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## Re: Effect of Silymarin on Streptozotocin-Nicotinamide-induced Type 2 Diabetic Nephropathy in Rats

Dear Editor,

The recently published article by Sheela and colleagues in the *Iranian Journal of Kidney Diseases*, entitled "Effect of silymarin on streptozotocin-nicotinamide-induced type 2 diabetic nephropathy in rats," had some interesting points that need to be explained more. In an experimental investigation, they found silymarin-treated groups showed significantly lower levels of blood glucose, glycosylated hemoglobin, urine volume, serum creatinine, serum uric acid, and urine albumin, when compared to the diabetic control group. In histopathological examination, they found a protective effect of silymarin, too. The authors concluded that silymarin had protective effects for kidneys affected by type 2 diabetes mellitus. They suggested that if the safety and efficacy of this herb is confirmed in human studies, silymarin would be a good medication to prevent nephropathy-induced premature death in diabetic patients.<sup>1</sup>

The first question is what the clinical significance of this experimental study is. To answer, I refer to our recently published study on silymarin in rats. We aimed to study the protective properties of silymarin and deferoxamine against iron dextran-induced renal iron deposition in male rats. We studied rats, which were allocated to 6 groups and received iron dextran (200 mg/kg) for a period of 4 weeks every other day, but at the beginning of week 3, they also were subjected to a 2-week (every other day) treatment with vehicle (group 2, positive control), silymarin (200 mg/kg; group 3), deferoxamine (50 mg/kg; group 4), silymarin (400 mg/kg; group 5), and a combination of silymarin and deferoxamine (200 and 50 mg/kg, respectively; group 6). The results of this study showed that silymarin and deferoxamine treatments reduced the intensity of the kidney

iron deposition, but only in the silymarin group, a significant reduction in kidney iron deposition was observed. We concluded that silymarin was a nephroprotective agent against injurious insult of iron deposition in the kidneys of animal models.<sup>2</sup>

While, nephropathy is one of the most important complications of diabetes mellitus,<sup>3-6</sup> I would like to mention a few points about the study conducted by Sheela and colleagues. In type 2 diabetes, metformin has been widely used for the treatment blood glucose elevation.<sup>7-10</sup> Recently, attention has been made toward the possible kidney protective properties of metformin.<sup>7</sup> Morales and coworkers observed that gentamicin-induced renal tubular injury was attenuated by metformin.<sup>9</sup> To find the potential efficiency of metformin to renal protection against gentamicin-induced acute renal injury and also to examine whether postpone treatment with metformin in acute kidney injury, exerts similar benefits on gentamicin-renal toxicity in rats, we conducted a study on Wistar rats.<sup>12</sup> We found that metformin was able to prevent and attenuate gentamicin-induced acute kidney injury. Hence, it might be beneficial in patients under treatment with this drug.<sup>11</sup> More recently, to test the efficacy of co-administration of garlic extract and metformin for prevention of gentamicin-induced renal toxicity in Wistar rats, we conducted another study on 70 male Wistar rats,<sup>12</sup> while we also showed the renoprotective efficiency of garlic juice alone in an another study, too.<sup>13</sup> The result of this study demonstrates that metformin and garlic juice or their combination has both curative and protective effects against gentamicin nephrotoxicity. Likewise to these studies, silymarin extract could safely be used together with metformin to increase the antioxidant potency and better renoprotection beyond, the control of diabetes, while most of

type 2 diabetic patients are under the treatment of metformin too. Similar results were also found in the study of Bruckbauer and colleagues to evaluate the synergistic effects of metformin, resveratrol and hydroxymethylbutyrate on insulin sensitivity.<sup>14</sup> They suggested that resveratrol-hydroxymethylbutyrate combined with metformin might act synergistically on adenosine monophosphate-activated protein kinase-dependent pathways, leading to increased insulin sensitivity, which might reduce the therapeutic doses of metformin necessary in the treatment of diabetes. Thus, according to the renoprotective efficacy of silymarin in our study and hypoglycemic effect of this medicinal plants in the study conducted by Sheela and colleagues, it is possible that the combination of metformin and silymarin may have additive renoprotective efficacy beyond better controlling the diabetes.<sup>13-16</sup> In this regard, to better understand the renoprotective properties of silymarin, especially in combination with metformin, more experimental rat models and clinical studies are suggested.

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