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Research Article

A SYNERGISTIC NEPHROPROTECTIVE ACTIVITY OF A MIRACLE DRINK AYURVEDIC PROPRIETARY MEDICINE RENAL SUPPORT A NOVEL THERAPY FOR CHRONIC KIDNEY DISEASE IN HUMAN

S. M. Raju
M/s Mallur flora & Hospitality Pvt Ltd, R.T. Nagar Main Road, Bangalore, Karnataka, India.

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ABSTRACT

Miracle drink "Renal Support (S-5)" an Ayurvedic formulation in conjugation with other cardiovascular support (S3), Sugar Care (S10), and liver health support (S4) was scientifically evaluated on 12 humans subjects for its therapeutic potential in treating chronic kidney diseases caused due to: a) Induce of pain killers medication, and other medications, b) Chronic diabetes, c) Blood pressure. Patients suffering from renal failure due to over medications, pain killer medication and BP were advised to take 15ml of Renal Support and S3 twice a day morning and evening before food, and 15ml of S4 trice a day. As the main biomarker of kidney disease, creatinine was monitored every month till three months of treatment whereas; blood urea and hemoglobin were screened at month end. Cytotoxicity and nephroprotective activity of Renal Support were evaluated on Baby Hamster Kidney Fibroblast cells (BHK-21). Radical decline in serum creatinine content was observed from 6.31mg/dl to 1.80mg/dl (68%), 1.20mg/dl (79%), and 0.84mg/dl (82%) on 30, 60, and 90 days of treatment respectively and in 90 days of treatment most of the patients showed 50 to 83% creatinine reduction. A significant decrease in the blood urea from 91mg/dl to 30mg/dl(67%) and hemoglobin content from 7.27 to 11.77g% was observed in 30days of treatment and the majority of patients showed >50% of blood urea reduction. No toxicity of Renal Support towards BHK-21 was noticed and showed 40.92% and 47.54% nephroprotective activity. A novel, natural-based, and safe Ayurveda formulation with significant nephroprotective potential for CKD treatment was proposed in the present study.

INTRODUCTION

Kidneys play a central role in retaining Homeostasis in the body as they regulate red blood production, water, acid-base balances, sodium, potassium, bone minerals, and electrolytes through their core function is the excretion of waste products in urine. The use of drugs is often associated with impairment of renal function in clinical practice as 1/3rd of drugs from the body are eliminated unchanged through the kidney.[1]

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Diseases associated with kidney include Acute Kidney Injury (AKI), Chronic Kidney Diseases (CKD), and glomerular diseases. Additionally, long-term anti-inflammatory medication, diabetes, Alport disease, chronic conditions of glomerulonephritis and pyelonephritis, autoimmune diseases, hypertension, polycystic kidney disease, and congenital malformations main causes of CKD.[2] AKI is characterized by the abrupt decrease in kidney function, elevated concentration of urea, and creatinine that results in uremia due to the toxicity of urea. AKI leads to disturbance in homeostasis of fluid and electrolytes resulting in overloading of water and sodium, hyperkalemia, and metabolic acidosis. [3]

Today, kidney diseases are a serious global health concern as they are associated with huge mortality and morbidity, increased risk of contracting other major diseases like cardiovascular diseases, diabetes, malaria, human immunodeficiency virus, and

hypertension.[4] Furthermore, the kidney disease burden is increasing annually, particularly in low and middle-income nations, and is expected to name as 5th major cause of years of life loss globally by 2040. [5] For instance, the global mortality rate of all-age CKD from 1990 to 2017 is raised by 41.5% and the death aroused as results of CKD diagnoses in 2017 is 1.2 million is anticipated to reach 2.2 to 4.0 million by 2040. [6]

CKD is defined by the structural and functional abnormalities associated with kidney like GFR (glomerular filtration rate) less than 60ml/min/ 1.73m^2, albuminuria of ≥30mg/24 hours, and kidney damage markers like hematuria and dysplastic or polycystic or kidneys continuously possess for three months. [7] The severity of CKD is categorized based on GFR as mild, moderate, severe, and kidney failure attributed to GFR of 60-89, 30-59, 15-29 ml/min/ 1.73m^2, and less than 15 (or dialysis) ml/min/1.73m^2 respectively. Serum creatinine level is the most frequently monitored biomarker in the assessment of kidney function. [8]

As for as treatment modalities are concerned, as discussed above CKD enhances the risk of contracting other ailments hence treatment relies on types of other complications. However, each of these therapies suffers from one or other setbacks. Early diagnosis, prolonging disease progress, slowing down the damage, and taking treatment for the specific kidney disease are very important in the management of CKD. Though kidney transplantation and dialysis are the most often opted treatment modalities but these methods are costly, painful, possess side effects and needs repeated hospital visit. Presently, medical science is unable to provide a complete solution to CKD treatment. Hence, a novel, natural-based therapy with few side effects that can be offered by the common population for the treatment of CKD is urgently required.

Ecofriendly-based treatment with no side effects, natural-based therapy, and permanent cure is always the most preferred treatment modality by the majority of patients. Hence in the present investigation, the author with a long-term experience of 35 years in Ayurvedic medicine practice has treated human subjects of well-known CKD with a novel Ayurvedic formulation a Miracle drink of Renal care "Renal Support" in combination with S3 cardiovascular support and S4 a liver health support. The human subjects under treatment were monitored for various biochemical markers for strong CKD indicators such as levels of creatinine, urea, and hemoglobin. Creatinine content of all selected patients was assessed every month from the 0th day to 90 days of treatment. Blood urea and hemoglobin were analyzed monthly. The cytotoxicity and nephroprotective potential of Miracle drinks formulation "Renal Support" were further assessed in hydrogen peroxide toxicity induced Baby Hamster Kidney Fibroblasts cell lines i.e., BHK-21.

MATERIALS AND METHODS

Renal support product: the key constituents of this formulation are *Gokshura*, *Ashwagandha*, *Haritaki*, *Nimba*, etc., each plays a significant role in preventing CKD. *Gokshura* eliminates the excess accumulation of creatinine, urea hence preventing CKD, renal parenchymal disease, pyelonephritis, and other kidney disorders. The formulation also avoids kidney stone formation and breaks down the stone into a smaller size as result it prevents cystitis and polycystic kidney disease. *Ashwagandha* regenerates kidney function and repairs kidney injuries as it possesses antioxidant and anti-inflammation property. The diuretic action of *Haritaki*, and *Nimba* decreases fluid accumulation by flushing out the toxins thereby increasing urine output and decreasing burning micturition and pedal edema.

Human Subjects: Patients with well-known CKD of age ranging between 45 to 83 years were selected for the treatment with Renal Support.

Cell Line Cultivation: BHK-21 cultured in minimum essential medium (MEM) containing Fetal Bovine Serum (FBS) at 10% and antibiotics *viz.,* amphotericin B, penicillin, and streptomycin at 5µg/ml, 100 IU/ml, and 100µg/ml respectively. Cell lines were grown at 5% CO_2 in a humidified atmosphere at a temperature of 37°C until confluent. Dissociation of cells was carried out by treating with Trypsin Phosphate Versene Glucose Solution (TPVS) solution containing 0.02% EDTA, 0.05% glucose, and 0.2% trypsin in phosphate buffer saline. Cultivation of stock cultures was done in 25 cm^2 culture flasks and all experiments were conducted in 96 well microtitre plates.

Preparation of Renal support for cell toxicity study: In 0.1ml of Dimethyl sulfoxide (DMSO) 10mg of Renal support was added and mixed thoroughly. The solution was further diluted with 0.9ml of MEM containing 10% FBS to get a stock of 10mg/ml concentration. The solution was filter-sterilized using a syringe filter and two-fold serial dilution was carried out to get the concentration of 31.25, 62.5, 125, 500, and 1000µg/ml before using it for cytotoxicity studies.

Treatment protocol of Renal Support: Human subjects in the age range 45 to 83 years old selected for present study were tested for various biochemical parameters associated with CKD before to treatment with Renal Support formulation (S5) in combination with S3 (cardiovascular support) and S4 (Liver health support). Each patient was prescribed 15ml of renal support syrup twice a day morning and evening before food. Along with S5, 15ml of S3 was prescribed thrice a day morning, afternoon, and night before food, and 15ml of S4 was advised to take morning and night before food intake. Treatment was continued for 90 days. At the end of each month biochemical

parameters particularly creatinine levels associated with CKD were analyzed for 90 days. Blood urea and hemoglobin content were determined on 0th and 30days. The effect of renal support in CKD was evaluated by comparing the results of biochemical profiles before and after treatment.

Estimation of Biochemical Markers: At every month's end blood was withdrawn from human subjects treated with renal support and serum was separated. Biochemical markers of CKD such as creatinine, urea, and hemoglobin were estimated using commercially supplied diagnostic kits supplied from Span Diagnostic ltd., Surat, and star 21 semi-auto biochemistry analyzer (Rapid Diagnostic Pvt., Ltd., Delhi).

Cytotoxicity Assay: In 96 well microtitre plates, 0.1ml of cell suspension containing $1x10^5$ cells/ml of MEM containing 10% FBS was taken and the plate was incubated at 37°C, with 5% CO_2 concentration for 24h. Post incubation, the partial monolayer formed and the medium was removed. The layer was further washed with MEM and treated with 0.1ml of different concentrations of two-fold serially diluted test drug *i.e.,* 31.25, 62.5, 125, 500, and 1000µg/ml. Incubation was further continued at 37°C, with a 5% CO_2 concentration for 24h. Followed by the incubation, the drug in the well was discarded and 50µl of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) prepared in PBS (phosphate buffer saline) was added. After gentle shaking, the plate incubation was continued for 3h at 37°C, with 5% CO_2. The medium was discarded and 0.1ml of DMSO was added for dissolve formazan and absorbance was recorded at 540nm. Cell growth inhibition by test drug was calculated and the concentration of the test sample to inhibit cell growth by 50% (CTC_{50}) was determined. [9]

The Nephroprotective Activity of Renal Support

Cell lines obtained from monolayer trypsinization were adjusted to $1x10^5$ cells/ml of MEM supplied with 10% FBS and 0.1ml of this cell suspension was taken in a microtitre plate. The cells were grown at 37°C, with 5% CO_2 until a partial monolayer is formed. After 24h, the medium was discarded and the monolayer was washed with sterile MEM and treated with H_2O_2 for 3h at 37°C with 5% CO_2 to induce toxicity. Followed by this, cells were treated with a non-toxic concentration of Renal Support for 24h at 37°C with 5% CO_2. Ascorbic acid at 100µM was maintained as positive control along the test sample. The Microtitre plate was further incubated for 24h at 37°C with 5% CO_2. As described in the earlier step MTT assay was conducted and absorbance was noted down at 540nm. [10]

Statistical Analysis

The results of each experiment conducted in triplicates were expressed as mean±SD. The mean values of different time points i.e., 30, 60, and 90 days treatment were compared with control values using Two-way ANOVA followed by Tukey's multiple comparison test using GraphPad Prism 9.3.1 version. The significance level was adjusted at $p<0.001$ with 99% confidence interval. Blood urea and Haemoglobin results were analysed by simple paired *t*-test with $p<0.05$.

RESULTS

The therapeutic potential of an Ayurvedic formulation i.e., Renal Support in combination with S3 and S4 in the treatment of kidney-related diseases like CKD was evaluated in the current investigation on 12 human subjects of ages ranging from 45 to 83 years old. Human subjects were analysed for various biochemical parameters indicating kidney diseases before treatment. The subjects revealed the highest toxicity towards the kidney as witnessed by elevated concentration of creatinine, urea, and declined concentration of hemoglobin which were beyond that of the standard recommended limit of the normal range. Hence, from the biochemical markers, it is confirmed that the patients possess well-known kidney defects suffering from various diseases and disorders. The know kidney patients were treated with 15ml of Renal support twice a day morning and night before food along with S3 and S4 showed substantial improvement in the patient health like increased urine output, decreased edema, and decrease of loss apatite. The Monthly sero-biochemical profile of all patients revealed a significant improvement in CKD biomarkers.

Effect of Renal Support on Creatinine Level: All human subjects who underwent Renal support treatment revealed a significant decline in the creatinine concentration tested after one month of therapy to 3 months (Table 1). Additionally, majority of the patients responded with excellent urine output and a decline in loss of appetite indicating substantial recovery from CKD or other regular complications. After treatment of one month with renal support, more than 50% of the decrease in creatinine was noticed in the human subjects of age 77, 64, 55, 59, and 46 years with 68.3%, 55.81%, 54.31%, 51.29%, and 50.68% creatinine reduction respectively (Figure 1 & 2). The lowest amount of creatinine eliminated by Renal Support was found to be in patients with ages 83, 74, 52, 45, 72, and 80 years corresponding to the 10.71%, 20.22%, 28.13%, 29.14%, 31.93%, and 33.54% creatinine reduction. Statistical analysis of all results showed highly significant value with $p<0.001$. The result indicated no significant correlation between the ages of the patients and decline in the creatinine level.

Table 1: Monthly evaluation of Renal Support therapy on creatinine level of 12 human subjects

Human Subjects	Age (Years)	Creatinine content (mg/dl)						
		0 day treatment	30 days treatment	% Reduction	60 days treatment	% Reduction	90 days treatment	% Reduction
Patient 1	64	4.30 ±0.20	1.80 ±0.10	55.81	1.20±0.10	72.09	0.84±0.05	80.47
Patient 2	59	6.31 ±0.02	3.04 ±0.03	51.29	1.89±0.03	70.10	1.07±0.04	83.10
Patient 3	77	3.37 ±0.15	1.00 ±0.12	68.32	0.69±0.12	79.60	0.60±0.03	82.18
Patient 4	72	7.91 ±0.02	5.37±0.02	22.62	5.42±0.05	31.55	4.80±0.06	39.39
Patient 5	52	4.27 ±0.21	2.90±0.15	28.13	2.18±0.15	48.98	1.51±0.03	64.61
Patient 6	74	6.10 ±0.20	4.90±0.06	20.22	3.77±0.06	38.25	3.43±0.06	43.72
Patient 7	46	4.87±0.15	2.40±0.10	50.68	1.71±0.10	64.86	1.03±0.04	78.77
Patient 8	80	5.37 ±0.21	3.40±0.21	33.54	2.80±0.21	47.76	2.17±0.05	59.63
Patient 9	45	9.27 ±0.21	6.50±0.06	29.14	5.60±0.06	39.57	4.70±0.20	49.28
Patient 10	50	9.40 ±0.26	6.20±0.15	34.40	5.67±0.15	39.72	4.67±0.12	50.35
Patient 11	83	4.23 ±0.06	3.76±0.02	10.71	2.60±0.02	38.58	2.08±0.16	50.94
Patient 12	55	5.84 ±0.20	2.60±0.12	54.31	1.74±0.12	70.13	1.12±0.06	80.81

Normal range: Creatinine-0.7-1.3mg/ml, Blood urea-6-24mg/dl, Uric acid-3.5-7.2mg/dl, and Hemoglobin – 14-18 gms%

Analyses of Blood Urea: Among the 12 human subjects, patients 1, 3, 8, 9, 10, 11, and 12 were subjected to blood urea analyses indicating an excellent reduction of urea in the blood. All tested patients revealed significant urine output and improvement in loss of appetite after treatment with renal support for one month. A substantial decline in blood urea was also observed in most of the patients (Table 2 & 3). The reduction of blood urea in most of the patients ranged from 56 to 67% and the minimum percentage of reduction of blood urea was found to be 43% and 45%. The highest reduction of blood urea was noticed in 64 and 55 years old patients corresponding to a 66.67% and 61.22% decline in blood urea. Statistical analysis of experimental data indicated the significant with p value 0.007 when analysed with 95% confidence limit.

Table 2: Blood urea analyses in patients treated with Renal Support

Human Subjects	Age (Years)	Blood Urea (mg/dl)		
		0 day treatment	30 days treatment	% Reduction
Patient 1	64	91.33	30.33	66.67
Patient 3	77	56.67	24.00	57.40
Patient 8	80	105.33	57.3 3	45.91
Patient 9	45	129.00	56.67	56.19
Patient 10	50	116.33	66.00	43.91
Patient 11	83	31.00	39.67	-27.96
Patient 12	55	160.00	61.67	61.22

Hemoglobin content: In patients treated with Renal Support increased Hemoglobin contents were observed followed by one-month of treatment. Around 31% and 24% of the increase in hemoglobin concentration were noticed in patient 9 and patient 10 respectively (Table 3). Patient 1 and patient 12 showed 21.63% and 16.62% hemoglobin when treated with Renal Support (Figure 4). Results indicated substantial nephroprotective potential of Renal Support with statistically significant value p=0.005.

Table 3: Hemoglobin content of patients treated with Renal Support

Human Subjects	Age (Years)	Hemoglobin (g%)		
		0 day treatment	30 days treatment	% Reduction
Patient 1	64	8.33	10.63	21.63
Patient 9	45	7.27	10.57	31.23
Patient 10	50	8.90	11.77	24.36
Patient 12	55	9.20	11.03	16.62

Cytotoxicity Assay of Renal Support: BHK-21 cells were treated with different concentrations of Renal Support ranging from 31.25 to 1000µg/ml. The growth of BHK-21 cell was inhibited with increased concentration of Renal Support in a dose-dependent manner. The highest inhibition of growth of BHK-21 cells i.e., 37% was noticed at 1000µg/ml of Renal formulation. The Renal Support was found to be safe after 250µg/ml onwards when tested on BHK-21 cells with statistical significant value $p<0.001$. However, the determination of the CTC_{50} value of Renal Support on BHK-21 cells was found to be greater than 1000µg/ml (Table 4 and Figure 5). Hence, cytotoxicity results indicated that the Renal Support was found to be safe and non-toxic to BHK-21 cells.

Table 4: Inhibition of growth of BHK-21 cells by Renal Support

Conc. Renal Support (µg/ml)	% Cytotoxicity	CTC50 (µg/ml)
1000	37.97±2.15	>1000
500	24.64±2.77	
250	13.41±0.45	
125	8.19±3.02	
62.5	0.80±0.45	
31.25	0.51±0.57	

The Nephroprotective Potential of Renal Support: Furthermore, the nephroprotective activity of Renal Support evaluated at 125µg/ml and 250µg/ml in H_2O_2 toxicity induced BHK-21 cells showed a significant percentage of cell protective activity when compared to the protective activity of positive control ascorbic acid. The formulation showed 40.92% and 47.54% nephroprotective activity over H_2O_2 induced toxicity control in BHK-21 cells when treated at 125 and 250µg/ml concentration of Renal Support. However, the percentage of protection of H_2O_2 toxicity induced BHK-21 cells by 100µM of Ascorbic acid was found to be 55% (Table 5). Therefore, the Renal Support tested on BHK-21 revealed non-toxic activity and significant nephroprotective activity.

Table 5: Nephroprotective Potential of Renal Support against H_2O_2 induced toxicity in BHK-21 cells

Sample	Concentration tested	% Protection over H2O2 induced control
Renal Support	125 µg/ml	40.92±2.592
	250 µg/ml	47.54±3.79
Ascorbic acid	100 µM (17.61µg/ml)	55.02±2.75

The therapeutic potential of Renal Support therapy in combination with S3 and S4 was found to be significant in treating CKD-associated human subjects as witnessed by the decrease in creatinine, blood urea, and increased hemoglobin content. Renal Support formulation has proven safe in the treatment of CKD patients and possesses significant nephroprotective activity as evidenced by cytotoxicity studies conducted on BHK-21 cells.

Figures

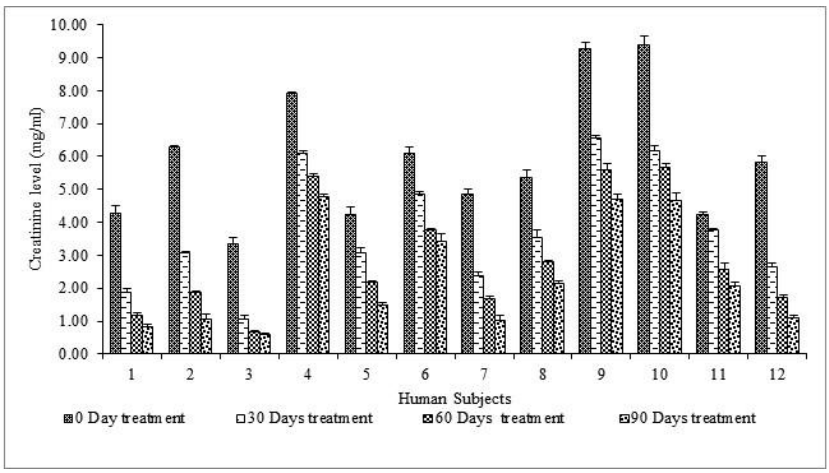

Figure 1: Bar graph representation of creatinine level in Renal Support treatment patients

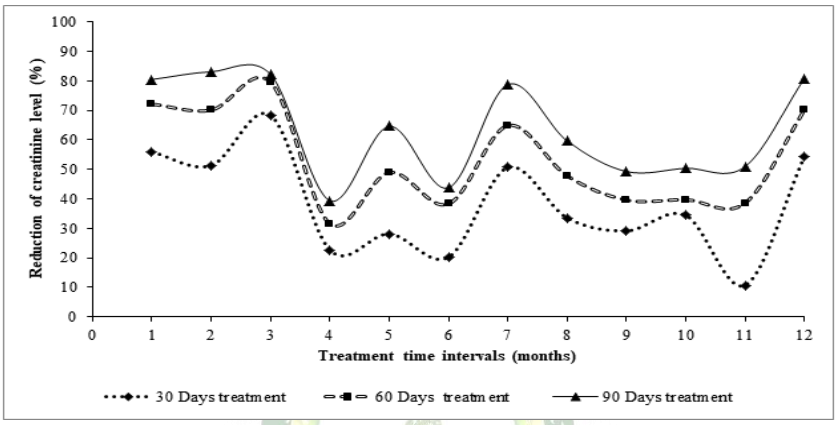

Figure 2: Percentage reduction of creatinine level in Renal Support treated patients

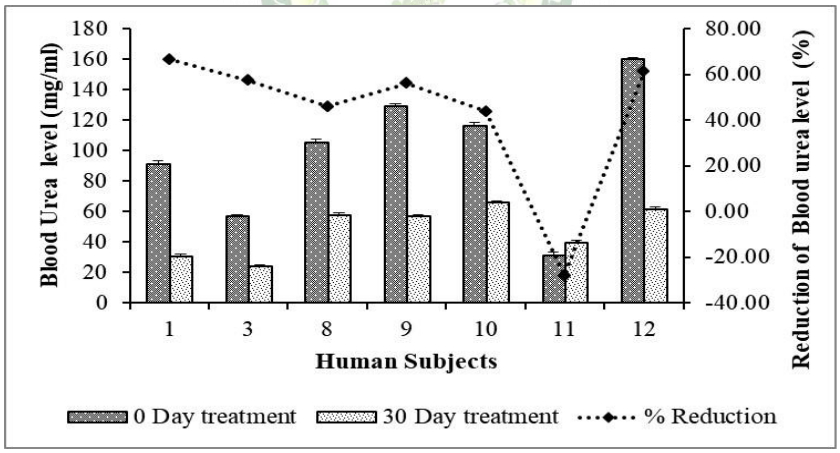

Figure 3: Graphical representation of blood urea level in treatment groups

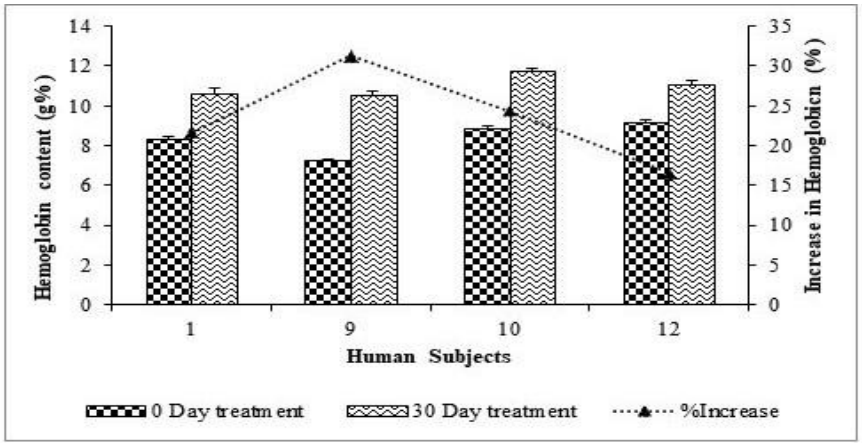

Figure 4: Hemoglobin level and its % increase observed in Renal Support treated patients

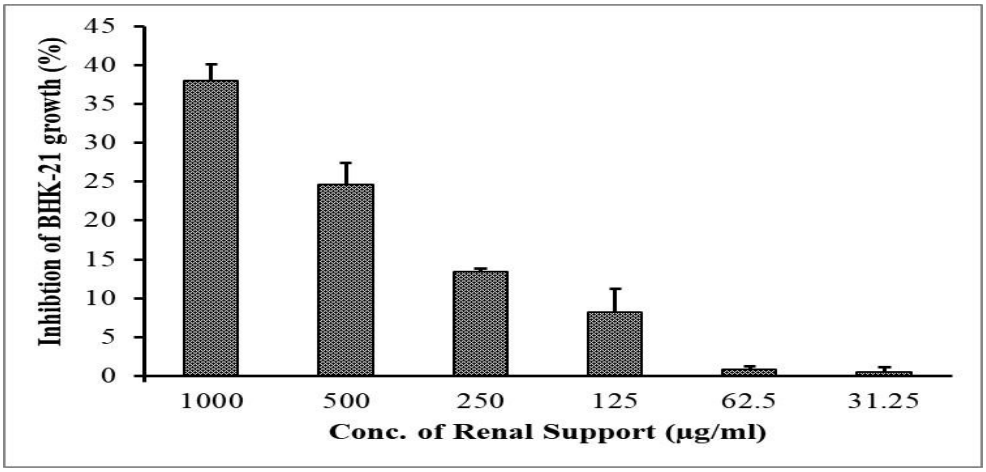

Figure 5: Determination of cytotoxicity of Renal Support on BHK-21 cell lines

DISCUSSION

One of the great challenges that faced by medical science in treating CKD is the disease is associated with other complications such as diabetes, cardiovascular diseases and hypertension, etc rather than being a single disease. As a progressive disease, CKD has no cure and is one of the serious concerns of the low and middle-income nations that is associated with high mortality and morbidity. Pharmaceutical treatment strategies for CKD include the usage of inhibitors of SGLT2 (Sodium-glucose Cotransporter-2) and renin-angiotensin-aldosterone pathway modulators to preserve functions of the kidney and protection of kidney using novel antagonists of non-steroidal mineralocorticoid receptor.[11] CKD optimal management comprises reducing the risk of cardiovascular diseases using statins, albuminuria treatment by inhibitors of angiotensin-converting enzymes, prevention of potential nephrotoxins usage to avoid AKI, and monitoring other patients complications like hyperphosphatemia, hyperkalemia, anemia, and hyperparathyroidism, etc.[7]

Non-pharmaceutical approaches for CKD treatment such as changing lifestyle, dietary adjustment, management of risk factors, and herbal-based Ayurveda therapy drawing more attention in recent days as the pharmaceutical strategies are costly and possess severe side effects. Herbal-based therapies are cheap, have lesser side effects and are accessible to the common population, and on the long-term treatment, they provide a permanent solutions. Even western countries like the US used herbals for around 25% of medicine between 1990 and 1997.[12] It has been estimated by Insight SLICE that the global market size of herbal medicine is anticipated to increase from US$ 83 billion in 2019 to US$ 550 billion in 2030.[13]

Plant played a significant role in treating kidney diseases for thousands of years. Several Chinese herbal medicines have been reported to possess the therapeutic potential for CKD with other complications like anemia, idiopathic membranous nephropathy, primary nephrotic syndrome, etc. Herbal medicine prepared from *Polyporus umbellatus, Centella asiatica, Acacia Senegal, Vachellia (Acacia) seyal,* and Abelmoschus manihot are used treatment of CKD.[14] The Ayurvedic formulation "Renal Support", a miracle drink evaluated for its therapeutic potential on 12 human subjects with known CKD in the present investigation witnessed significant results. After one month of treatment with formulation CKD patients showed an excellent recovery as evidenced by high-level urine output, reduction of edema, and improved decline in loss of appetite. The therapeutic potential of Renal Support formulation was further supported by a drastic decline in serum creatinine content in CKD patients after three months of treatment. During 90 days of treatment maximum patients showed a substantial decrease in creatinine that ranged from 50 to 83%. The formulation was successfully declined the blood urea and substantially increased hemoglobin content in CKD patients after 30 days of treatment. Cytotoxicity studies of Renal Support assessed indicated no cytotoxicity and the formulation was found to be safe for the treatment of CKD patients. Additionally, the formulation revealed excellent nephroprotective potential when tested in 12 well-known CKD patients. Hence, a novel therapy is proposed in the current investigation for the treatment of CKD in humans and therapy needs further scientific evaluation to study the underlying molecular mechanism in justifying its therapeutic potential.

CONCLUSION

Patients with CKD and other complications showed significant improvement in kidney diseases when treated with Renal Support in combination with S3 and S4 formulations. In this process the edema is completely disappearing in 10 days to 15 days, the patient who are having uncontrolled BP will be getting in to normal within 20 days and similarly those who

are not having sleeping, they can get sleep within 10 days and also appetite will improves, weight gain well reduces within 10 days from one dialysis to another and number of dialysis will start dropping within 15 days strict renal diet should be followed for effective results and those who are having allopathic medication in which except BP and diabetes medicine other medications such as statins, blood thinner, uric acid medicines and other supplements related to sodium, calcium, vitamin D, vitamin B12 can be stopped. The patients who are having diabetes medication, they have to taper down the medications within 3 to 4 days by observing the sugar level, similarly BP patients have to taper down the medications after 15 days of the treatment by observing the BP level. The patients can be seen the impact in the body within 3 to 10 days. Those patients who are having creatinine level up to 12 with good urination and without having breathing problem and having the haemoglobin level more than eight can overcome from the dialysis, during the course of the treatment laid down diet and home remedies should be followed religiously. Further cytotoxicity studies of formulation indicated no toxicity on BHK-12 cells and showed potent nephroprotective activity when tested on BHK-12 cell lines.

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***Address for correspondence**
Dr. S. M. Raju
M/s Mallur flora & Hospitality Pvt ltd, R.T. Nagar Main Road, Bangalore, Karnataka.
Email: smraju777@gmail.com