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# Effect of the Herbal Combination Canephron N on Diabetic Nephropathy in Patients with Diabetes Mellitus: Results of a Comparative Cohort Study

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## Abstract

***Objectives:*** Diabetic nephropathy (DN) is a serious and common complication of diabetes mellitus leading to end-stage renal disease in up to 30% of diabetic patients. The first manifestation of DN in humans is microalbuminuria, which arises from the increased passage of albumin through the glomerular filtration barrier. Reactive oxygen species, inflammatory cytokines, and growth factors are key players in the context of damage to the glomerular filtration barrier.
***Interventions:*** In this study the herbal combination Canephron® N, containing lovage root, rosemary leaves, and centaury herb, was administered to patients with DN to study the effects on microalbuminuria and overall oxidant/antioxidant status. An open study involving 59 patients with DN was performed to compare the effects of Canephron N administered concomitantly with standard antidiabetic therapy and an angiotensin-converting enzyme (ACE) inhibitor, with the standard therapy and ACE inhibitor treatment alone.
***Results:*** After 6 months of therapy the level of microalbuminuria decreased significantly in the study group compared with the control group. Canephron N had a positive effect on the antioxidant defense status and lipid peroxidation levels. In addition, liver aminotransferase levels did not change.
***Conclusions:*** With respect to the excellent tolerability, the study results encourage use of the herbal combination as an add-on therapy in patients with DN.

## Introduction

There is a high risk of chronic complications arising from microvascular and macrovascular changes in diabetic patients.[1] Incidence of these complications increases with the duration of disease. Long-term vascular complications related to micro- and macroangiopathies are diabetic nephropathy (DN) and cardiovascular disease, respectively, with the latter being one of the major complications and causes of death in patients with type 2 diabetes mellitus (T2DM).[2]

Diabetic nephropathy is a serious and common complication of diabetes mellitus that leads to end-stage renal disease in up to 30% of diabetic individuals.[3] The first manifestation of DN in humans is microalbuminuria, which arises from increased passage of albumin, an important plasma protein, through the glomerular filtration barrier. Even at the early stages of renal structure lesions albumin can be found in urine, with its concentration being directly proportional to the severity of renal filter dysfunction.[4–6] The importance of microalbuminuria as an independent predictor of progressive renal disease and cardiovascular mortality was demonstrated in several prospective and epidemiologic studies, particularly in patients with diabetes.[7–9] The study by Adler et al.[10] demonstrated a 2%–3% risk of progression per year from normo- to microalbuminuria, from micro- to macroalbuminuria (see Table 1 for classification details), and from macroalbuminuria to chronic renal failure. To prevent or reverse the course of DN, risk factors involved in the etiology of the disease must be defined.

Understanding the pathophysiologic mechanisms through which microalbuminuria occurs holds the key to designing therapies to arrest its development and prevent the later manifestations. Reactive oxygen species, inflammatory cytokines, and growth factors are key players responsible for the damage to the glomerular filtration barrier.[11] Intracellular protection mechanisms from reactive oxygen species include antioxidant enzymes (superoxide dismutase [SOD], catalase, and glutathione peroxidase) and low-molecular-weight antioxidants, including thiols (SH groups). The SH

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Table 1. Classification of Albumin Clearance

| *Type* | *Albumin clearance (mg/d)** |
|---|---|
| Normoalbuminuria | 0 to ≤20–30 |
| Microalbuminuria | 20–30 to ≤300 |
| Macroalbuminuria | ≥300 |

*Adler et al., 2003.[10]

groups are particularly well known to protect membrane lipid ingredients from lipid peroxidation.[12,13] The authors have shown (unpublished data) that the levels of SH groups are significantly decreased in patients with T2DM in various stages of chronic renal failure when compared with healthy individuals ($68.5 \pm 1.25$ μmol/L versus 120–155 μmol/L). In addition, the lipid peroxidation end-product malondialdehyde was elevated in patients with T2DM compared with healthy individuals ($5.47 \pm 0.20$ μmol/L versus $2.52 \pm 0.09$ μmol/L). This is supported by data from a recent study that found elevated markers of oxidative and glycoxidative protein damage in elderly prediabetic and diabetic persons.[14]

The treatment strategy for diabetic patients with microalbuminuria should be multipronged: In addition to standard antidiabetic medication, medicines that lower blood pressure and medicines that protect the kidneys are needed. These medicines may reverse kidney damage and should be started as soon as any degree of microalbuminuria is observed. Many herbal drugs are known to improve hypoglycemia in diabetes. Most data derive from chemically induced diabetes in the rat model, with studies demonstrating hypoglycemic activity as well as improvements in lipid metabolism, antioxidant status, and capillary function.[15] Furthermore, some human studies have shown benefits in diabetic patients with the use of herbal drugs, including milk thistle, fenugreek, cinnamon, bitter melon, ginseng, and garlic.[16] One aspect of the increasing interest in herbal drugs is their overall safety, even with long-term use.[17–19] Patients with diabetes increasingly seek advice about alternative and complementary medicines due to inadequacies in current (standard) treatment regimens.[20] However, until now the evidence for clinical efficacy has remained limited.[21,22]

The herbal combination Canephron® N (Bionorica, Neumarkt, Germany) is an approved medicinal product that contains a fixed combination of centaury herb (*Centaurium* sp.), lovage root (*Levisticum officinale* Koch), and rosemary leaves (*Rosmarinus officinalis* L.). It has been available on the European market for more than 40 years. The drug exerts diuretic,[23,24] spasmolytic,[25,26] anti-inflammatory,[27–29] antimicrobial,[30–33] and nephroprotective effects.[34] Some clinical studies revealed a therapeutic benefit in patients with urinary tract infections, as well as in patients with nephrolithiasis or urolithiasis.[35,36] In Ukraine, the product is registered for sole or adjuvant therapy of acute and chronic infections of the bladder (cystitis) and kidney (pyelonephritis), in cases of chronic noninflammatory diseases of the kidneys (glomerulonephritis, interstitial nephritis), and for the prevention of urinary stones.

Because of the reported anti-inflammatory, vasodilatory, and spasmolytic properties, as well as an ability to decrease the permeability of renal glomerular filtration capillaries, Canephron N has been used in the authors' department as a supportive add-on therapy in diabetes. The supportive treatment has already demonstrated some positive effects, such as an improvement in several clinical-chemical markers. Therefore, an open study was designed to systematically investigate, for the first time, the efficacy and safety of treatment with Canephron N, in combination with antidiabetic standard therapy (pharmacotherapy and diet) and an angiotensin-converting-enzyme (ACE) inhibitor, in patients with T2DM who have microalbuminuria, measured with distinct laboratory parameters. The effects were compared with those in a cohort of patients who received antidiabetic standard therapy and an ACE inhibitor only.

## Materials and Methods

The study was conducted as an open-label, prospective, randomized, parallel-group, single-site phase IV cohort study at the Nephrologic Department of Ternopil State Medical University, Ukraine, in patients with T2DM and microalbuminuria.

The efficacy of Canephron N as add-on therapy, together with standard antidiabetic diet and pharmacotherapy in combination with the ACE inhibitor enalapril, was compared with the effects of standard antidiabetic therapy plus enalapril alone. One coated tablet of the study medication Canephron N contains 18 mg of powdered *Herba centaurii* (common centaury herb), 18 mg *Levistici radix* (lovage root), and 18 mg *Folia rosmarini* (rosemary leaves). The daily dose was two tablets of the herbal combination three times daily and 20 mg enalapril two times daily. The standard antidiabetic pharmacotherapy consisted of metformin, and in some cases also gliclazide, glimepiride, or glibenclamide; these drugs were prescribed at the dose required to achieve glycemic control in each individual with reference to the summary of product characteristics (Table 2). The study period was 6 months.

Inclusion criteria were (1) T2DM diagnosed at least 6 months before examination; (2) established microalbuminuria (>30 mg a day or ≥3 mg/dL in spontaneous urine sample, or ratio of urine albumin:urine creatinine < 2.26 mg/mmol) for at least 3 months before entering the study; (3) level of glycosylated hemoglobin < 9.5%; and (4) well-motivated patients willing and able to accept and fulfill the rules of participation in the study. T2DM was diagnosed in accordance with criteria recommended by the International Diabetes Federation.[37]

Exclusion criteria were (1) use of the study medication Canephron N or any other herbal medicinal product during the 3 months before study enrollment; (2) T2DM decompensation, ketoacidosis, or hyperosmolar coma requiring hospitalization during the 6 months before inclusion in the

Table 2. Dosages of Standard Antidiabetic Medication in Patients of Both Groups

| *Medication* | *Daily dosage (mg)* |
|---|---|
| Gliclazide | 160–240 |
| Metformin | 1500–2000 |
| Glimepiride | 2–4 |
| Glibenclamide | 5–10 |

Dosages were defined individually according to the patient's glycemia level.

Table 3. Demographic and Anamnestic Data in Both Study Cohorts at Study Entry

| *Variable* | *Study group (Canephron + enalapril)* (n = *36*) | *Control group (enalapril only)* (n = *23*) | p-*Value*[a] |
|---|---|---|---|
| Demographic and anamnestic data | | | |
| Women/men (*n/n*) | 25/11 | 13/10 | > 0.05 |
| Age (y) | 58.27 ± 1.29 | 61.81 ± 1.85 | > 0.05 |
| Disease duration (y) | 8.14 ± 0.46 | 8.56 ± 1.24 | > 0.05 |
| Systolic blood pressure (mm Hg) | 138.6 ± 1.93 | 143.48 ± 3.52 | > 0.05 |
| Diastolic blood pressure (mm Hg) | 85.00 ± 1.50 | 91.09 ± 3.11 | > 0.05 |
| Antidiabetic medication (*n*) | | | |
| Gliclazide | 4 | 3 | – |
| Metformin | 36 | 23 | – |
| Glimepiride | 8 | 5 | – |
| Glibenclamide | 2 | 1 | – |
| Antidiabetic diet | 36 | 23 | – |
| Concomitant diseases (*n*) | | | |
| Chronic gastroduodenitis | 2 | 1 | – |
| Chronic bronchitis | 0 | 1 | – |
| Stable angina functional class 2/NYHA II | 3 | 2 | – |
| Chronic cholecystitis | 3 | 1 | – |
| Osteoarthritis | 4 | 2 | – |

Values expressed with a plus/minus sign are the mean ± standard deviation.
[a]*p*-Value calculated for the difference between both study groups.
NYHA, New York Heart Association.

study; (3) acute or chronic hepatitis, symptoms of liver disease, alanine aminotransferase level (ALT) exceeding three times the upper normal limit; (4) anamnestic tumors; (5) severe renal dysfunction (glomerular filtration rate <30 mL/min per 1.73 $m^2$); (6) congestive heart failure (New York Heart Association class III or IV); (7) pregnancy; and (8) alcohol and drug abuse.

The local university ethics committee approved the study. All patients gave signed informed consent for participation in the study. Patients were randomly assigned to the two study groups during hospitalization. Each patient him- or herself chose an envelope indicating the study group.

The main evaluation parameters for the efficacy of concomitant treatment with Canephron N were the dynamics of microalbuminuria, the status of the oxidant/antioxidant system, and the lipid levels. As a secondary parameter, renal function, assessed by the glomerular filtration rate, was analyzed.

Albumin was measured as concentration in morning urine and as excretion per day; further, the ratio of urine albumin:urine creatinine was calculated. Microalbuminuria level was determined by enzyme-linked immunoassay using a D-10 device (Bio-Rad Laboratories, Hercules, CA, USA). Kidney function was assessed by glomerular filtration rate, calculated using the Cockcroft-Gault formula. Blood protein composition and creatinine and urea concentrations were assessed by the kinetic turbidimetric method; C-reactive protein level was measured by enzyme-linked immunoassay. Lipid peroxidation status was evaluated by measuring the concentration of malondialdehyde in blood serum using the method of Placer and colleagues.[38] All parameters for the evaluation of antioxidant protection status were measured in plasma. The concentration of reduced glutathione was determined by using the Ellman method.[39] The SOD activity level was measured as the degree of inhibition of nitroblue tetrazolium reduction within 10 minutes in the presence of NADH and phenazine

Table 4. Microalbuminuria at Study Entry and After 6 Months of Treatment with Canephron N plus Standard Therapy (Study Group) and Standard Therapy Only (Control Group)

| *Parameter* | *Study group* (n = *36*) | | *Control group* (n = *23*) | | p-*Value* |
|---|---|---|---|---|---|
| | *Baseline* | *After treatment* | *Baseline* | *After treatment* | |
| Microalbuminuria (mg/dL) | 5.86 ± 0.78 | 1.8 ± 0.13<br>$p_1 < 0.01$ | 8.08 ± 1.22 | 4.94 ± 0.62<br>$p_2 < 0.05$ | < 0.01 |
| Microalbuminuria (mg/24 h) | 138.17 ± 19.23 | 34.25 ± 3.45<br>$p_1 < 0.01$ | 180.71 ± 24.58 | 91.37 ± 11.69<br>$p_2 < 0.01$ | < 0.01 |
| Urine albumin:creatinine (mg/mmol) | 7.39 ± 0.80 | 3.96 ± 0.36<br>$p_1 < 0.01$ | 10.54 ± 1.54 | 7.38 ± 0.79<br>$p_2 > 0.05$ | < 0.01 |

*p*, significance calculated for difference of post-treatment results between study group and control group; $p_1$, significance calculated for difference of results after treatment compared with baseline in study group; $p_2$, significance calculated for difference of results after treatment compared with baseline in control group.

methosulfate.[40] Catalase activity was determined by using the method by Koroluy and colleagues.[41] Triglycerides and total cholesterol were measured by enzymatic methods, and high-density lipoprotein (HDL) cholesterol by the selective sedimentation method; low-density lipoprotein levels were also calculated.

For the evaluation of safety, liver aminotransferase levels (ALT and aspartate aminotransferase) were monitored. The patients were also asked to report any adverse reactions during therapy.

Study data were analyzed by using Excel (Microsoft, Redmond, Washington). Data are shown as mean ± standard deviation. The independent *t*-test for paired values was used to reveal significant differences between both groups, as well as to detect significant differences in the same group before and after treatment. *p*-values less than 0.05 were considered to represent statistically significant differences.

## Results

The study was conducted between March 2010 and March 2011. A total of 59 patients were enrolled and divided into two groups. The study group consisted of 36 patients (25 women and 11 men) who received Canephron N at a daily dose of two tablet three times daily in addition to standard therapy (antidiabetic diet and pharmacotherapy plus enalapril). The control group, consisting of 23 patients (13 women and 10 men), received standard therapy only. Both groups were observed over a treatment period of 6 months. The groups did not significantly differ regarding age, sex, time since diagnosis of diabetes, level of microalbuminuria, vital parameters, lipid levels, glycemia level in fasted state, and glycated hemoglobin level. The urine albumin-creatinine index confirmed established microalbuminuria, and renal function revealed stage I–II chronic renal disease (Tables 3 and 4).

### *Microalbuminuria*

After 6 months of therapy microalbuminuria significantly decreased (evaluated by albumin excretion within 24 hours) in the concomitant Canephron N treatment group, with a reduction to normoalbuminuria levels in 18 of those patients. The decrease (pre-/post-treatment comparison) was 75.2% in the study group and 49.4% in the control group. Furthermore, the albumin:creatinine ratio decreased significantly compared with the baseline level: by 46.4% in the study group and by 30% in the control group. The observed effect on each microalbuminuria parameter was significantly greater ($p < 0.01$) in the study group compared with the control group (Table 4).

### *Oxidant/antioxidant status*

The combination therapy led to a significant decrease in malondialdehyde concentration of 38.6%. The antioxidant defense parameters, catalase activity, SOD activity, and SH group concentration increased significantly by 56.1%, 26.7%, and 33.3%, respectively, compared with baseline values (all $p < 0.01$) in the study group. the lipid peroxidation level and antioxidant status did not significantly differ in the control group. A comparison of the parameters between the two groups revealed significant changes ($p < 0.01$) in favor of the combination group (Fig. 1).

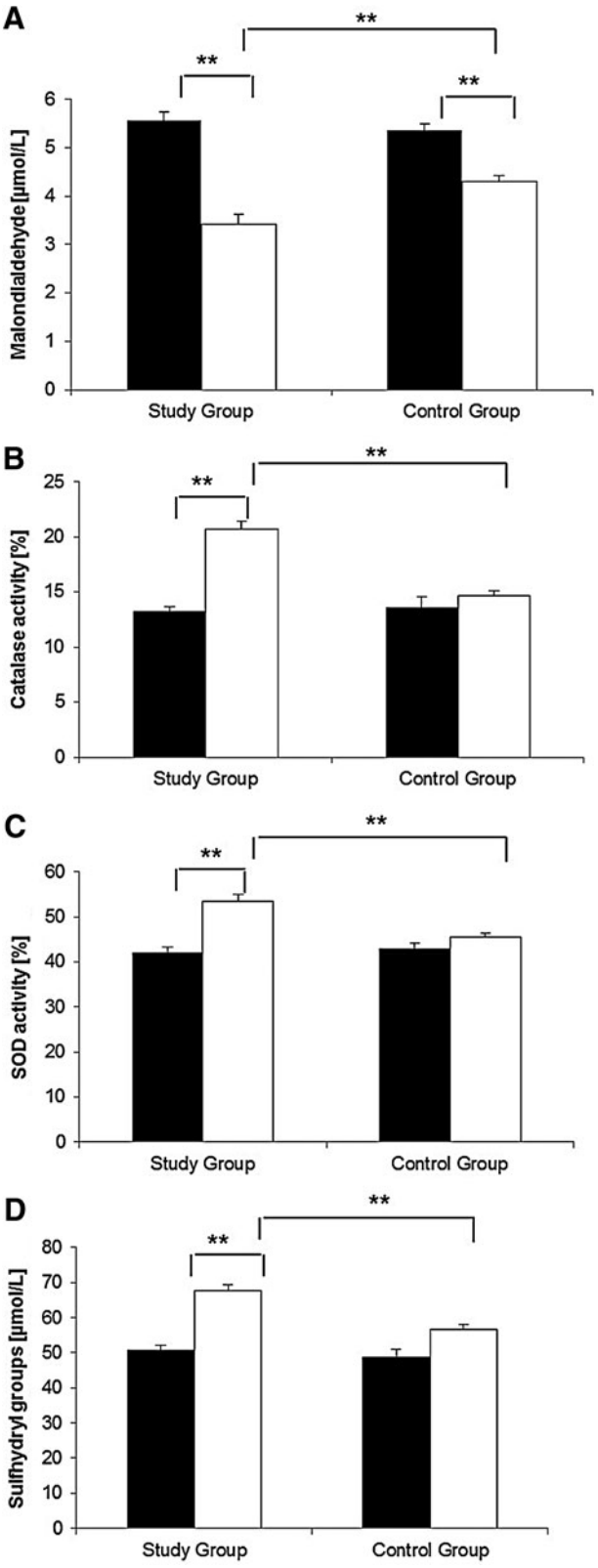


**FIG. 1.** Level of lipid peroxidation **(A)** and parameters of antioxidant system **(B–D)** at study entry (black) and after 6 months of therapy (white). The study group ($n = 36$) was treated with Canephron® N in addition to standard antidiabetic therapy and enalapril. The patients of the control group ($n = 23$) received standard antidiabetic therapy and enalapril only (**$p < 0.01$). SOD, superoxide dismutase.

Table 5. Lipid Levels at Study Entry and After 6 Months of Treatment with Canephron N plus Standard Therapy (Study Group) and Standard Therapy Only (Control Group)

| | *Study group* (n = *36*) | | *Control group* (n = *23*) | | |
|---|---|---|---|---|---|
| *Variable* | *Baseline* | *After treatment* | *Baseline* | *After treatment* | p-*Value* |
| Total cholesterol (mmol/L) | 6.67 ± 0.17 | 5.91 ± 0.17<br>$p_1 < 0.01$ | 6.24 ± 0.29 | 6.43 ± 0.24<br>$p_2 > 0.05$ | > 0.05 |
| HDL cholesterol (mmol/L) | 1.23 ± 0.04 | 1.54 ± 0.06<br>$p_1 < 0.01$ | 1.24 ± 0.05 | 1.32 ± 0.07<br>$p_2 > 0.05$ | < 0.05 |
| LDL cholesterol (mmol/L) | 4.38 ± 0.16 | 3.92 ± 0.18<br>$p_1 > 0.05$ | 3.99 ± 0.25 | 3.98 ± 0.21<br>$p_2 > 0.05$ | > 0.05 |
| Triglycerides (mmol/L) | 3.01 ± 0.15 | 1.73 ± 0.08<br>$p_1 < 0.01$ | 3.08 ± 0.25 | 2.44 ± 0.21<br>$p_2 < 0.05$ | < 0.01 |

$p$, significance calculated for difference of post-treatment results between study group and control group; $p_1$, significance calculated for difference of results after treatment compared with baseline in study group; $p_2$, significance calculated for difference of results after treatment compared with baseline in control group.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

### *Lipid level*

Lipid measures in the study group changed significantly ($p < 0.01$); total cholesterol decreased by 11.4%, low-density lipoprotein cholesterol (nonsignificantly) by 10.5%, and triglycerides by 42.5%, whereas HDL cholesterol increased by 25.2%. In the control group, the only significant decrease observed during the study period was in triglyceride levels. In comparing the study and control groups, the observed changes were significantly in favor of the combination group for the increase in HDL cholesterol ($p < 0.05$) and decrease in triglycerides ($p < 0.01$) (Table 5).

### *Renal function*

To assess the renal function in both groups, the glomerular filtration rate was analyzed. Glomerular filtration before and after the treatment period did not significantly differ. No significant difference was seen between the two study groups (Fig. 2).

### *Safety*

No patient was lost to follow-up; all patients finished the study. Adherence was rated as excellent. The reported adverse events were dry cough in three cases in the study group and two cases in the control group. These adverse events were evaluated as not being related to the study medication(s). The analysis of clinical chemistry revealed no significant changes in the levels of the liver aminotransferases, alanine aminotransferase (study group, 21.38 ± 1.3 to 17.8 ± 1.16 U/L, control group, 21.27 ± 1.34 to 18.03 ± 1.38 U/L) and aspartate aminotransferase (study group, 22.96 ± 0.78 to 20.64 ± 0.75 U/L, control group, 23.98 ± 0.83 to 20.98 ± 1.01 U/L), in either group.

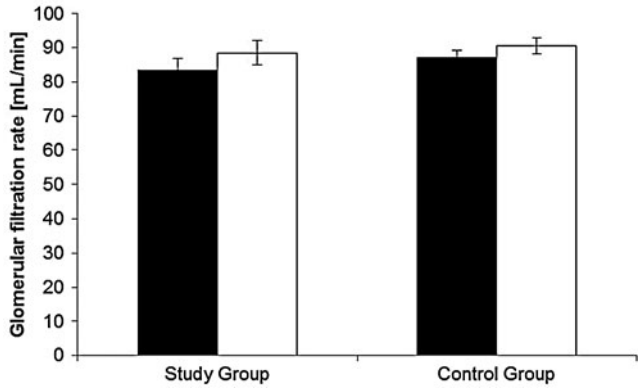


**FIG. 2.** Glomerular filtration rate at study entry (black) and after 6 months of therapy (white) with Canephron N plus standard therapy (study group) and standard therapy only (control group).

## Discussion

Treatment of DN is complex, requiring medicines that lower blood pressure and simultaneously protect the kidneys. These medicines may reverse kidney damage and are started as soon as microalbuminuria is diagnosed. Renal damage is still reversible at the microalbuminuria stage, so an early diagnosis and consequent treatment of all comorbid conditions are crucial for the long-term prognosis of patients, and may prevent the burden of future dialysis.[11]

Canephron N treatment, in addition to standard antidiabetic and antihypertensive medicines, significantly reduced the level of microalbuminuria. In a large proportion of the study group, the renal albumin content even decreased to normoalbuminuria levels. This was not observed for the patients receiving standard therapy alone. Patients in both groups were treated with an ACE inhibitor, so the observed reduction in urine albumin in the Canephron N group cannot be explained by a decrease in blood pressure. Previous studies have already shown that Canephron N treatment decreases the permeability of renal glomerular filtration capillaries.[34] There are many theories regarding the initiating factors for the pathogenesis of glomerular dysfunction. Most include hyperglycemia, hyperlipidemia, and an increase in reactive oxygen species.[11] Hyperlipidemia is common in diabetes. Raised plasma triglycerides and low levels of HDL have been associated with the development of DN, as well as with cardiovascular diabetic complications.[42,43] To obtain more detailed insight into the mechanism leading to the decrease in urinary albumin content observed after Canephron N treatment, we further investigated the lipid levels and antioxidant/

oxidant status of the patients. The study results showed significantly increased HDL and significantly lowered triglyceride levels in the study group patients. However, a significant benefit in the control group was observed only for the level of triglycerides. These results indicate that Canephron N positively influences lipid levels.

Several studies in patients with T2DM have revealed a decrease in the antioxidant defense system and an increase in oxidative damage markers.[44] Free radicals have extremely short half-lives, so in most cases oxidative stress is measured by specific end-products of the process. In this study malondialdehyde, an end-product of lipid peroxidation, was determined. In the study group the malondialdehyde levels were significantly reduced. In parallel, the antioxidant defense mechanisms, measured as SOD and catalase activities, were significantly improved in the study group. This is of particular importance because hyperglycemia is known to increase oxidative stress through an overproduction of superoxide and other reactive oxygen species.[11] This beneficial effect of Canephron N on antioxidant status was further confirmed by the significant increase in thiol groups observed in the study group. Thiols are considered to be major antioxidants in plasma.[45] Because of the pivotal role that oxidative stress plays in the progression of chronic renal failure, focus on antioxidant therapy is increasing.[46]

Published studies examining other herbal or natural products have also shown beneficial effects in patients with diabetes, particularly improvements in glucose and lipid metabolism, but also antioxidant status and capillary function.[47] It is unknown whether Canephron N acts directly at the glomerular filtration barrier or whether the observed improvement in microalbuminuria is due to a decrease in the endogenous reactive oxygen species that are involved in damage of the glomerular epithelium. Investigating the underlying mechanism in more detail was beyond the scope of this study but will be of great interest in the future.

In the literature there is a single reported case of hepatotoxicity probably related to Canephron N treatment.[48] In the current study, after 6 months of therapy, neither changes in liver aminotransferases nor any other adverse reactions associated with Canephron N occurred. This finding is supported by a recent review by Naber[36] that included 17 clinical studies with more than 3000 adults and children treated with Canephron N for up to 6 months: The only adverse event reported was one episode of skin rash in a child with a history of severe allergic reactions. Therefore, the case of hepatotoxicity remains as a single case without any confirmation from other findings or data.

In conclusion, the data from this study support the inclusion of Canephron N into a treatment regimen for patients with diabetic renal lesions at the microalbuminuria stage. On the basis of the promising results of this study, a prolonged course of supportive treatment with Canephron N in patients with T2DM could be recommended. Canephron N was safe during the 6 months of use; no drug-related adverse reactions were reported, and there were no effects on liver aminotransferases. This is in accordance with the already known safety profile of this herbal combination as seen in other clinical studies. To confirm the study results, further studies with more patients would be of interest.

## Acknowledgments

Bionorica SE provided the study medication.

## Disclosure Statement

The study was conducted as an investigator-initiated study by the authors. No competing financial interests exist.

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