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EVALUATION OF EFFECT OF AYURVEDIC PREPARATIONS ON NEPHROPATHY IN DIABETIC WISTAR RATS

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Keywords:

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ABSTRACT: Introduction: Type 2 diabetes, which is the most common type, is often a result of excess body weight and physical inactivity in genetically predisposed individuals. Over due course of time diabetes can cause blindness, kidney damage, neurological problems, and coronary artery disease. Improvement in glycemic control is important factors in delaying the onset and progression of diabetes-related complications. In spite of the availability of newer antidiabetic drugs, prevention of complication is still a challenge. Nishamalaki, Patoladi Yoga and Shobhanjan are the Ayurvedic formulations claimed to be effective in preventing nephrotoxicity. **Objective:** To evaluate the therapeutic efficacy of Nishamalaki, Patoladi Yoga, and Shobhanjan in diabetic nephropathy. **Materials and Methods:** Total of 36 Wistar rats were used for the study. Diabetes was induced in 30 Wistar rats of either sex with STZ (35 mg/kg) i.p followed by High Fat High Fructose diet (HFHF), (coconut oil+ vanaspati) till the development of Diabetic nephropathy (10wks) which was confirmed by Sr. creatinine, blood urea levels. Out of six groups included in the study, group I was without diabetes, Diabetic animals were divided into five groups Group II-Diabetic control, Group III- Nishamalaki, Group IV- Patoladi Yoga, Group V- Shobhanjan & Group VI- Enalapril and drug treatment was given according to groups orally for 45days. Blood sugar levels, BUN, creatinine were tested weekly. **Results:** Nishamalaki significantly ($p<0.001$) improved Creatinine level compared with the diabetic control group. Reduction in BUN values was more with Patoladi ($p<0.001$) than Shobhanjan ($p<0.01$). Results of Nishamalaki, Patoladi yoga, and Enalapril were comparable to the control group. Patoladi appeared significantly more effective in reducing BUN & Creatinine values than shobhanjan. Nishamalaki additionally showed a blood sugar lowering effect. **Conclusion:** Nishamalaki, Patoladi yoga has shown a protective effect against diabetic nephropathy. Both are effective in delaying the progression of nephropathy in diabetes mellitus.

INTRODUCTION: Diabetes is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, and negative nitrogen balance. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. [1]

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India is expected to be world diabetes capital as Indians have genetic predisposition to develop diabetes mellitus, which is further aggravated by changing lifestyle [2]. Clinically encountered major types of diabetes are type I and Type II.

Out of these two, type II diabetes is the most prevalent type of diabetes. In type II DM, the disease course is primarily characterized by insulin resistance and in due course, the decline in β-cell function. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems [3].

Though the exact pathophysiology is not known, morphologically, diabetic nephropathy is characterized by progressive thickening of the glomerular basement membrane and expansion of the mesangial matrix which correlates to the alteration in the glomerular filtration function. Hyperglycemia is considered to be the basic insult resulting in various changes at the tissue level. Control of hyperglycemia remains the basic management of diabetes and its complications. But controlling only hyperglycemia does not completely halt the development of complications, like nephropathy. ACE inhibitors, working by different mechanism, are shown to be highly effective in the prevention and treatment of diabetic nephropathy.

Nishamalaki (NA), a combination product of *Curcuma longa* and *Emblica officinalis* is advocated in Ayurveda for Diabetes mellitus (DM). It is taken lifelong after DM is diagnosed. Nishamalaki is shown to have many actions-reducing hyperglycemia; reduction in aldose reductase; reduction in oxidative stress, *etc*. It has been shown to have a favorable effect of controlling DM and its ocular complications [4]. Curcuma and Emblica are individually shown to have protective value in diabetic nephropathy [5, 6]. Our preliminary study has shown kidney protective action of Nishamalaki [4]. NA was included in this study to confirm this effect.

Patoladi yoga is a combination of Patola, Sariva, Musta, Patha, and Kutki. All of these are supposed to have blood purifying action. Individually, these agents are shown to have many actions like reducing hyperglycemia, anti-inflammatory, etc. Being plant products, all of these would have anti-oxidant action, in common. In clinical practice, this combination was shown to postpone the requirement of dialysis in diabetes-induced end-stage renal disease. But there is a paucity of authentic information regarding the utility of this preparation in diabetic nephropathy. Patoladi yoga was, therefore, evaluated for its effect on diabetic nephropathy. Shobhanjan (*Moringa oleifera*) plant is reported to have potent antidiabetic, anti-inflammatory, diuretic, antioxidant, antihyper-tensive, hepatoprotective, antibacterial and antifungal properties [7]. Caceres A has demonstrated that it has diuretic action also [8].

Considering its anti-diabetic, anti-inflammatory and diuretic actions, this agent was also evaluated for its utility in diabetic nephropathy.

So, the present study was planned to evaluate the therapeutic efficacy of Nishamalaki, Patoladi Yoga, and Shobhanjan in diabetic nephropathy.

MATERIALS AND METHODS: Wistar rats of either sex having an average weight of 150-200g were used for the study. As per CPCSEA guideline, five animals were housed in single standard cage. The animals were given food and water *ad libitum* and were exposed to to12 h light and dark cycle. The study started after obtaining the approval (BVDUMC/3080/2014-15) from Institutional Animal Ethics Committee of the Bharati Vidyapeeth (Deemed to be University) Medical College, Pune (CPCSEA - 258).

Drugs and Chemicals:

- Inj. Streptozotocin (STZ) was purchased from Anand pharmaceuticals, Pune.
- Nishamalaki- was obtained from Bharati Vidyapeeth Ayurved College, Pune.
- Patoladi yoga and Shobhanjan- were obtained from Ayurvedic physician, Sangli.
- Enalapril- was obtained from Bharati Medical Store, Pune.
- Vanaspati ghee and coconut oil were obtained from super shopee, Dhankawadi.

Induction of Diabetes in Rats: Streptozotocin (STZ) dissolved in citrate buffer (0.01M, pH 4.5) was given to 30 rats in the dose of 35 mg/kg intra-peritoneally to induce diabetes mellitus.

It was followed by high fat (Coconut oil and Vanaspati ghee- 2:3) and a high fructose diet (10%) [9].

Confirmation of Development of Diabetes: Development of diabetes was confirmed with the measurement of Blood sugar level (BSL). BSL above 250mg % was considered to be diabetic.

Confirmation of Development of Diabetes Nephropathy: Development of diabetes nephropathy was confirmed with the measurement of Blood urea nitrogen (BUN) and Creatinine.

BUN and Creatinine level twice above baseline was considered as diabetic nephropathy.

Grouping: After confirmation of the development of diabetic nephropathy; 30 rats were divided into five groups of (n=6).

Group I: Control, without diabetes, without any treatment
Group II: Diabetic control
Group III: Nishamalaki (0.9 gm/Kg)
Group IV: Patoladi Yoga (27 mg/Kg)
Group V: Shobhanjan (27 mg/Kg)
Group VI: Enalapril (10 mg/kg)

The dose of Nishamalaki, Patoladi Yoga, Shobhanjan & Enalapril were extrapolated from the human dose [10]. Animals received drug treatment for the next 45 days as per the groups. Monitoring of BSL, BUN, and Creatinine was done on every 15th day.

Parameter Assessed: Blood Urea level, Creatinine, Blood sugar level.

After Sacrificing the Animals: Histopathology of the kidney.

For Histopathology of Kidney: The kidneys were washed with saline and fixed in 10% formalin. Slides were prepared by embedding the kidney in paraffin and cut into 4um thickness sections. Staining was done with hematoxylin and eosin. Kidney sections were analyzed under a light microscope for features of degeneration and vascular defects.

Microscopic: Histopathologically, kidney damage was scored based on kidney architecture in the following manner.

0-no change;
1-mild changes;
2-moderate changes; and
3-severe changes.

And all were scored by using the following points.

- **a.** Tubular Epithelial Cell Degeneration (0-3)
- **b.** Tubular Epithelial Cell Necrosis (0-3)
- **c.** Atrophic Glomerulus and Tubules (0-3)
- **d.** Interstitial Mononuclear Cell Filtration (0-3)
- **e.** Increased Fibrous tissue (0-3)
- **f.** Hyperemic vessels in the interstitium (0-3)

Addition of all scores was taken as "Total Score" for one animal.

Statistical Analysis: Results were expressed as mean ± SEM. The data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. $P<0.05$ was considered statistically significant.

RESULTS:

Effect of Drugs on BUN Level Table 1: In the control group, BUN level remained constant throughout the experiment, *i.e.* till 45 days. All other groups showed significant ($p<0.001$) increase in BUN values at baseline, in comparison to control. In DM control group, BUN remained high throughout the study. In the NA group significant ($p<0.05$) reduction was seen on day 30 and day 45 ($p<0.01$) in comparison to the DM control group. Results of NA were comparable to Enalapril.

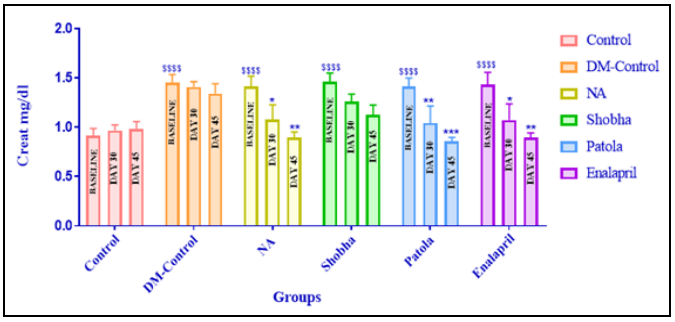
In shobhanjana group, BUN reduction was insignificant. Patoladi yoga was more effective amongst all the drugs. It reduced BUN significantly ($p<0.01$) on day 30, and the further reduction were seen on day 45 ($p<0.001$) compared to the DM control group. It was more effective than Enalapril. When the results of Nishamalaki, Patoladi yoga and Enalapril were compared, the difference was not significant.

TABLE 1: EFFECT OF DRUGS ON BUN LEVEL

	Control	DM-Control	NA	Shobha	Patola	Enalapril
Day 0	18.68 ±0.40	30.65 ±0.47$^{\$\$\$\$}$	28.85 ±0.77$^{\$\$\$\$}$	30.06 ±0.67$^{\$\$\$\$}$	28.69 ±2.00$^{\$\$\$\$}$	28.02 ±0.59$^{\$\$\$\$}$
Day 30	18.09 ±0.22	29.13 ±0.20$^{\$\$\$\$}$	24.37 ±1.08*	27.18 ±0.44	23.68 ±1.11**	24.15 ±1.05**
Day 45	17.36 ±0.16	27.26 ±0.79$^{\$\$\$\$}$	21.99 ±0.71**	25.56 ±0.84	21.44 ±0.44***	22.04 ±0.65**

Values are expressed as Mean ± SEM; $^{\$\$\$\$}$ $P<0.0001$ in comparison with control; *$P<0.05$, **$P<0.01$, ***$P<0.001$ in comparison with diabetic control. NA- Nishamalaki, Shobha-Shobhanjana, Patola-Patoladi yoga

Effect of Different Drugs on Creatinine Level Graph 1: In comparison to control, all other groups showed a significant increase in creatinine level, at the baseline. On day 30, a significant reduction was seen in Patola, NA, and Enalapril groups. Maximum reduction was seen in the Patola group ($p<0.01$). NA and Enalapril were comparable ($p<0.05$).



GRAPH 1: EFFECT OF DIFFERENT DRUGS ON CREATININE LEVEL. Values are expressed as Mean ± SEM; $$$$ P<0.0001 in comparison with control; *P<0.05, **P<0.01, ***P<0.001 in comparison with diabetic control. NA- Nishamalaki, Shobha-Shobhanjana, Patola-Patoladi yoga

The non-significant reduction was seen in Shobhanjana group. On day 45, the further reduction was seen in all the groups. The profile of reduction was similar to day 30.

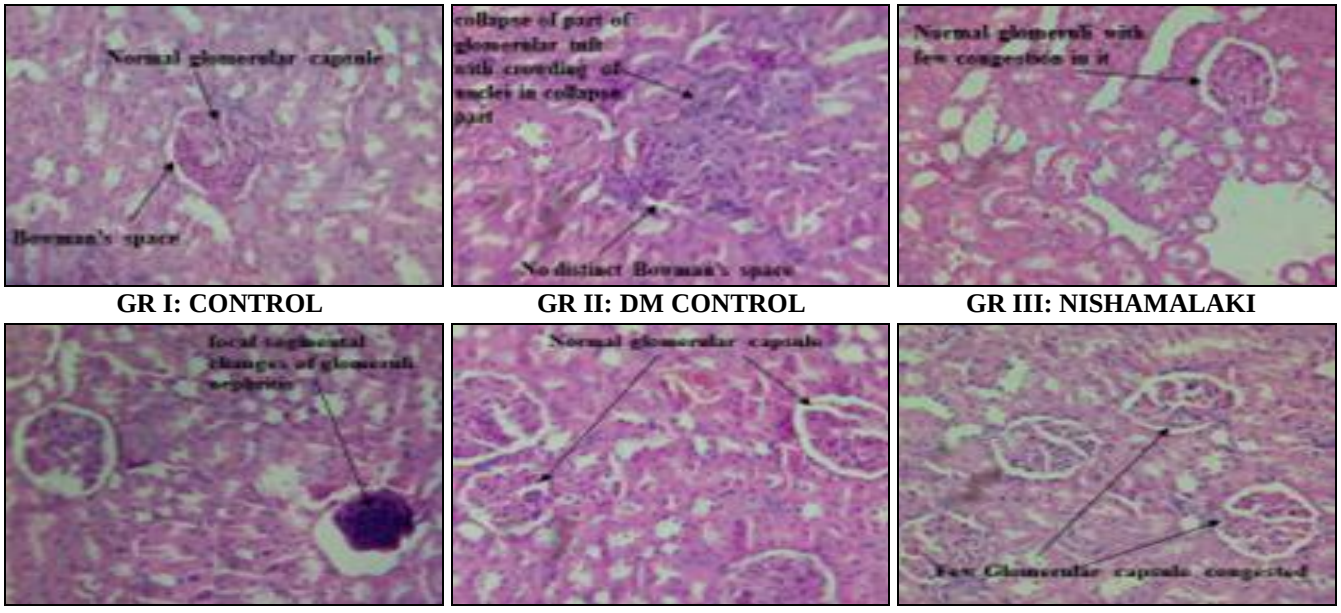
Effect of Different Drugs on BSL Level Table 2: In the control group, there was no significant change in BSL levels throughout the study period *i.e.* on day 0, 30 & 45. In all other groups, BSL was significantly ($p<0.001$) increased at the baseline. The increase was maintained in DM control group throughout the experiment. In NA group significant ($p<0.05$) reduction was seen on day 30 and day 45 ($p<0.01$) in comparison with the DM control group. Results of NA were comparable to Enalapril. In shobhanjana group, BSL reduction was seen, but significance was seen on day 45 only. Patoladi yoga was more effective amongst all drug-treated groups. It reduced BSL significantly ($p<0.01$) on day 30 and day 45 ($p<0.001$) compared to the DM control group. It was more effective than Enalapril.

TABLE 2: EFFECT OF DIFFERENT DRUGS ON BSL LEVEL

	Control	DM-Control	NA	Shobha	Patola	Enalapril
DAY 0	114.5±2.66	233±9.14$^{\$\$\$\$}$	241.33±7.29$^{\$\$\$\$}$	236.16±5.13$^{\$\$\$\$}$	241.1±7.00$^{\$\$\$\$}$	229.33± 7.72$^{\$\$\$\$}$
DAY 30	119.66±5.03	236.83±9.72	192.16±10.22*	219.66±5.04	187.16±4.05**	196.5±10.19*
DAY 45	113.83±3.38	239.5±11.1	124.66±3.29**	198.66±3.54*	119.83±3.70***	125±4**

Values are expressed as Mean ± SEM; $$$$ P<0.0001 in comparison with control; *P<0.05, **P<0.01, ***P<0.001 in comparison with diabetic control. NA- Nishamalaki, Shobha-Shobhanjan, Patola-Patoladi yoga

Histopathological Changes with Drug Treatment in Kidney: In diabetic control group, there was significant disruption in the kidney architecture. NA and Enalapril showed comparable, significant ($p<0.01$) decrease in kidney damage score in comparison to DM control. Patoladi was more effective ($p<0.001$) & Shobhanjana less effective ($p<0.05$) in this regard.



GR I: CONTROL **GR II: DM CONTROL** **GR III: NISHAMALAKI**

GR IV: SHOBHA **GR V: PATOLA** **GR VI: ENALAPRIL**

FIG. 1: HISTOPATHOLOGICAL CHANGES WITH DRUG TREATMENT IN KIDNEY

TABLE 3: HISTOPATHOLOGICAL SCORE OF CHANGES WITH DRUG TREATMENT ON KIDNEY

Parameter	Control	DM Control	NA	Shobha	Patola	Enalapril
Histopath Scores of Kidney damage	0±0	5.83±0.40	3.16±0.60**	4.66±0.33*	2.66±0.55***	3±0.68**

n= 6, the observations are mean ± SEM; *P<0.05, **P<0.01, ***P<0.001 in comparison with DM control

DISCUSSION: Diabetes mellitus (DM), according to WHO projection, will be the single largest non-communicable disease worldwide by the year 2025 with the largest diabetic population in India [12]. DM is a heterogeneous disorder primarily of carbohydrate metabolism with multiple etiologic factors that generally involves absolute or relative insulin deficiency or insulin resistance or both, which results in hyperglycemia. The major problem of DM is the occurrence of its complications, whether or not DM is controlled.

Generally, the injurious effects of hyperglycemia can be divided into macrovascular and microvascular complications. One of the microvascular complications is Diabetic Nephropathy. Other than ACE inhibitors, not many drugs are available in the treatment of diabetic nephropathy. In spite of this treatment, diabetic patients eventually land in chronic kidney disease with a progressive reduction in renal function, ultimately requiring dialysis. Once diabetes is diagnosed, an Ayurvedic formulation- Nishamalaki- is advocated for lifelong treatment. It is supposed to have antidiabetic action and prophylactic effect for diabetic complications. Patoladi yoga and Shobhanjan are clinically found to postpone the requirement of dialysis in DM nephropathy.

So, in the present work, efforts were made to study the effect of Nishamalaki (NA), Patoladi yoga and Shobhanjan on DM nephropathy and compare it with that of Enalapril.

There are many models to induce diabetes. We selected a model which could induce diabetes & its complications slowly, as it occurs in humans. STZ and HFHF model was used to induce DM. STZ is a pancreatic cell toxin that induces rapid and irreversible Necrosis of cells [13]. If many β cells are damaged, the type I DM would be induced. To produce lesser damage to β cells, the low dose of STZ was used. This was followed by high fat, high fructose diet. With this schedule, it took about 14 days for consistent hyperglycemia, similar to type II DM, to develop. After that, animals were followed by blood bl. urea and creatinine check to see the development of Nephropathy. It took 10 weeks to increase urea and creatinine twice the basal value, which were the criteria considered for the development of diabetic nephropathy.

How hyperglycemia produces complications is not exactly known, and postulations for this effect have kept changing over the years. When blood sugar level rises, intracellular hyperglycemia occurs. Individual cells try to reduce this hyperglycemia by reducing the entry of sugar inside the cell. But those cells which are not able to control this entry, kidney cells are one such type of cells, become prone for all ill effects of hyperglycemia. Intracellular hyperglycemia is shown to induce a variety of changes- increase in polyol and hexosamine flux, increased advanced glycosylated end products, and an increase in protein kinase C activity.

Eventually, it was shown that hyperglycemia-induced oxidative stress is the most important detrimental effect [14], which then acts by the above-mentioned pathways. Oxidative stress occurs due to an imbalance between Reactive Oxygen Species (ROS) and intracellular antioxidants [15].

If we consider this hypothesis, all the diabetic complications should occur in every patient. But clinically this is not true. Individual variation is observed in the development of diabetic complications. Pathologically, in diabetic nephropathy, thickening of the glomerular basement membrane, mesangial expansion, nodular sclerosis, tubular interstitial fibrosis, and arteriosclerosis is seen indicating increased pro-sclerotic activity. It was observed that Enalapril has an anti-proteinuric effect independent of reduction of systemic blood pressure and also is effective in reversing the detrimental effect on kidney function in patients with diabetic nephropathy Enalapril is not reported to have antihyperglycemic action. This implies that the mechanism other than hyperglycemia may be responsible for diabetic nephropathy.

The induction of cytokine growth factors has been shown for most of these pathobiochemical pathways *in-vitro*. Therefore the de novo synthesis of several of these cytokines has been studied in renal tissue of diabetic rats. The results show that transforming growth factor β 1 (TGF-β1) is the first and most prominently induced growth factor [16,] which is a known prosclerotic agent. Studies showed that neutralizing this factor is useful for delaying nephropathy. Kagami *et al*., [17] could demonstrate that angiotensin II induces the production of TGF- β1 similar to high glucose levels. This common pathogenetic pathway may explain the basis of the usefulness of angiotensin-converting enzyme (ACE) inhibition in diabetic patients with nephropathy. ACE inhibitors are effectively used clinically in diabetic nephropathy. So, in our study, we used Enalapril as control. Enalapril is highly effective in reducing TGF- β 1. Recently, Enalapril is reported to have antioxidant action [18]. It is seen in our study that Enalapril has anti-hyperglycemic action also.

Nishamalaki (NA) is a combination of *Curcuma longa* and *Emblica officinalis*. Individual agents are found to be effective in diabetes and its complications. Curcuma is shown to have anti-oxidant, anti-inflammatory, anti-hyperglycemic, and also nephroprotective action [19]. *Emblica officinalis* reduces hyperglycemia by insulin release and has reno-protective action also [19]. Both *Curcuma* and *Emblica* were shown to reduce age-related renal dysfunction in Rats [19]. Age-related organ changes are due to the formation of advanced glycation end products. Recently, V. Soetikno *et al*., have reported inhibition of activation of pro-inflammatory cytokines like NF kB and TGFβ1 by Curcumin [20]. This indicated that NA might be working through multiple mechanisms. In the treatment of DM nephropathy, anti-hyperglycemic and reduction in TGFβ1 may be more important. Since the action profile of NA is similar to that of Enalapril, we probably have got comparable nephroprotective effects by both these drugs.

Despite the benefits derived from the current therapeutics for diabetic nephropathy like- strict control of glucose, BP control, reduction of TGF-β1, *etc*., these strategies still provide imperfect protection against progression of renal disease [21]. So, the need for newer therapeutic agents having better potential to counter the primary pathogenesis of diabetic nephropathy remains.

With the observation that Patoladi yoga is more effective in reducing DM nephropathy parameters than NA and Enalapril, we tried to find out its possible mechanism of action.

In Ayurveda, treatment of DM nephropathy is given in the following steps-

- Pachan- is the first step, for correction of the local abnormal processes.
- Shodhan- for removing the unwanted accumulated waste products.
- Prasadan- regeneration of cells which are disease free.

Though these are the separate processes, they occur simultaneously. So, agents producing Pachan, Shodhan, and Prasadan are used concurrently. In Ayurveda, diabetic nephropathy is postulated to be due to altered metabolism at the cellular level leading to the development of functional blockages in the kidney. To remove these blockages and to reinstate the excretory function is the aim of treatment.

Patoladi yoga is the mixture of five ingredients- Patolapatra (*Trichosanthes dioica*), Sariva roots (*hemidesmus indicus*), Musta roots (*Cyperus rotundus*), Patha roots (cissampelouspareera), Kutki roots (*Picrorrhiza curroa*). Patola [22], Musta [23,] and Patha [24] are reported to act on various kidney structures like glomerulus & blood vessels to reduce abnormal local metabolism and also having anti-diabetic properties. Kutki [46] and Patha [25] are diuretic and work to remove the local and circulatory waste products generated before & during the corrective process. Regeneration, which also starts simultaneously, is supported by Sariva [26].

In the present study, Patoladi yoga was most effective. It had more efficacy than Enalapril and NA. On histopathological evaluation also, it was effective in reverting changes induced by Diabetes, almost to normal **Fig. 1**. Since clinically, Patoladi yoga shows efficacy in end-stage renal disease, it probably has additional mechanisms of action. With the evidence that hyperglycemia and TGF- β 1 are only partly responsible for complex

pathophysiology of diabetic nephropathy, search for additional contributory factors continued. Involvement of additional immunologic and inflammatory mechanisms was demonstrated in DM nephropathy. Eventually, many cytokines were demonstrated to play a pivotal role in its Development like- IL1, IL6, TNFα *etc*. [27] Since, Patoladi yoga has action more than Enalapril, which works by reducing TGF- β 1; it probably has action at IL1, IL6 or TNF- α level. Further studies are required to confirm this finding.

Shobhjana: Shobhjana is *Moringa oleifira*. *Moringa oleifera* is reported to have the action of inhibition of α-glucosidase, pancreatic cholesterol esterase activity, as well as bile acid binding and inhibiting the formation of cholesterol micellization [28]. The aqueous extract of *M. oleifera* leaves been reported to possess potent anti-hyperglycemic and anti-hyperlipidaemic effects in both insulin-resistant and insulin-deficient rat models [29]. Efiong *et al*. (2014) showed that shobhanjan reduce the Urea & Creatinine levels [30].

But in the present study, it only reduced hyperglycemia on day 45. It did not produce any significant action on nephropathy parameters. This could be because Shobhanjan was used as a single agent whereas NA and Patoladi yoga are the combination preparations.

CONCLUSION: Patoladi yoga, Nishamalaki, and Shobhanjana were evaluated for diabetic nephroprotective effect, in comparison to Enalapril. The results indicate-

1. Nishamalaki has equieffective nephroprotective action similar to Enalapril,
2. Patoladi yoga is more effective,
3. Shobhanjana has minimal effect on kidney functions.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

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