

## Original Article



# Immunomodulating and Antiproteinuric Effect of Hippophae Rhamnoides (Badriphal) in Idiopathic Nephrotic Syndrome

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## Abstract

**Objective:** The treatment of idiopathic nephrotic syndrome is still not well settled and at times is very frustrating. Number of protocols have been reported with variable results outcome in various conditions. The main pillar of treatment of idiopathic nephrotic syndrome is use of immunomodulating and suppressive drugs in various combinations. The herbal preparations have also been reported to have immunomodulating property. The study has been planned to record Immunomodulating and antiproteinuric effect of Hippophae rhamnoides.

**Material and Methods:** In the present study had 2 groups having 28 patients of idiopathic nephrotic syndrome in each group have been included. The patients were subjected to haematological, biochemical, immunological investigation at 0, 1, 2 and 3 months interval with dietic advise. Group A have been put on standard treatment, whereas group B on Badriphal in the well worked up doses. The hydroalcoholic extract of 350 mg twice daily of Badriphal was given to group B as add on treatment. Patients were followed up with definite protocol at monthly interval for 3 months.

**Results:** At the end of 3 month patients showed improvement in the symptoms of oedema, anorexia, oliguria in the herbal group. The urinary estimation of protein showed significant decrease in Group B with elevation of S. albumin levels. The inflammatory cytokines has showed significant decrease at the end of 3 month.

**Conclusion:** Thus the pilot study showed beneficial effect of the herbal preparation Hippophae rhamnoides as add on treatment. A large perspective study is recommended to establish these findings.

## Introduction

Idiopathic nephrotic syndrome (INS) comprising mainly of four primary glomerular diseases namely Minimal Change Disease (MCD), Focal segmental glomerulosclerosis (FSGS), Membranous glomerulopathy and membrano proliferative glomerulonephritis (MPGN). Various treatment protocols had been developed for treatment of idiopathic Nephrotic Syndrome, using various immunosuppressive medications like steroids, cyclophosphamide, cyclosporine chlorumfucial and some newer monoclonal antibodies.

Despite using various drugs 5-10% of INS patient remains refractory to treatment and having increasing proteinuria which can produce further damage to the kidney and patients may develop chronic glomerular nephritis (CGN), leading to chronic kidney disease (CKD).

Management of difficult nephrotic syndrome patients is at times frustrating both for patients and physicians and main moto is to reduce proteinuria and every possible effort should be explored for the same.

The very aim of the present work is to explore use of traditional and herbal medicines for the reduction of proteinuria including nephrotic syndrome. We used Hippophae rhamnoides as add on treatment for reduction of proteinuria in nephrotic patients.

Hippophae Rhamnoides is also known as Badriphal and this

plant has been used for more than 2000 years as medicine and food additive in Europe, Russia and Asia. It is a hardy deciduous shrub. The fruit of this plant is used for various pharmacological preparation in Ayurveda, It is quiet rich in protein, fat, amino acids and vitamin C. Ripe fruit contains malic acid, oxalic acid and various phospholipids including Lecithin, Cephalin, Phosphatidylinositol and multiple unidentified alkaloids. Its leaves contain more than hundred types of active elements and they work on capillaries, works as rheological agents, work on immune system, cardiovascular system and also cognitive function.<sup>1-4</sup> It has also been claimed to have anti oxidant and anti inflammatory.<sup>4,5</sup>

In Ayurveda Hippophae rhamnoides is prescribed for respiratory disorders in form of drink for protection of body from cold, for treatment of pneumonia, upper respiratory tract infections as anti inflammatory and expectorant remedy.<sup>5,6</sup>

We used hydro alcoholic extract of leaves and fruits of Hippophae rhamnoides for forming medication in capsulated form, the drug formulation was developed by expert in our group. Safety and efficacy profile was tested in animal using on charts-foster rats and albino-rats. The result revealed that, drug is quiet safe and having immunomodulatory properties. The clinical studies on Hippophae rhamnoides has shown efficacy in cold stress, has shown its antihyperlipedemic effects and has also shown positive modulating effects on mental and general health status.

## Material and Methods

This study was conducted in Department of Nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Patients included in this study were biopsy proven case of minimal changes disease (MCD), Focal Segmental Glomerulosclerosis (FSGS), membrano proliferative glomerulonephritis (MPGN),

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**Table 1 : Clinical presentation**

Symptoms	Group A (n=28)		Group B (n=28)	
	Visit - 0	Visit - 3	Visit - 0	Visit - 3
Anorexia				
Present	20 (71.43%)	8 (28.57%)	22 (78.57%)	4 (14.28%)
Absent	8 (28.57%)	20 (71.43%)	6 (21.43%)	24 (85.72%)
Weakness				
Present	18 (64.28%)	4 (14.28%)	20 (71.43%)	6 (21.43%)
Absent	10 (35.72%)	24 (85.72%)	8 (28.57%)	22 (78.57%)
Oliguria				
Present	5 (21.74%)	0	6 (21.43%)	0
Absent	23 (78.26%)	28 (100%)	22 (78.57%)	28 (100%)

and membranous glomerulonephritis. The various criteria used in the study was as follows -

#### Inclusion Criteria

1. Biopsy proven cases of MCD, FSGS, MPGN and MGN of unknown eti.
2. Patients with serum creatinine <3 mg% at the time of entry in the study.

#### Exclusion Criteria

1. Nephrotic Syndrome due to secondary causes.
2. Patient with serum creatinine > 3mg% at baseline
3. Patients using ACE's or ARB in treatment.
4. Non willing patients.

Termination criteria included as -

1. Doubling of serum creatinine from baseline during treatment.
2. Increased proteinuria above 50% from baseline.
3. Severe drug related side effects like profuse vomiting, skin rashes several allergy etc.
4. No effect on proteinuria with 8 weeks of therapy with herbal drug.

Patients of nephrotic syndrome were divided into two groups A and B Each group had 28 patients randomly allocated. Both groups were treated by standard treatment protocol for specific histological type. Which is as follows:

Standard treatment of each group:

- i. Minimal change disease (MCD):  
Prednisolone 2 mg/kg AD for 4-6 weeks or till patient becomes a proteinuric (urinary protein were <250mg/d). If response, reduce the dose of prednisolone gradually (taper the dose in 2-4 weeks) or  
Prednisolone: 60mg/m<sup>2</sup>/day (Max. 80mg/day) for 4-6 weeks  
Followed by 40 mg/m<sup>2</sup> A/D for 4-6 weeks  
The intensity of the initial therapy for minimal change lesion appears to determine the rate of subsequent relapse.
- ii. Focal Segmental Glomerulosclerosis (FSGS):
  1. Prednisolone 2mg/kg AD for 4-6 weeks or patient becomes a proteinuric (protein <250mg/dl). If response, reduce dose of prednisolone to 2 mg/kg AD 4 weeks.
  2. Prednisolone 0.5-2 mg/kg/day  
Continue treatment for 6 months before declaring the patient steroid resistant.  
Remission is associated with steroid dose of at least 60mg/day for 3 months.  
If necessary decrease dose to 0.5mg/kg/day after 3 months.
  3. Cyclophosphamide or chlorambucil may be used as a

second line treatment.

#### iii. MGN

Idiopathic Membranous Nephropathy : (MGN)

(Ponticelli C et al, 1998)

Prednisolone 1-2mg/kg/day + Cyclophosphamide (1.5 to 2.5mg/kg/day) orally for 6-12 months. Taper steroids as soon as response is evident.

IV Methylprednisone 1gm x 3 days followed by oral prednisolone 0.4 mg/kg/day for 27 days. Subsequently Chlorambucil 0.2mg/kg/day for 28 days. Such 3 cycles for 6 months.

#### iv. Mesangiocapillary Glomerulonephritis (MCGN):

1. Idiopathic MCGN with normal renal function and asymptomatic non-nephrotic proteinuria → No specific therapy is required, But close follow up is advised for BP control, protein, S. Creat.
2. Children with MCGN and nephrotic range proteinuria and or impaired renal function.

Prednisolone: 40 mg/m<sup>2</sup> A/D for 6-12 months.

In group B standard treatment plus Hippophae rhamnoides 350mg twice a day was given for 12 weeks as add on treatment.

Complete remission was defined as urine protein excretion < 250mg/day and partial remission was defined as proteinuria less than 1gm/day. Patients were followed up every two weeks initially and then once in four weeks up to 12 weeks. All patients included in the study were thoroughly evaluated clinically and underwent all baseline investigations as Complete Blood Count (CBC), estimate of Haemoglobin (Hb%), Urine analyses 24hr. Urine protein estimation, serum albumin, serum globulin, lipid profile, and specific tests like IL-6, Apolipo protein B, C-reactive protein (CRP).

## Observations

Both the groups had 28 patients each and age range was 5-65 years in all groups. There was 79% male patients and 21% of female patients in group A and 86% of male patients and 14% of female patients in group B and C.

Histologically group A had 27.3% MCD (Minimal Changes Disease) patients and group B had 30.3% patients, A had 46% of FSGS (Focal Segmental Glomerulosclerosis) and B had 30.4% FSGS patients, similarly Group A had 10.71%, group B had 28.6% and group MGN (Membranous glomerulonephritis) patients, whereas group A had 14.2%, group B had 25% (Membranous proliferative glomerulonephritis) patients, this shows that distribution of particular histology was insignificant between groups.

Clinically edema was present in all the of patients at time of presentation and after 12 weeks of therapy 71% patient in group A, and 68% patient in group B was edema free and this clinical presentation was statistically insignificant. Other clinical features are shown in Table 1.

Anorexia was present in nearly 71% of patients in group A and 78% in group B respectively and at the end of study group A and B there was 29% and 14% patients had anorexia. Oliguria was present in 22%, and 21% patients in group A, group B respectively but at the end of study period no patient in any group had oliguria. Change in systolic Blood Pressure was statistically insignificant between group A and group B. Diastolic Blood Pressure change had similar trend as systolic Blood Pressure (Table 2). Change in weight, haemoglobin, and S. creatinine was insignificant between two groups.

**Table 2 : Systolic blood pressure (mmHg)**

Group	Visit				't' test O Vs 3	P value
	0	1	2	3		
Group - A (n=28)	133.17 ± 24.06	130.57 ± 17.28	125.78 ± 15.85	122.85 ± 14.71	2.482	0.02
Group - B (n=28)	127.71 ± 21.14	123.57 ± 17.98	122.57 ± 13.58	123.71 ± 13.55	0.993	0.329

**Table 3 : 24 hour urine protein (gm), serum albumin (gm/dl) and serum globulin (gm/dl)**

24 hour Urine Protein (gm)	Visit				't' test O Vs 3	P value	
	0	1	2	3			
Group - A (n=28)	5.37 ± 3.42	3.35 ± 1.98	2.70 ± 2.62	2.11 ± 2.98	3.856	<0.001	
Group - B (n=28)	7.77 ± 8.35	4.49 ± 3.42	3.10 ± 3.73	2.53 ± 4.14	2.949	0.007	
<b>Serum Albumin (gm/dl)</b>							
Group - A (n=28)	2.46 ± 0.86	2.42 ± 0.63	2.70 ± 0.58	2.90 ± 0.57	0vs1 0.305	0vs3 2.394	0.024
Group - B (n=28)	2.19 ± 0.59	2.3±0.62	2.68 ± 0.68	2.93 ± 0.67	2.114	5.105	0.000
<b>Serum Globulin (gm/dl)</b>							
Group - A (n=28)	2.38 ± 0.60	2.51 ± 0.48	2.5±0.58	2.79 ± 0.08	0vs1 0.943	0vs3 2.057	0.049
Group - B (n=28)	2.30 ± 0.49	2.27 ± 0.049	2.29 ± 0.62	2.45 ± 0.46	0.307	1.277	0.212

There was no statistically significant change in S. creatinine, S. Phosphorous and Blood urea between two groups after 12 weeks of treatment. S. Cholesterol had shown significant reduction in the treated groups. The 24hr urinary protein had also shown significant reduction (Table 3).

IL-6, Apolipo protein B and CRP had shown statistically significant change in the treated group (Table 4).

## Discussion

The treatment of idiopathic nephrotic syndrome have shown tremendous changes and number of addition in treatment protocol in last two decades, one school of experts feel that all the, at least adult patient should be subjected for the biopsy even during their first episode of having proteinuria and based on underlying histology, the treatment protocol may be pursued. Based on histology based on protocol number of centre and group have developed their own protocol and few of the series have result of large trials and in some situation, the agreement is more or less reaching among the majority of experts.

Further, the various combinations of immunosuppressive and cytotoxic drugs including steroids, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, chromifical and immunomodulating drug like bromiside have been tried in various permulation and combination with varying results and reports. The quest for newer drugs with less toxicity and more effectiveness is an on going process various centres. In this attempts, number of herbal drugs have been claimed to have immunomodulating effect leading to various outcomes. In this study as add on treatment the herbal plant based preparation of Hippophae rhamnoides (Badriphal) have been tried. In 'Badriphal', group, the beneficial effect have been shown in symptoms like anorexia, oedema, oliguric etc. and even improvement in the systolic BP has been noticed. Similarly,

**Table 4 : Interleukin – 6 (IL-6) Pg/ml, apolipoprotein B (mg/dl) and C- reactive Protein (mg/dl)**

Group	Interleukin – 6 (IL-6) Pg/ml		P value
	Visit - 0	Visit – 3	
Group – A	3.08±0.475	2.89±0.762	<0.05
Group – B	3.29±0.875	2.17±0.627	<0.001
<b>Group Apolipoprotein B (mg/dl)</b>			
Group – A (n=28)	118.36±12.86	111.36±10.88	<0.05
Group – B (n=28)	120.75±9.85	110.35±8.79	<0.001
<b>Group C-reactive Protein (mg/dl)</b>			
Group – A	2.99±0.752	2.62±0.667	<0.05
Group – B	3.28±0.667	2.29±0.572	<0.001

as add on treatment has shown improvement in cholesterol, triglyceride, S. albumin and 24 hour urinary protein excretion in the herbal group as add on treatment (group B). Similarly, the inflammatory cytokines like Inter Lukin-6 have shown more significant decrease in Badriphal group because of their anti inflammatory effect. The beneficial effect has also been observed in the levels of Apolipoprotein and C-creative protein. Thus this shows that by reducing these inflammatory markers probably this herbal drug also reduce their proteinuria which have been noticed in this patient. The anti inflammatory action of hippophae has also been reported by earlier.<sup>4,5</sup>

In order to established than finding a large perspective study is recommended to substantiate.

It can be modestly concluded that the Hippophae rhamnoides has shown significant reduction in 24hr. proteinuria, serum cholesterol and inflammatory markers like, CRP and IL-6 and Apolipo protein B.

This pilot study shown that anti-inflammatory and anti proteinuric effects of Hippophae rhamnoides can be used as add on therapy in difficult idiopathic nephrotic syndrome patients.

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