is not recommended for all CKD and kidney transplant patients if possible. Although glucosamine is thought to be mostly renally eliminated, given conflicting evidence about its effectiveness, its potential to increase bleed risk and no current data supporting safe use in dialysis, patients receiving dialysis may use glucosamine with caution, and its efficacy and side-effects should be monitored.

OTHER RESOURCES

The herbal supplements discussed in this article are only a few of the most commonly used in the community. As there are many other supplements available, and as more studies and case reports are published, it is imperative to know appropriate resources and tools to keep up with current evidence and guidelines. Table 1 is a helpful list of tools and resources that can help in researching herbal supplements and providing up-to-date evidence to help determine whether they are safe to use in patients. HerbalCKD.com, a Canadian website, is a useful tool to find information about natural health products and their use specifically in CKD, dialysis, and kidney transplant patients.

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Table 1

Tools and Resources for Herbal Supplement Information

- HerbalCKD.com
<https://www.herbalckd.com>
- Natural Medicines
<https://naturalmedicines.therapeuticresearch.com/>
- National Kidney Foundation
<https://www.kidney.org/>
<https://www.kidney.org/atoz/content/herbalsupp>
<https://kidneyhi.org/use-of-herbal-supplements-in-chronic-kidney-disease/>
<https://kidneyhi.org/dietitian-blog/herbal-supplements-and-chronic-kidney-disease/>
- Healthcare professionals such as pharmacists and dietitians

CONCLUSION

Herbal supplements are popular and will continue to be used by many patients including those with CKD, receiving dialysis, or who have had kidney transplants. Despite this, data and evidence supporting safety of herbal supplements remain limited in these populations. It is, therefore, important to gather a comprehensive patient history and consult resources available on the herbal supplement in order to make sound clinical judgement. The risks and benefits of continuing a herbal supplement should be weighed to ensure patient safety.

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