Clinical and Experimental Health Sciences

Can *Juniperus communis* L. oil improve nephropathy in diabetic rats

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ABSTRACT

Objective: *Juniperus communis* L. (*J. communis*) is a shrub belonging to family Cupressaceae L. mainly growth in Eurasia. The antioxidant and antidiabetic activity of aqueous extract of *J. communis* L. berries indicated benefits as a potent antidiabetic in streptozotocin induced diabetic albino rats. This study was carried out to determine whether *J. communis* L. oil supplement will effectively manage renal dysfunction in diabetic rats.

Methods: Twenty eight rats were divided into 4 equal groups as follows; control group, diabetic group (45 mg/kg, i.p. streptozotocin) , *J. communis* L. oil (200 mg/kg) treated group, and diabetic+*J. communis* L. oil (200 mg/kg) treated group. At the end of the experimental period, all rats were sacrificed and renal function parameters such as kidney antioxidant and lipid peroxidation markers and serum glucose, HbA1c, creatinine, serum urea, blood urea nitrogen (BUN), and serum total protein levels were measured in all groups.

Results: HbA1c, serum glucose, urea, creatinine, BUN and, kidney lipid peroxidation levels increased ($p<0.05$), but serum total protein and antioxidant levels decreased in diabetic group comparing with control group ($p<0.05$). Furthermore, HbA1c, serum glucose, urea, creatinine and BUN and, kidney lipid peroxidation levels decreased and also, serum total protein and antioxidant levels increased in diabetic group treated with *J. communis* L. oil comparing with diabetic group ($p<0.05$).

Conclusion: This study has provided that *J. communis* L. oil provide a protective effect on the kidney as evidenced by an improvement of the renal function tests as well as reduction in oxidative stress parameters in experimental diabetic nephropathy model.

Keywords: *Juniperus communis* L., diabetes, nephropathy, antioxidant, lipid peroxidation, oxidative stress

1. INTRODUCTION

Diabetes, characterized by hyperglycemia and metabolic disturbance on lipids, carbohydrates, and proteins, affect the life quality of patients by bringing huge pressure to society and public health (1). Nearly 2.2% of total death in the world is caused by diabetes (2). Type II diabetes, considered as the common form of diabetes, will affect the health of 8 billion people in the world till 2025 (3). Persistent hyperglycemia in diabetes mellitus (DM) leads to the development of secondary complications including neuropathy, nephropathy, and retinopathy (2). Diabetic nephropathy is the major cause of end-stage renal disease with high mortality and morbidity (4). A major clinical manifestation of diabetic nephropathy is that microalbuminuria follows macroalbuminuria and further leads to renal dysfunction which is the reduced capacity of the kidney to excrete metabolic products which accumulate in the body system and can be detected via renal function test (5). Therefore, due to numerous degenerative effects of untreated DM on human system, numerous researches have been carried out and still ongoing for the management and treatment of DM. Management of DM usually involves adjustment of the diet of the individual, exercise at regular interval, health education, measurement of blood glucose level on a regular level, and, in case of insulin dependent DM, supplementary therapy with insulin (6,7).

Juniperus communis L. is a shrub belonging to family Cupressaceae L. mainly growth in Eurasia, North Africa and North America at an altitude of 1500–4000. Fruit is subspherical, purplish-black and seed contained 2-3 layers of thin-walled cells. The seeds and fruits of the plant contain camphene, d-α-pinene, formic acid, acetic acid, wax, gum, cyclohexinol, terpene, ascorbic acid, dihydrojunene, cadinene, juniper, and camphor (8,9). *J. communis* L. berry oil mainly contained monoterpene hydrocarbons such as α-pinene (51.4%), β-pinene (5.0%), sabinene (5.8%), and myrcene (8.3%) (10). *J. communis* L. can be used (traditionally) for renal suppression, acute

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and chronic cystitis, catarrh of the bladder, albuminuria, leucorrhoea, and amenorrhoea. *J. communis* L. fruit can be used as being antiseptic, stimulant, and styptic. It can also be used in the treatment of migraine, infantile tuberculosis, rheumatic and painful swellings, chronic Bright's disease, piles, and nephrotic dropsy of children (11). The plant was reported to have analgesic, antibacterial, hepatoprotective, antihypercholesterolemic, antiinflammatory, antioxidant, antidiabetic, antihyperlipidemic, anticataleptic, and antimicrobial activities (9).

The antioxidant and antidiabetic activity of aqueous extract of *J. communis* L. berries indicated potential benefits as a potent antidiabetic in streptozotocin (STZ) induced diabetic albino rats (12). *J. communis* L. berries was also a good scavenger for nitric oxide radicals and has a potential source of natural antioxidant. *J. communis* L. berry has also nutraceutical uses and is used in treatment of hypercholesterolemia and hyperglycemia, and also, as a nutritional supplementation, it can be prescribed as food appendage for coronary artery disease patients along with their regular medicines (9).

Therefore, since renal dysfunction has been on increase in diabetic patients without a promising remedy, this study was carried out to determine whether dietary intake of *J. communis* L. oil will protectively or effectively manage renal dysfunction via examination of renal function parameters such as kidney antioxidant and oxidative stress markers and serum creatinine, serum urea, blood urea nitrogen (BUN), and serum total protein estimation in diabetic rats.

2. METHODS

2.1. Animals

All adult male Wistar albino rats were purchased from the Animal Experimental Center of Van Yuzuncu Yil University, aged 3-4 months with weights ranging from 300 to 350 g. Ethical approval of the study was obtained from Van Yuzuncu Yil University Ethical Commission for Animal Experiments (Decision number: 2015/14, Date: 24.12.2015). All animals were housed in a comfortable environment (12 h light-dark cycle, 20–25 °C temperature, 40-60 % humidity) and fed with rodent chow and water *ad libitum*.

2.2. Reagents

All the chemicals and reagents were supplied by Sigma-Aldrich, Merck or other standard suppliers.

2.3. Preparation of J. communis L. oil

The fresh air dried *J. communis* L. berries (300-400 g) were subjected to water-distillation boiling (>100 °C) for 3 h by using a Clevenger-type apparatus. The obtained essential oil was dried over anhydrous sodium sulfate and after filtration through Whatman filter paper (No. 1) stored at 4 °C until tested.

2.4. Experimental Procedure

Type 1 DM was induced by a single intraperitoneal (i.p.) injection of 45 mg/kg STZ to overnight fasted rats. STZ solution was freshly prepared by dissolving in 0.1 M cold citrate buffer (pH 4.5). In spite of the possibility of sudden hyperglycaemic shock following STZ injection in animals, this dose was considered appropriate. Diabetes was confirmed through the determination of blood glucose levels at 72 hr using OneTouch UltraMini glucometer (LifeScan, Inc., California, USA). Rats with blood glucose levels higher than 300 mg/dL were considered diabetic and selected for further experiments. Diabetes was further verified by measuring blood glucose levels 7 days after STZ injection. Normal control rats received a single i.p. dose of physiological saline. Twenty eight rats (14 diabetic and 14 normal) were divided into 4 equal groups (n=7) as follows; Group I (Control group): Nondiabetic rats received physiological saline orally for 21 days, Group II (Diabetic group): Diabetic rats received physiological saline by oral gavage for 21 days, Group III (*J. communis* L. oil group): Nondiabetic rats received *J. communis* L. oil (200 mg/kg) dissolved in 5% Na-CMC by oral gavage for 21 days, and Group IV (Diabetic+*J. communis* L. oil group): Diabetic rats received *J. communis* L. oil (200 mg/kg) dissolved in 5% Na-CMC by oral gavage for 21 days. Ethical approval of the study was obtained from Ethical approval of the study was obtained from Van Yuzuncu Yil University Ethical Commission for Animal Experiments (Decision number: 2015/14, Date: 24.12.2015).

2.5. Preparation of Serum and Kidney Tissue

At the end of the experimental period, all rats were fasted for 12 hours before being sacrificed by intraperitoneal injection of ketamine hydrochloride (15 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). Kidney tissues were immediately excised from the surrounding tissues and were subsequently weighed. Immediately following collection, kidney tissues were washed with ice-cold phosphate-buffered saline (PBS). The samples were homogenized in phosphate buffer (25 mM, pH 7.4) to make approximately 10% w/v homogenates. The homogenates were centrifuged at 1700 rpm for 10 min, and the supernatant was collected and stored at −70°C for further biochemical analysis. The protein concentration in the supernatant was estimated by Lowry et al's method.

2.6. Serum Preparation and Biochemical Measurements in Serum

Blood samples were placed in dry test tubes and were allowed to coagulate at ambient temperature for 30 min. Serum was separated by centrifugation at 3500 rpm for 15 min. Enzymatic colorimetric kits (Bioscience, Cambridge, UK) were used to measure serum glucose, total protein, creatinine, urea, and blood urea nitrogen (BUN) levels.

2.7. Measurement of serum glycosylated hemoglobin (HbA1c) Level

Serum HbA1c levels were measured in whole blood using an automated chemistry analyzer (Roche Cobas Integra 800 Chemistry analyzer, Roche Diagnostics, Mannheim, Germany).

2.8. Measurement of lipid peroxidation and antioxidant enzyme activities in kidney

The supernatants obtained after this procedure was used for the analyses of MDA, NO, and GSH levels and SOD and catalase activities.

MDA Level: MDA reacts with thiobarbituric acid (TBA), giving a spectroscopically readable final product at 532 nm. MDA levels were expressed as nmol/mg protein using the extinction coefficient value of $1.56x10^5$ $M^{-1}.cm^{-1}$ (13).

Nitrite/Nitrate levels: Tissue nitric oxide is rapidly converted to nitrate and nitrite in aqueous solutions. Hence, for accurate assay of the total nitric oxide, both nitrate and nitrite levels must be determined. Tissue nitrate is chemically reduced to nitrite by granulated cadmium. Griess reagent reacts with total nitrite, and forms a coloured complex. The intensity of the colour is proportional to the concentration of the nitrite in the sample, which can be measured spectrophotometrically (14).

GSH level: GSH analysis was performed according to the method reported by Beutler et al (15). In this method, all proteins that do not carry the sulfhydryl in the tissue homogenates are precipitated. In the obtained clear liquid, the yellow complex formed by 5,5'-Dithiobis (2-nitrobenzoic acid) (DTNB) and sulfhydryl groups is measured colorimetrically at a wavelength of 412 nm.

SOD Activity: The principle of measurement of SOD enzyme activity, which accelerates the aquatic and molecular oxygen dismutation of endogenous and exogenous sources of toxic superoxide radicals generated during the production of oxidative pathway energy, is based on the spectrophotometric measurement of superoxide radicals which are released by xanthine oxidase in the presence of xanthine in the presence of nitroblue tetrazolium (NBT) at 560 nm according to Sun et al (16).

Catalase Activity: The activity of the enzyme catalase was analysed according to Aebi method (17), measuring the initial rate of H2O2 decomposition at 240 nm. Catalase activity was expressed as U/mg protein.

Tissue Protein Content: In the alkaline solution, a copper-protein complex is formed. This complex reduces the phosphomolybdate phosphotungstate reagent (Folin-Ciocalteus-Phenol Reagent) and forms a dark blue color. The resulting darkness is directly proportional to the protein concentration in the medium according to Lowry el al (18).

2.9. Statistical Analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) plus Tukey post-hoc analysis. Statistical analyses were performed using the SPSS software version 15.0 (SPSS Inc., Illinois, USA). All data are indicated as means ± SD. In addition, increases or decreases between the groups are indicated as percentages. $p<0.05$ was considered statistically significant.

3. RESULTS

Compared with Group I, the enhanced serum glucose, HbA1c, creatinine, urea, and BUN levels were observed after STZ injection in Group II ($p<0.05$). There was a significant decrease in serum total protein level of diabetic rats when compared to control group ($p<0.05$). *J. communis* L. oil at 200 mg/kg resulted in 12.7% reduction of serum HbA1c level, 73.6% reduction of serum glucose level, 19.2% reduction of serum creatinine level, 28.5% reduction of serum urea level, 28.5% reduction of BUN level, on the other hand, 16.4% augmentation of serum total protein level compared with the diabetic group. All parameters showed significant differences between Group II and Group III ($p<0.05$). Results on serum glucose, HbA1c, total protein, creatinine, urea, and BUN levels were shown in Table 1.

Table 1. *Effect of administration of J. communis L. oil for 21 days on serum glucose, serum HbA1c, serum creatinine, serum urea, BUN, and serum total protein levels in diabetic rats.*

	Group I	Group II	Group III	Group IV
Serum glucose level (mg/dL)	62.54±7.94	397.77±47.2[a]	70.51±8.93	105.08±12.85[a,b]
Serum HbA1c level (%)	5.8±0.47	7.1±0.43[a]	5.6±0.33	6.2±0.38[b]
Serum creatinine level (mg/dL)	0.57±0.04	0.73±0.06[a]	0.61±0.08	0.59±0.07[b]
Serum urea level (mg/dL)	36.7±4.59	49.84±4.76[a]	38.09±4.07	35.64±4.15[b]
BUN level (mg/dL)	17.14±1.35	23.26±1.68[a]	17.77±2.39	16.63±2.24[b]
Serum total protein level (g/dL)	8.19±0.64	6.75±0.46[c]	8.47±0.73	7.86±0.55[d]

[a] Significantly higher than Group I ($p<0.05$), [b] Significantly lower than Group II ($p<0.05$), [c] Significantly lower than Group I ($p<0.05$), [d] Significantly higher than Group II ($p<0.05$)

Oxidative stress has been implicated in inflammation which is directly related to the level of MDA, NO and GSH and activities of SOD and catalase. Low tissue concentrations of SOD, GSH, and catalase and high tissue concentrations of MDA and NO were noted in Group II compared with Group I ($p<0.05$). *J.*

communis L. oil at dose of 200 mg/kg enhanced 73.7% of SOD activity ($p<0.05$), 52.7% of catalase activity ($p<0.05$) and 38.8% of GSH level ($p<0.05$), besides this, decreased 31.4% of MDA level ($p<0.05$) and 29.8% of NO level ($p<0.05$) in kidney tissue of diabetic rats. Results on SOD, and catalase activities and GSH, MDA, and NO levels in kidney tissue were shown in Table 2.

Table 2. *Effect of administration of J. communis L. oil for 21 days on MDA, NO, and GSH levels and SOD and catalase activities in diabetic rats.*

	Group I	Group II	Group III	Group IV
MDA level (nmol/mg protein)	28.73±3.97	46.51±6.84[a]	30.71±4.87	31.92±4.5[b]
NO level (nmol/mg protein)	14.62±1.57	22.05±2.47[a]	15.18±2.93	15.47±2.19[b]
GSH level (nmol/mg protein)	69.81±5.35	51.64±4.43[c]	70.39±8.65	71.68±6.03[d]
SOD activity (U/mg protein)	3.91±0.38	2.13±0.27[c]	3.76±0.49	3.7±0.42[d]
Catalase activity (U/mg protein)	395.62±37.61	264.44±31.95[c]	388.52±40.17	403.86±37.51[d]

[a] Significantly higher than Group I ($p<0.05$), [b] Significantly lower than Group II ($p<0.05$), [c] Significantly lower than Group I ($p<0.05$), [d] Significantly higher than Group II ($p<0.05$)

4. DISCUSSION

Diabetic nephropathy like any other chronic diabetic complications is caused by various reasons, including poor glycemic control, high blood pressure, and high cholesterol (especially hypertriglyceridemia) (19). In this study, it was found that *J. communis* L. oil treatment could decrease the level of serum HbA1c and glucose levels, therefore *J. communis* L. oil could inhibit the development of diabetic nephropathy.

Renal dysfunction as a result of DM can be assessed by serum creatinine, urea, BUN, and total protein. Therefore, this suggested that there is strong relationship between these parameters and renal dysfunction. Thus, an increase in creatinine, urea, and BUN occurs when there is renal dysfunction or damage. The increment in serum creatinine, urea, and BUN observed in this study clearly indicated that DM causes damage or dysfunction of the kidney in diabetics. Hence, the results of this study were in accordance with various studies which showed raised serum creatinine, urea, and BUN levels in diabetic patients (20). Also, in this study, there were increased levels of these kidney function parameters (except serum total protein level) in diabetic control group when compared to normal control and diabetic test group. The increment observed in diabetic control group revealed that untreated DM caused severe dysfunction of the kidney compared to treated DM through dietary consumption of *J. communis* L. oil.

According to previous research, *J. communis* L. oil were reported to have renoprotective and regenerative effects on the kidney of hypercholesterolemic rats (21). Therefore, it is not unreasonable to suggest that *J. communis* L. oil has remedial and protective effects on the kidneys of diabetic rats.

However, the remedial effect of *J. communis* L. oil may probably be due to the earlier reported antioxidant and anti-inflammatory properties of *J. communis* L. oil as a result of its chemical components especially medium chain fatty acids (22,23).

In addition, in this study, it was observed that there was a decrease in serum total protein of diabetic group compared to control and diabetic group treated with *J. communis* L. oil. This was probably because of the damaging effects DM has on the kidney tissues of diabetic control group which was minimized in diabetic test group as a result of dietary consumption of *J. communis* L. oil.

Kidney is abnormally sensitive to oxidative stress; under the condition of high glucose, reactive oxygen species (ROS) can induce renal cell apoptosis and drop from basement membrane, causing damaged glomerular filtration membrane integrity and even proteinuria; moreover, thereby promoting the development of diabetic nephropathy (24). There are mainly several kinds of antioxidant defense system, including glutathione (GSH), catalase, and superoxide dismutase (SOD) (25). Unfortunately, in some cases antioxidant defense system mentioned cannot overcome the elevation of oxidative stress. Therefore, an excess oxidative stress can attack the cell components especially the polyunsaturated fatty acids leading to the increase level of MDA, a lipid peroxidation product (26). The role of nitric oxide in diabetic nephropathy is a rather controversial issue. Some researchers have reported that nitric oxide increased kidney injury through its reactions with a superoxide radical and generation of a cytotoxic peroxynitrite (27,28). The impairment in the oxidant/antioxidant equilibrium also induces tissue damage and diabetic complications (24). In this study, the level of GSH and activities of SOD and CAT and the content of MDA in serum and kidney tissue for analyzing systemic and local ability to clean the free radicals were detected. Compared with Group I, the level of GSH and activities of catalase and SOD in kidney tissue was decreased and level of MDA and NO was increased in diabetic rats; therefore the ability of scavenging free radicals was destroyed in diabetic nephropathy model. After *J. communis* L. oil treatment, the level of GSH and activities of catalase and SOD in kidney tissue were obviously increased, and the levels of MDA and NO were obviously decreased, therefore *J. communis* L. oil treatment was promoted to scavenge free radicals in kidney through regulating enzymatic and non-enzymatic antioxidants.

5. CONCLUSION

It could be concluded that *J. communis* L. oil succeeded in controlling hyperglycemia in rats with STZ induced diabetes. Furthermore, this study has provided direct evidence of a link between DM and diabetic nephropathy and demonstrated that *J. communis* L. oil provide a protective effect on the kidney as evidenced by an improvement of the renal function tests as well as reduction in oxidative stress parameters.

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