Innovative Strategies to Combat Kidney Disease

By Julius Goepp, MD

SILYMARIN

Silymarin is extracted from milk thistle (*Silybum marianum*), a plant rich in the flavonolignans silychristin, silydianin, silybin A, silybin B, isosilybin A and isosilybin B, which are collectively known as the silymarin complex.

This safe, natural compound has a long history as a traditional therapy for liver and kidney conditions. It has been used in Western medical practice for more than a quarter of a century as the treatment of choice for the serious kidney injury resulting from severe mushroom poisoning, owing to its potent antioxidant and nephron-protective effects. In fact, we’ve known since 1979 that kidney injury by mushroom poisoning in animals pre-treated with silymarin can be almost entirely prevented. These effects make it a natural choice for protection against drug-induced kidney damage, since so many drugs can act like poisons, exerting extreme oxidant stress on kidney tissue.

Mushroom poisons (mycotoxins) are among the most deadly natural toxins known. Their kidney toxicity is surpassed only by some of the most aggressive chemotherapy agents. Physicians have therefore looked to silymarin as a potential “renoprotective” agent for patients undergoing chemotherapy.

Silymarin is also protective against several classes of nephrotoxic drugs, in particular cisplatin and Adriamycin®, two of the most potent chemotherapeutic drugs—but also two of the most damaging to the kidney owing to oxidative damage and severe inflammation. Researchers around the world have found that silymarin and its components reduce and often entirely prevent the kidney damage caused by these drugs.

Silymarin’s ability to protect against the oxidative stress produced by potent drugs suggests that it may be useful in protecting against more subtle, chronic injury by free radicals, particularly those generated by chronic blood glucose elevations. German researchers, for instance, have found that silymarin could entirely prevent injury to renal cells incubated with elevated glucose concentrations while blocking production of oxidative stress markers.

Silymarin’s protective power also extends to ischemia/reperfusion injury (restoration of blood supply following restriction of blood flow). Turkish researchers demonstrated that they could completely prevent visible and functional damage to kidney structures exposed to this kind of injury by pre-treating animals with silymarin. Studies such as these have huge implications for the general population, because they suggest that by maintaining optimal antioxidant function through supplementation, we may be able to prevent much (if not most) of the chronic oxidative damage to which our kidneys are exposed daily.

RESVERATROL

The considerable advance in our understanding of the cyclical relationships between oxidative stress, endothelial dysfunction, inflammation, atherosclerosis, and chronic kidney disease points to resveratrol as an intervention in the chain of events that ultimately lead to renal failure.

Italian researchers are among the leaders in resveratrol research, and early in this century one group published remarkable research demonstrating the impact of resveratrol on preserving kidney structure and function in rats exposed to ischemia/reperfusion injury.

Japanese and Indian urologists followed that up in 2005 and 2006 with reports detailing the mechanisms by which resveratrol combats oxidative damage following reperfusion, markedly reducing kidney dysfunction. Overwhelming bacterial infections (sepsis) are a common cause of kidney failure in the intensive care unit and following surgery or trauma. Turkish physiologists demonstrated that resveratrol can reduce or prevent both kidney and lung injury in septic rats.
Resveratrol’s unmatched antioxidant and anti-inflammatory potential has been tapped in studies of its ability to prevent drug-induced kidney damage as well. Nephrotoxicity in rats exposed to the antibiotic *gentamicin* was significantly reduced and more rapid healing of injured kidney tissue was attained using resveratrol, with dramatic reduction in markers of oxidant injury.58 A team of toxicologists in Brazil demonstrated its kidney protective power against *cisplatin*, the powerful chemotherapy agent responsible for so much drug-induced kidney damage.59 Finally, Indian pharmacologists were successful in protecting animal kidneys from damage caused by another common chemotherapy and immune suppressant drug *cyclosporine A* by pre-treating the animals with resveratrol.56

Since diabetes is the leading cause of kidney disease—and because the damage it inflicts is largely mediated by free radical production resulting from destructive alteration of proteins by glucose (glycation)—researchers have explored resveratrol as a preventive in diabetic kidney damage. Promising work has come from Indian pharmacologists, who’ve shown that they could significantly attenuate kidney damage in rats with experimentally induced diabetes—even 4 weeks after the diabetes was induced.60

In the researchers’ own words, “*The present study reinforces the important role of oxidative stress in diabetic kidney disease and points towards the possible antioxidative mechanism being responsible for the renoprotective action of resveratrol.*”

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**LIPOIC ACID**

Like resveratrol, *lipoic acid* is a powerful antioxidant with few known side effects.76 Lipoic acid has been successfully employed in the laboratory to block the oxidative damage caused by ischemia/reperfusion injury, thereby opening the door to another effective treatment for this common cause of acute kidney failure.77 For example, in 2008 researchers showed that they could reverse all adverse effects on renal function and lab abnormalities produced following experimental ischemia/reperfusion injury in animals.78

Lipoic acid has been comprehensively studied worldwide for its power to prevent or mitigate drug-induced kidney damage. We know that lipoic acid is an effective kidney-protective agent against damage inflicted by *Adriamycin*®,79,80 the immunosuppressive drug *cyclosporine A*,76,81,82 and even against acute toxic doses of the pain reliever *acetaminophen*.83 In studies of protection against cyclosporine toxicity, lipoic acid also helped to normalize *blood lipid abnormalities*.82

Nephrologists at Georgetown University are examining lipoic acid in the context of diabetic kidney disease. Their results show it can improve renal function in diabetics by lowering sugar levels.84

They have also recently demonstrated that lipoic acid lowers protein loss in urine and improves kidney structure and function in diabetic laboratory animals by reducing oxidative stress.84

In yet another compelling study, Korean researchers recently showed that they could improve kidney patients’ responses to the vasodilator (blood vessel relaxer) nitric oxide (NO) by supplementing them with lipoic acid.85 Loss of endothelial responsiveness to NO is a cause of vascular disease in diabetics, and a chemical called asymmetric dimethylarginine (ADMA) is a sensitive marker and predictor of cardiovascular outcome in patients with end-stage renal disease. Fifty patients on hemodialysis were treated with lipoic acid 600 mg per day for 12 weeks. Levels of the marker ADMA remained unchanged in the control group, but fell significantly in the lipoic acid group, suggesting that lipoic acid may reduce the risk of cardiovascular complications in this group of patients.

**OVERCOMING CKD-INDUCED FATIGUE**

*L-carnitine*, an amino acid-derived nutrient crucial to cellular energy management, can play a vital role in kidney disease prevention and management.86,87 Carnitine deficiency is itself a known causative factor in the development of kidney disease. Conversely, patients with kidney disease frequently develop carnitine deficiency, especially those on dialysis. Carnitine therapy is known to lead to improvements in many kidney-disease-associated complications including cardiovascular disease, *anemia*, *decreased exercise tolerance*, *weakness*, and *fatigue*.87

As noted earlier, CKD sufferers are at very high risk for developing cardiovascular complications, including heart attacks and heart failure. This is thought to be in part related to massive oxidative stress induced by kidney disease, and partly to *inadequate* energy management in cardiac tissues induced by carnitine deficiency.88 The frequent result of these interrelated factors is a massive deterioration in energy, exercise tolerance, quality of life—and perhaps even longevity.89
As early as 1998 scientists in Kentucky discovered that supplementation with L-carnitine could improve patient-reported general health, vitality, and physical function in people on dialysis. In 2001, research by clinicians at Los Angeles Medical Center showed that L-carnitine, given intravenously to dialysis patients, could reduce fatigue and preserve exercise capacity. A literature review by nephrologists at Vanderbilt University in 2003 indicated that L-carnitine supplementation should be used to improve red blood cell count in dialysis patients whose anemia doesn’t respond to therapy with the hormone erythropoietin. Finally, more data from Italy demonstrate that L-carnitine supplements can help suppress levels of the inflammatory marker C-reactive protein, potentially reducing cardiovascular risk in dialysis patients.

UNDERSTANDING KIDNEY DISEASE

The kidney ranks among the most complex and delicately evolved of all the major organs, making it particularly vulnerable to damage and dysfunction. As the body’s primary filtration system, it must “process” roughly 200 quarts of blood per day, rendering about 2 quarts of waste products and water.

The fundamental structural unit of the kidney is the nephron. These high-pressure filtering mechanisms govern the removal of waste products and toxins, control blood pressure and volume, and regulate levels of electrolytes and metabolites in the blood. A healthy kidney contains approximately 800,000 to 1 million nephrons.

Housed within each nephron is a front-line filtration element called the glomerulus, a miniscule capillary coil. (The two together resemble an incandescent light bulb containing a convoluted filament.) The endothelial cells of the glomerular capillaries act as the direct physical exchange between the kidney and the bloodstream. Waste products and water are combined to form urine, while blood cells and protein remain in the circulatory system.

The kidney’s tight control of water and mineral flow, and its role in maintaining healthy blood pressure and mineral balance, rely on the optimal functioning of nephrons and glomeruli. For this reason, one of the primary markers of kidney function is the glomerular filtration rate (GFR), a measure of the volume of fluid the kidney is able to process at any given time.

The glomerular filtration rate; plasma concentrations of the waste substances creatinine, urea, and nitrogen (blood urea nitrogen or BUN); and levels of protein in the blood and urine are the most commonly used measures to determine the presence of CKD. Rapidly rising creatinine usually signals imminent kidney failure. There should be no protein in the urine if your kidneys are functioning optimally.

It should be noted that BUN and creatinine may not increase above the normal range until 60% of total kidney function is lost. This is why certain aging individuals should ask their doctors to test for cystatin-C in the blood. Cystatin-C is a protein produced by virtually all cells and tissues in the body. Because it is formed freely and at a near-constant rate—as opposed to albumin, which may fluctuate with dietary protein intake—plasma cystatin-C serves as a more accurate biomarker of renal function.

CKD may be categorized in one of 5 stages. Stage 1, the mildest, is defined only by the persistent presence of protein in urine (GFR may be normal); in each successively higher stage, GFR declines, until Stage 5 is reached, defining end-stage renal disease (ESRD), or kidney failure. ESRD is irreversible and results in death without dialysis or kidney transplant.