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Original Research Paper

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TO STUDY THE EFFECT OF CITRULLUS COLOCYNTHIS IN PATIENTS WITH DIABETIC NEPHROPATHY.

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ABSTRACT

Background: Diabetic nephropathy (DN) or diabetic kidney disease is a syndrome characterized by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, and loss of glomerular filtration rate (GFR) in diabetics. The "Citrullus colocynthis" is a member of the Cucurbitaceae family that is known as "bitter apple" globular bitter fruit. Researches have shown that the use of CCT extract leads toa reduction in glycosylated hemoglobin, The regulation of fasting blood glucose levels, and induction of insulin secretion. It has antioxidant effects and daily intake of 300 mg/kg of CCT seed powder results in a significant reduction in cholesterol and triglyceride levels in hyperlipidemia patients. It is a proven antioxidant, antimicrobial, antimalarial, hepatoprotective, Extracts of C. Colocynthis peel–aqueous, alkaloidal, saponin, and glycosidic–were examined for their effects on plasma glucose levels in rabbits. **Objective:** To estimate the levels of serum FBS, Urea, Creatinine, Plasma Glycated Haemoglobin (HbA1c) Urinary Microalbumin/Creatinine ratio. **Methodology:** The study was carried out at the Department. of Biochemistry, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda, District Kangra, Himachal Pradesh, India. Eighty participants were divided into an intervention group (receiving aqueous extract of Citrullus colocynthis at 1-2 ml/per day in divided doses for 8 weeks) and a control group (receiving placebo for same duration) with forty participants in each group. Exclusion Criteria: Subject's refusal, Subjects with chronic illness like tuberculosis, cancer or immune-compromised states, thyroid disorders, smokers, taking drugs like steroids, immunosuppressant. Inclusion Criteria: The patient suffering from diabetic nephropathy both sexes having age group of 18-70 years. **Result:** As per statistical analysis a significant drop the levels of serum fasting blood glucose and glycated haemoglobin (HbA1c) at 95% confidence interval (p=0.0121, p=0.0423) respectively in the case group when compare with pre-treatment and post treatment with Citrullus Colocynthis. But is no positive change in levels of serum urea, creatinine and urinary albumin/creatinine and ration in case as well as placebo groups. **Conclusion:** The present study shows that extract of C. Colocynthis fruit were have systemic therapeutic effect on lowering of blood glucose levels in type II diabetic nephropathy patients.

KEYWORDS : Diabetic nephropathy (DN), Citrullus colocynthis, Glycated Haemoglobin (HbA1c) Urinary Microalbumin/Creatinine ratio.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease caused by the body's inability to use insulin effectively or the cessation of hyperglycemia (increased sugar level in the blood) resulting from insufficient insulin production. The risk of ischemic heart disease and stroke increases 2-3 times in adults with diabetes. [1] Also, diabetic neuropathy (DN) causes involvement of the feet and ultimately leads to amputation of the limbs. Diabetes worldwide the world population has grown from 108 million in 1980 to 422 million in 2014. The prevalence of DM among adults aged 18 years and older increased by 4.7% in 1980 to 8.5% in 2014. [2] Rates are higher for low and low rates. middle-income countries. 1.5 million people died from diabetes in 2012. Almost half of all deaths from hyperglycemia occur before the age of 70. 2 The World Health Organization (WHO) predicts that diabetes will be the seventh cause of death by 2030. [3] most common cause of chronic kidney disease. Among adults, DN now accounts for at least 46% of chronic kidney disease. [4] The pathogenesis and development of DN may result from the interaction of metabolic and hemodynamic methods, which are often associated with the problem of diabetes. The metabolic and hemodynamic abnormalities seen in diabetes may be related to the pathways involved in the production of reactive oxygen species (ROS). The interaction of metabolic stimuli, hemodynamic factors and various reactive oxygen species affect gene regulation and activation in diabetes. Molecular activation and inhibition of various pathways lead to activity and changes that manifest clinically as DN, characterized by increased albuminuria and decreased renal function. Diabetic nephropathy (DN) or diabetic nephropathy is a condition caused by pathological albumin excretion, diabetic glomerulopathy, and decreased glomerular filtration rate (GFR) in diabetic patients. Diabetes can be divided into type 1 (autoimmune 3 cell damage and insulin deficiency), type 2 (relative insulin deficiency and resistance), and others (such as pancreatic disease). In 2015, the International Diabetes Federation estimated the prevalence of diabetes among people aged 20 to 79 to be 8.8%, affecting approximately 440 million people.[5] This number is expected to reach more than 550 million people by 2035.[6] An important aspect of diabetes treatment is its relationship with chronic tissue. Short-term hyperglycemia does not cause serious medical problems. The duration and severity of hyperglycemia are important causes of organ damage. Early morphological manifestations of kidney injury include kidney swelling and Doppler changes, but damage is best determined by proteinuria and glomerular filtration rate (GFR).[7] During the first 10 to 20 years after the onset of diabetes, the mean incidence of diabetic nephropathy is high (3% per year). The formation of small vessels in organs such as kidneys, eyes and nerves generally takes about 15 years. Based on the number of people with end-stage renal disease (ESKD) who need kidney treatment, it is estimated that more than 20% and up to 40% of patients will have chronic kidney disease (CKD). [8,9]

Citrullus colocynthis and belongs to the Cucurbitaceae family. It is often called bitter apple or kolokinth (Pravin et al., 2013).[10]

C. colocynthis is a perennial plant that grows well in sandy soils of West Punjab, Sindh, and central and southern India. It is also found in Arabia, Western Asia, tropical Africa, and the Mediterranean region (Borhade Pravin et al 2013).[10] Medicines are fruits, roots, and leaves. Indian Ayurvedic Pharmacopoeia states that its fruit is used to treat jaundice, its root to treat liver and spleen diseases, and its leaves to treat skin diseases and hair loss (Cp khare et al). It has traditionally been used in the treatment or prevention of many diseases such as diabetes, constipation, rheumatism, jaundice, malaria.

Citrullus colocynthis has been used medicinally for centuries. It is mentioned in the ancient Egyptian medical book Ebers Papyrus and was also used by Greek and Roman physicians. The plant is still used medicinally in many parts of the world, including India, China, and the Middle East. However, it is worth noting that the fruit can be toxic in large doses. It can cause nausea, vomiting, diarrhea, and even death. Therefore, it is important to use this plant under the guidance of a specialist doctor. Some of the herbal uses of the fruit are:

Laxatives and laxatives: The aromatic properties of the plant can irritate the intestines and stimulate bowel movement. Lifting. It is often used to treat constipation and other gastrointestinal problems.

Anti-diabetic: The plant has been shown to lower blood sugar in diabetics.

Anti-inflammatory: The plant's compounds have anti-inflammatory properties that help reduce pain and inflammation.

Anti-cancer: The compounds of the plant have been shown to have anti-cancer properties. Diabetic nephropathy (DN) is the main disease of diabetes (DM), which eventually leads to chronic kidney failure. People with diabetes are ten times more likely to develop end-stage kidney disease. The International Diabetes Federation (IDF) reported that 40 percent of people with diabetes may end up with kidney failure. In addition, diabetes, and high blood pressure together or alone cause about 80% of end-stage renal disease.[11]

MATERIAL& METHODS:

Study design and study subjects:

The study commenced after obtaining approval from the Protocol Review and Institutional Ethics Committee. Subjects were selected from T2DM with nephropathy patients coming to Department of Biochemistry, Dr. Rajendra Prasad Government Medical College, and Hospital Kangra at Tanda for clinical investigations. Voluntarily willing subjects were recruited for the study. Eighty T2DM with nephropathy patients were taken for the study. Eighty participants were divided into an intervention group and other as control group each consisting of 40 participants. Patients from intervention group were given aqueous extract of Citrullus colocynthis at 1-2 ml/per day for 8 weeks and in control group placebo was given for same duration. Written consent was obtained, and detailed clinical history was collected in a self-prepared questionnaire. Questionnaire comprised of Name, Age, Gender, Occupation, Address, Food Habits, History of smoking and alcohol intake. In Medical history duration of diabetes and hypertension were recorded. All the patients in both groups continued with their anti-diabetic drugs as usual.

General data collection: General data age, sex and other demography data were taken from the subject who attend outdoor as well indoor in Dr. Rajendra Prasad Government Medical College, Tanda at Kangra, Himachal Pradesh,

Blood samples: Blood samples were taken at the beginning and end of the 8th Week (56th Day) of the study to compare the mean fasting blood sugar (FBS), Glycated hemoglobin (HbA1c), Serum Urea, Serum Creatinine and Urinary Albumin/ Creatinine Ratio (UACR) levels in each group before and after intervention. Patients in the intervention group received Citrullus colocynthis per day justbefore meals, and controls group received the placebo at the same time.

Statistical Analysis: The data was analyzed using Student t-test between the groups by Statistical Package for Social Sciences (SPSS) software version 20. Data was expressed as mean ± standard deviation (SD) for continuous variables. Values with $p < 0.05$ calculated at 95 % confidence limit, were considered statistically significant.

RESULT:

The T2DM with nephropathy group comprised of 23 males and 17 females whereas the T2DM group administered Citrullus colocynthis extract comprised of 18 males and 22 females (Table 1).

Table 1: Sex distribution of T2DM with nephropathy patients and T2DM with nephropathy patients administered Citrullus colocynthis extract

	Number of T2DM With Nephropathy (N = 40)	Number of T2DM With Nephropathy+ CC Extract (N = 40)
Males	23	18
Females	17	22
Vegetarian	26	12
Alcoholics	8	6
Smokers	32	34

As far as the food preferences were concerned, 26 patients were vegetarian and rest were non-vegetarian in the T2DM with nephropathy group however, 12 patients were vegetarian and 28 were non-vegetarians in the T2DM group administered Citrullus colocynthis extract respectively (Table 1). In the T2DM with nephropathy group, 8 patients were alcoholic as compared to 6 patients who were alcoholic in T2DM group administered Citrullus colocynthis extract (Table 1). As far as the smoking profile was concerned 32 patients were smoker in the T2DM with nephropathy group whereas, 34 out of 40 patients were smoker in T2DM patients administered Citrullus colocynthis extract (Table 1)

Table 1: Serum & Urine Parameters of T2DM with nephropathy patients and T2DM with nephropathy patients administered Citrullus colocynthis extract.

Parameter (Serum& Urine)	Number of T2DM With Nephropathy (N = 40)			Number of T2DM With Nephropathy+ CC Extract (N = 40)		
	Week O (1st Day)	Week 8th (56th Day)	p value	Week O (1st Day)	Week 8th (56th Day)	p value
FBS (mg/dl)	208.4±54.91	199.1±50.1	p=0.43	232.1±70.6	150.3±53.7	p<0.05
HbA1c (g, %)	8.7±1.15	8.6±1.8	p=0.52	8.31±1.39	6.68±1.31	p>0.05
Serum Urea(mg/dl)	83.3±30.4	85.35±30.6	p=0.76	103.65±39.5	113.8±38.8	p=0.24
Serum Creatinine(mg/dl)	3.41±1.2	3.42±1.06	p=0.95	3.91±1.67	4.13±1.67	p=0.5
Urinary Albumin(g/dl)	280.05±87.7	294.39±123	p=0.54	499.3±310	503.775±325	p=0.94
Urine Creatinine(mg/dl)	63.75±17.6	65.31±16.07	p=0.68	63.32±33.78	59.5±35.78	p=0.63
Urine Albumin/Creatinine Ratio(mg/g)	4692.4±1778	4795.09±2284	p=0.82	9142.21±6892	9771.79±5831	p=o.66

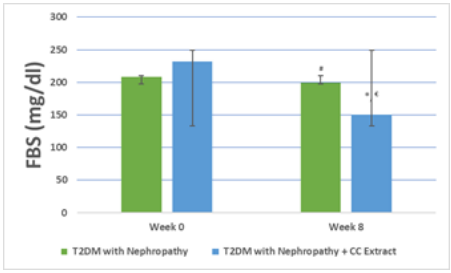

Figure 1: Histogram showing fasting blood sugar (FBS) levels of T2DM with nephropathy patients and T2DM patients administered Citrullus colocynthis extract.

Values are expressed as mean ± SD; (N = 40). # Different from T2DM with nephropathy group at week 0. *Significantly different from T2DM with nephropathy administered *Citrullus colocynthis* extract group at week 0. €Significantly different from T2DM with nephropathy group at week 8. ($p < 0.05$).

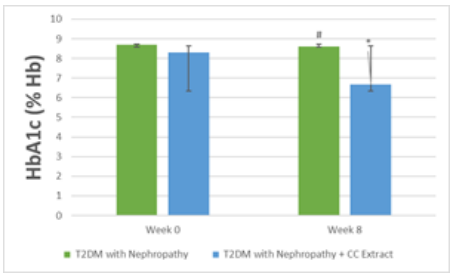

Figure 2: Histogram showing glycated hemoglobin (HbA1c) levels of T2DM with nephropathy patients and T2DM with nephropathy patients administered *Citrullus colocynthis* extract.

Values are expressed as mean ± SD; (N = 40). #Different from T2DM with nephropathy group at week 0. *Significantly different from T2DM with nephropathy administered *Citrullus colocynthis* extract group at week 8.($p < 0.05$).

Citrullus colocynthis from week 0 in the two groups individually as compared to week 8 ($p < 0.05$) respectively. However, Significant difference was observed in the mean HbA1c values at week 8 between the T2DM with nephropathy group and T2DM with nephropathy group administered *Citrullus colocynthis* extract respectively (**Table 2 & Figure 2**).

DISCUSSION

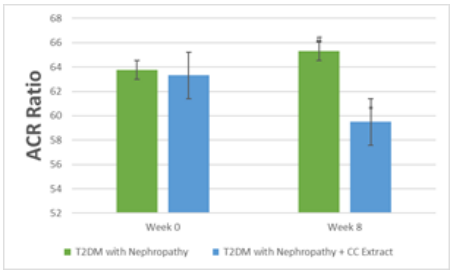

Figure 3: Histogram showing Urinary albumin / creatinine ratio of T2DM with nephropathy patients and T2DM with nephropathy patients administered *Citrullus colocynthis* extract.

Values are expressed as mean ± SD; (N = 40). #Different from T2DM with nephropathy group at week 0. *Not statically significantly different from T2DM with nephropathy administered *Citrullus colocynthis* extract group at week 8. ($p = 0.66$). (Table2)

DISCUSSION:

In the present study a statistically significant variance in the mean fasting blood sugar (FBS) levels was identified between two distinct groups: those afflicted with Type 2 Diabetes Mellitus (T2DM) accompanied by nephropathy. The first group exhibited a mean FBS value of 208.4±54.91 at the onset of the study, while the second group, treated with Citrullus colocynthis, displayed an initial mean FBS value of 232.1±70.6 at Week 0. After 8 weeks of intervention, noteworthy alterations in FBS levels were observed, with the T2DM with nephropathy group revealing a mean FBS value of 199.1±50.1, in contrast to the T2DM with nephropathy group administered Citrullus colocynthis extract, which exhibited a mean FBS value of 150.3±53.7. Furthermore, a substantial reduction ($p < 0.05$) was noted in the mean FBS values at the 8th-week mark when comparing the two groups: the T2DM with nephropathy group and the T2DM with nephropathy.

In contrast, the T2DM with nephropathy + CC Extract group exhibited a slightly lower mean HbA1c level of 8.31%, accompanied by a standard deviation of ±1.39. Upon analyzing the data at Week 8, a pivotal juncture in the study: The T2DM with nephropathy group displayed a modest decline in mean HbA1c levels, settling at 8.6%, albeit with a somewhat increased standard deviation of ±1.8. Intriguingly, the T2DM with nephropathy + CC Extract group demonstrated a notable and statistically significant reduction in mean HbA1c levels, which plummeted to 6.68%, accompanied by a standard deviation of ±1.31. The remarkable finding of a p-value less than 0.05 ($p<0.05$) underscores a compelling and statistically significant disparity in HbA1c levels between the two groups at Week 8. This outcome suggests a potential therapeutic benefit of Citrullus colocynthis extract in improving long-term blood glucose control in individuals grappling with T2DM and nephropathy, offering a glimmer of hope for enhanced glycemic management in this patient population. At the outset of the study (Week 0), the T2DM with nephropathy group exhibited a mean serum urea level of 83.3±30.4, while the T2DM with nephropathy + CC Extract group had a slightly higher mean serum urea level of 103.65±39.5. This baseline data indicated that the two groups had distinct serum urea levels at the start of the study. Upon reevaluation at Week 8, both groups displayed an increase in serum urea levels. The T2DM with nephropathy group had a mean serum urea level of 85.35±30.6, while the T2DM with nephropathy + CC Extract group exhibited a higher mean serum urea level of 113.8±38.8. Importantly, despite these increases over the 8-week period, there were no statistically significant differences observed between the two groups at either time point.

At the study's outset (Week 0), the T2DM with nephropathy group displayed a mean serum creatinine level of 3.41±1.2, while the T2DM with nephropathy + CC Extract group had a slightly higher mean level of 3.91±1.67. However, at Week 8, both groups exhibited modest increases in serum creatinine levels. The T2DM with nephropathy group recorded a mean level of 3.42±1.06, while the T2DM with nephropathy + CC Extract group showed a higher mean level of 4.13±1.67. Importantly, statistical analysis indicated that these changes were not statistically significant.

The p-value of 0.5 suggests that there were no statistically significant differences between the two groups at either time point. This implies that the administration of Citrullus colocynthis extract did not lead to significant short-term alterations in serum creatinine levels compared to the T2DM with nephropathy group not receiving the extract. While these findings provide valuable insights, it's essential to recognize that managing nephropathy in T2DM patients often requires longer-term strategies. Further research over extended periods may offer a more comprehensive understanding of the potential effects of CC extract on renal function in this patient population. Nonetheless, the absence of adverse effects in this

study is a promising starting point for future investigations into nephropathy management.

Urinary albumin levels were assessed at two pivotal time points, Week 0 and Week 8, to explore potential changes in renal function. At the commencement of the study (Week 0), the T2DM with nephropathy group exhibited a mean urinary albumin level of 280.05±87.7, while the T2DM with nephropathy + CC Extract group had a notably higher mean level of 499.3±310. This baseline data indicated that the two groups had distinct urinary albumin levels at the initiation of the study.

Upon re-evaluation at Week 8, both groups displayed an increase in urinary albumin levels. The T2DM with nephropathy group recorded a mean urinary albumin level of 294.39±123, while the T2DM with nephropathy + CC Extract group showed a higher mean level of 503.775±325. Importantly, the statistical analysis revealed that these changes were not statistically significant. The p-value of 0.94 indicates that there were no statistically significant differences between the two groups at either time point. This suggests that the administration of Citrullus colocynthis extract did not lead to significant short-term alterations in urinary albumin levels compared to the T2DM with nephropathy group not receiving the extract. While these findings may suggest a lack of immediate impact of CC extract on urinary albumin levels in T2DM patients with nephropathy, it's essential to recognize that nephropathy management is often a long-term endeavor. Further research over extended periods may provide more comprehensive insights into the potential effects of CC extract on renal function and urinary albumin levels in this patient population.
The objective was to investigate potential changes in renal function by measuring urinary creatinine levels at two key time points, Week 0 and Week 8. At the commencement of the study (Week 0), the T2DM with nephropathy group exhibited a mean urinary creatinine level of 63.75±17.6, while the T2DM with nephropathy + CC Extract group had a comparable mean level of 63.32±33.78. This baseline data indicated that the two groups had similar urinary creatinine levels at the outset of the study. Upon reevaluation at Week 8, both groups displayed modest changes in urinary creatinine levels. The T2DM with nephropathy group recorded a mean urinary creatinine level of 65.31±16.07, while the T2DM with nephropathy CC Extract group exhibited a slightly lower mean level of 59.5±35.78. Importantly, the statistical analysis revealed that these changes were not statistically significant. The p-value of 0.63 indicates that there were no statistically significant differences between the two groups at either time point. This suggests that the administration of Citrullus colocynthis extract did not lead to significant short-term alterations in urinary creatinine levels compared to the T2DM with nephropathy group not receiving the extract.

These findings suggest that CC extract did not have a notable impact on urinary creatinine levels in T2DM patients with nephropathy within the study's duration. However, it's crucial to consider that urinary creatinine levels are influenced by various factors, and longer-term studies may be necessary to comprehensively assess the potential effects of CC extract on renal function in this patient population. Additionally, monitoring other renal markers and clinical parameters over an extended period could provide a more comprehensive understanding of the extract's impact on nephropathy management.

The Urine albumin/creatinine ratio (UACR) serves as a crucial marker for evaluating renal function and potential changes in nephropathy management. At the initiation of the study (Week 0), the T2DM with nephropathy group exhibited a mean UACR of 4692.4±1778, while the T2DM with nephropathy + CC Extract group had a notably higher mean UACR of 9142.21±6892. These baseline measurements indicated a significant difference in UACR levels between the two groups. Upon reevaluation at Week 8, both groups displayed increases in UACR levels. The T2DM with nephropathy group recorded a mean UACR of 4795.09±2284, while the T2DM with nephropathy + CC Extract group showed a higher mean UACR of 9771.79±5831. However, it is noteworthy that the statistical analysis revealed that these changes were not statistically significant. The p-value of 0.66 suggests that there were no statistically significant differences between the two groups at either time point.

These findings suggest that the administration of Citrullus colocynthis extract did not lead to significant short-term alterations in UACR compared to the T2DM with nephropathy group not receiving the extract. While these results indicate that CC extract did not have a substantial immediate impact on UACR levels in T2DM patients with nephropathy, it's essential to acknowledge that managing nephropathy is often a long-term endeavor. Further research over extended periods may provide more comprehensive insights into the potential effects of CC extract on renal function and UACR levels in this patient population. Additionally, exploring a broader range of clinical parameters and renal markers may offer a more comprehensive understanding of the extract's potential role in nephropathy management. In a study done by Youshan Li et al., (2015) the Citrullus colocynthis, A daily dosage of 1 gram was administered to a cohort of diabetic patients over a 30-day period, with the dosage divided into two equal parts and administered at 12-hour intervals. Subsequently, a washout phase spanning from day 30 to day 40, encompassing 10 days, transpired during which no dosage was administered; nevertheless, blood samples were procured on day 40 for the evaluation of drug efficacy. This investigation elucidates that the utilization of Citrullus colocynthis for the stipulated 30-day duration elicited a noteworthy reduction ($p < 0.05$) in the serum glucose levels of diabetic subjects in comparison to their baseline levels on day 0. The data manifest a 35% decline in serum glucose levels among diabetic individual's consequent to the administration of a 1-gram dose of Citrullus colocynthis.[12]

CONCLUSION:

The study's key findings revealed statistically significant differences in mean FBS and HbA1c values within each group from Week 0 to the 8th week. Notably, there was a significant reduction in both FBS and HbA1c values between the T2DM group and the T2DM group with nephropathy, who were administered Citrullus colocynthis extract. These results suggest a potential beneficial effect of Citrullus colocynthis extract in improving glycemic control in both T2DM and T2DM with nephropathy patients. It is important to acknowledge that this study provides valuable insights into the potential therapeutic benefits of Citrullus colocynthis extract in diabetes management. However, further research, including larger sample sizes and longer-term follow-up, is necessary to confirm these findings and elucidate the underlying mechanisms of action. Additionally, the influence of dietary preferences, alcohol consumption, and smoking habits on treatment outcomes should be explored in more detail in future studies.

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