The present study was designed to investigate the role of Rutin, on nephropathy, one of the serious complications associated with diabetes. The total trial was conducted with a gap of 60 days each. The trial consisted 50 patients who were having diabetes mellitus since last 10 years. The targeted patients were in the age group of 50-60 years. All of these patients were given Rutin Supplementation Tablets over the period of 120 days along with their regular medications. Serum Urea & Serum Creatinine were measured at baseline and then after every 60 days i.e. on 60th & 120th Day. Then Rutin Supplementation tablets were stopped for the next 120 days but their regular medication was not altered. The Serum Urea & Serum Creatinine was again measured at the end of 180th & 240th day. The results showed that rutin decreased the levels of Serum Urea and Serum Creatinine in patients with diabetes mellitus which lowered the chances of kidney damage.

Key words: Rutin, Nephropathy, Serum Urea, Serum Creatinine

INTRODUCTION

Flavonoids are dietary phenolic compounds. These flavonoids are distributed widely in nature and are found in plants, fruits, seeds and vegetables. Flavonoids are characterized by anti inflammatory, antiviral, antioxidant, hepatoprotective, antithrombotic, anticarcinogenic, and other biological effects.\cite{1}

Rutin (3, 3’, 4’, 5, 7-pentahydroxyflavone-3-rhamnoglucoside) is one of the flavonoid of the flavonol type.

![Chemical structure of the rutin.](image)

Rutin is found in many plants and it also constitutes an important dietary constituent of food and plant-based beverages.\cite{2} Rutin has many pharmacological properties e.g. anticarcinogenic, cytoprotective, antiplatelet, antithrombic, vasoprotective and cardio protective activities.\cite{1,2,3,4} It was also proved in an in vitro study that rutin is the major low-density lipoprotein (LDL) antioxidant compound of mulberry.\cite{5}

Diabetes is a metabolic disorder in which human body either does not produce insulin or does not properly use insulin. Insulin is a naturally occurring hormone that is required to convert sugar, starches, and other food into energy.\cite{6,7,8}

Most of the people have “type 2 diabetes” i.e Adult Onset Diabetes. In this type, the body does not produce enough insulin or the insulin is not able to transfer glucose into cells. On the other hand people with “Type 1 diabetes” i.e. Juvenile Onset Diabetes has a condition in which the body is not able to produce any insulin at all. People with this kind of diabetes have to depend on insulin and close monitoring to control their blood sugar level throughout their life.\cite{9,10}

According to a research conducted by the World Health Organization (WHO) and several European universities, the number of people with diabetes will double worldwide by 2030.\cite{11}

Blood glucose levels if left uncontrolled can damage the body’s organs. Possible complications include damage to large and small blood vessels, which can lead to heart attack, stroke and problems with the kidneys, eyes, feet and nerves.

However this article focuses only on the patients with “Type-2 Diabetes” who have developed nephropathy after some time. The proteins eaten by us turns in waste product through a process. Capillaries, millions of tiny blood vessel with even tinier than holes in them act as filters in kidneys.

Small molecules such as waste products squeeze through the holes as blood flows through the blood vessels. In this way the waste products become part of the urine. Other useful substances such as protein and red blood cells stay in the blood as they are too big to pass through the holes in the filter.

This system is damaged by diabetes. High levels of blood sugar make the kidneys filter too much blood. All this extra work is hard on the filters. Over a period of time, they start to leak and useful protein is lost in the urine. Having small amounts of protein in the urine is called micro albuminuria. Having larger amounts of protein in the urine is called macro albuminuria. End-Stage Renal Disease (ESRD) usually follows if the disease is caught during macro albuminuria. A person with ESRD needs to have a kidney transplant or to have the blood filtered by machine (dialysis).

But not all people with diabetes develop nephropathy and are more common to occur after puberty. It happens in about 1 in 3 persons in people who have had type 1 diabetes for 15 years or longer. Poor blood glucose control, high blood pressure, and smoking or chewing tobacco also increase the risk of kidney failure.

There are no symptoms or signs until serious kidney damage have occurred. Symptoms and signs may include high blood pressure than usual, puffy ankles due to water retention (Edema), too much protein in the urine (Proteinuria), very high waste levels in the blood (high concentration of Creatinine and Urea).

The liver creates ammonia during the metabolism of protein in the body. This ammonia further break down into a by-product called urea. Kidney filters excess urea into the urine and in sweat and some goes into the bloodstream as serum urea.

A high level of Serum urea indicates that the kidneys are not filtering properly whereas low level of serum urea indicates trouble with liver. High level of serum urea could mean the person is dehydrated which causes the kidneys to reabsorb more urea. Diet enriched with high or low protein can also alter the serum urea level giving false indication of kidney or liver problem. The normal serum urea level for healthy individuals is 15-40 mg/dL in adults.

Muscle metabolism generates a chemical waste molecule known as creatinine, which is produced from creatinine, a molecule of major importance for energy maintenance of the body. It is cleaved from the body’s muscle and released in the blood. The amount in the blood is usually about 1500 mg daily. In the urine creatinine is used as a marker of kidney function. Creatinine is an end product of muscle metabolism and is not filtered by the kidneys. Whenever the muscle breaks down, creatinine is produced. And it is this production that is measured. Creatinine is produced at a steady rate when muscle mass is constant. So it can be used to measure the size of the muscle mass. There are many factors that can affect the rate of creatinine increase in the blood. For example, people who exercise regularly tend to have a higher creatinine level. Changes in diet can alter the rate of creatinine production and, therefore, the creatinine level. This is called a “false normal creatinine.” The creatinine level is usually given as mg/dL. The lab will give the lab results in mg/dL or μmol/L, which is the same as mmol/L.

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production in muscles. On an average 2% of the body’s creatine is converted to creatinine every day which is transported through the bloodstream to the kidneys. Most of the creatinine is filtered by kidneys and the same is disposed off in the urine. The muscle mass in the body is relatively constant from day to day. As a result of this the creatinine level in the blood normally remains on a daily basis.

The kidneys maintain the blood creatinine in a normal range. A rise in the serum creatinine level indicates that the kidneys become impaired and warns of possible malfunction or failure of the kidneys. The normal range of serum creatinine is 0.6-1.2 mg/dL or 71-106 mcmol/L in men and 0.4-1.0 mg/dL or 36-90 mcmol/L in women.[14]

Diabetes is a critical risk factor for Nephropathy.[15-17] This accounts for nearly half of all incident cases of End-stage Renal Disease in the U.S.[18] Several studies have shown that the prevalence and incidence of diabetes continue to increase.[19-22] The increase in number of U.S. adults with diabetes has lead to an increase in the attributable risk for diabetes as a kidney damage or failure.[23]

Research Design & Methods
The study was conducted at Rajah Muthiah Medical College Hospital, Annamalai University, Annamalainagar. Fifty diabetic patients were included in the trial. The patients were chosen by a simple randomized sampling method. The selected fifty diabetic patient’s life styles and physical activities were less or more equal to each other. All of these patients were in the age group of 50-60 years. Each patient’s age, sex, type and duration of diabetes mellitus along with their initial blood sugar levels, blood pressure ranges and lipid profiles were noted accordingly.

Patients were supplemented with Rutin tablets in 500 mg (Rutin 500 mg, Natural Bioflavonoid, manufactured by Nutraceutical Corp., USA) for 60 days to be taken once a day and test results were noted within every 30 days. Data were retrieved from the records of diabetic section of Rajah Muthiah Medical College Hospital, Annamalai University, Annamalainagar, Tamil Nadu (India).

Smart Lab Auto Analyzers (Transacia Germany) was used to measure serum urea and serum creatinine. Statistical analysis were done with Graphpad Prism by Anova followed by Dunn’s Multiple Comparison Test, the values with different superscript (a,b,c) differs from each other at $p < 0.0001$.

RESULTS AND DISCUSSION

### Table 1. Serum Urea Levels on Rutin Supplementation Tablets and after withdrawal of Rutin Supplementation Tablets

<table>
<thead>
<tr>
<th>Parameter (mg/dl)</th>
<th>0 day (Baseline)</th>
<th>60 days</th>
<th>120 days</th>
<th>180 days</th>
<th>240 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Urea</td>
<td>32.65 ± 4.90</td>
<td>30.49 ± 4.68</td>
<td>27.86 ± 5.80</td>
<td>29.24 ± 4.01</td>
<td>31.46 ± 4.80</td>
</tr>
</tbody>
</table>

The above table shows that the level of serum urea in patients with diabetes mellitus was decreased with supplementation of Rutin Tablets. Whereas discontinuing the supplementation of rutin tablets from 120th day onwards the level of serum urea had shown a tendency of increase.

### Table 2. Serum Creatinine Levels on Rutin Supplementation Tablets and after withdrawal of Rutin Supplementation Tablets

<table>
<thead>
<tr>
<th>Parameter (mg/dl)</th>
<th>0 day (Baseline)</th>
<th>60 days</th>
<th>120 days</th>
<th>180 days</th>
<th>240 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>0.81 ± 0.10</td>
<td>0.71 ± 0.09</td>
<td>0.66 ± 0.09</td>
<td>0.74 ± 0.09</td>
<td>0.76 ± 0.09</td>
</tr>
</tbody>
</table>

The above table shows that the level of serum creatinine in patients with diabetes mellitus was declining with supplementation of Rutin Tablets. Whereas discontinuing the supplementation of rutin tablets from 120th day onwards the level of serum urea was again started to increase.

This can be conferred from the above figure that rutin supplementation decreases the serum urea levels and its withdrawal reverses the levels back to pathologic levels which reflect that supplementation of Rutin tablets is beneficial and is to be continued along with patient’s regular medication. The data are given as mean ± SD, for 50 patients. The data are analyzed with Graphpad Prism by Anova followed by Dunn’s Multiple Comparison Test, the values with different superscript (a,b) differs from each other at $p < 0.0001$.

CONCLUSION
From the results obtained, it could be concluded that rutin decreases the levels of Serum Urea and Serum Creatinine in patients with diabetes mellitus by virtue of its antioxidant property. Decrease in the level of Serum Urea and Serum Creatinine minimizes the risk associated with Kidney damage or failure.

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Figure 2. Serum urea levels in patients during rutin supplementation for 60 and 120 days and its withdrawal effects at 180 and 240 days.

Figure 3. Serum creatinine levels in patients during rutin supplementation for 60 and 120 days and its withdrawal effects at 180 and 240 days.
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