

Nephroprotective Effect of Arumuga Chendooram in Experimental Hypothyroid Rats

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Abstract: *The functioning of the kidneys is efficiently monitored and regulated by hormonal feedback mechanisms involving the hypothalamus. One of the major functions of the Urinary system is the process of excretion. Excretion is the process of eliminating, from an organism, waste products of metabolism and other materials that are of no use. The primary function of the kidneys is to maintain a stable internal environment (homeostasis) for optimal cell and tissue metabolism. They do this by separating urea, mineral salts, toxins, and other waste products from the blood. They also do the job of conserving water, salts, and electrolytes. In the present study, prominent increase in creatinine, urea, sodium and decrease in potassium concentrations are suggested as a sign of significant functional impairment of kidney in methimazole treated group. Administration of Arumuga chendooram along with methimazole treated in the curative groups helped in restoring the creatinine, urea, sodium and potassium concentration to near normal levels. This probably points towards the nephroprotective property of Arumuga chendooram.*

Keywords: Kidney, Nephroprotective, Methimazole, Arumuga chendooram

1. Introduction

The functioning of the kidneys is efficiently monitored and regulated by hormonal feedback mechanisms involving the hypothalamus. One of the major functions of the Urinary system is the process of excretion. Excretion is the process of eliminating, from an organism, waste products of metabolism and other materials that are of no use. The primary function of the kidneys is to maintain a stable internal environment (homeostasis) for optimal cell and tissue metabolism. They do this by separating urea, mineral salts, toxins, and other waste products from the blood. They also do the job of conserving water, salts, and electrolytes. The kidneys provide the final common pathway for the excretion of many drugs and their metabolites and therefore are frequently subjected to high concentrations of potentially toxic substances (Asiiley, 2004). Kidneys endowed with million units are termed as nephrons that act as natural sieves. Unfortunately, kidney diseases may be silent for long time. Early detection is the key to preventing kidney diseases, thereby significantly reducing the associated morbidity and mortality (Rayrose, 2005).

The interplay between thyroid and the kidney in each other's functions is known for many years. Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. Thyroid dysfunction affects Renal Blood Flow (RBF), Glomerular Filtration Rate (GFR), tubular function, electrolyte homeostasis, and kidney structure (Gopal Basu and Anjali Mohapatra, 2012).

2. Materials and Methods

Animals

Male albino rats of Wistar strain approximately weighing 180-190g were used in this study. They were healthy animals purchased from the Indian Institute of Science,

Bangalore. The animals were housed in spacious polypropylene cages bedded with rice husk. The animal room was well ventilated and maintained under standard experimental conditions (Temperature $27 \pm 2^\circ$ C and 12 hour light/dark cycle) throughout the experimental period. All the animals were fed with standard pellet diet and water were provided *ad libitum*. They were acclimatized to the environment for one week prior to experimental use. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

Chemicals

Nitroblue tetrazolium (NBT), ethylenediaminetetra acetic acid (EDTA), Trichloro acetic acid (TCA), Thiobarbituric acid (TBA), 5,5'-dithio-bis (2-nitrobenzoic acid), glutathione (reduced), glutathione (oxidized) and Nicotinamide adenine dinucleotide phosphate (NADP⁺/NADPH) were purchased from Sigma Chemical Company (St. Louis, MO, USA). All other chemicals used were of analytical grade and were obtained from Glaxo Laboratories, Mumbai, India, and Sisco Research Laboratories, Mumbai, India.

Preparation of Arumuga chendooram

The Siddha medicine Arumuga chendooram was prepared at its different stages of preparation in departmental laboratory with the help of a traditional siddha medical practioners as per the IMCOPS method.

In the first stage of the preparation of Arumuga chendooram. Five parts of purified mercury (Suththi seitha rasam), nine parts of purified sulphur (Suththi seitha kanthakam), seven parts of purified lode stone (Suththi seitha kantham), twelve parts of purified iron filing (Sutht.hi seitha ayapodi), four parts of rock salt (Induppu) and eight parts of desiccated borax (Poriththa venkaram) were ground with sufficient quantity of aloe juice (Kumari charu for five days continuously. This was then made into small cakes and dried. It was then sealed in discs and burnt for 24 hours. If

the colour of the chendooram does not appear as dark purple the grinding and burning are usually repeated equal to pH and then attractive particle interactions predominate which may influence the drug delivery.

Experimental design

Body weights of the animals were recorded and they were divided into 4 groups of 6 animals each as follows. First group was normal rats fed with standard diet and served as a control which received saline. Second group was negative control administered Methimazole (40mg/kg) induced experimental hypothyroidism for 40 consecutive days Third group was treatment group treated with Methimazole (40mg/kg) along with Arumuga chendooram (10mg/kg) for 40 days. Fourth group was positive control treated with Methimazole (40mg/kg) along with standard throxine sodium (20µg/kg) for 40 days.

Collection of samples

On completion of the experimental period, animals were anaesthetized with thiopentone sodium (50mg/kg). The blood was collected with or without EDTA as anticoagulant. Plasma was separated for the estimation of various biochemical parameters.

Biochemical Estimation

Urea was estimated by the method of Natelson (1957). Serum creatinine was carried out by alkaline picrate method of Boneses and Taussk (1945). Potassium and Sodium estimated by Maruna (1957) and Maruna and Trinder SR (1958) respectively.

3. Results and Discussion

The interplay between thyroid and the kidney in each other's functions is known for many years. Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. Thyroid dysfunction affects Renal Blood Flow (RBF), Glomerular Filtration Rate (GFR), tubular function, electrolyte homeostasis, and kidney structure (Gopal Basu and Anjali Mohapatra, 2012).

The RBF is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects), increased peripheral vascular resistance, intrarenal vasoconstriction (Bradley *et al.*, 1982), reduced renal response to vasodilators and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF-1). In addition, pathologic changes in the glomerular structure in hypothyroidism, such as glomerular basement membrane thickening and mesangial matrix expansion, may also contribute to reduced RBF (Katz *et al.*, 1975; Montenegro *et al.*, 1996).

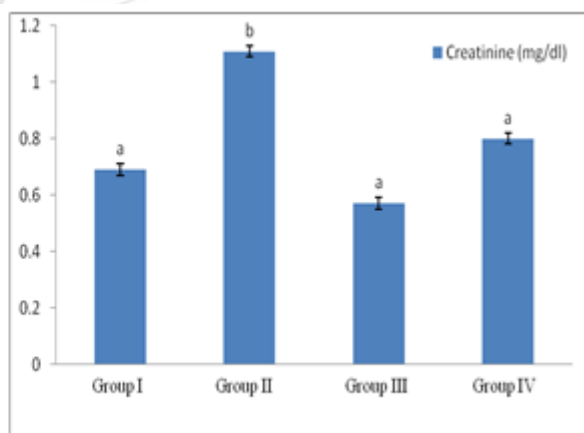
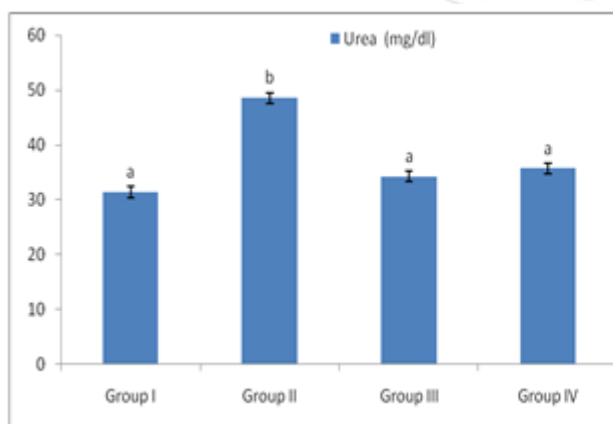
In the present study, prominent increase in creatinine, urea, sodium and decrease in potassium concentrations are suggested as a sign of significant functional impairment of kidney in methimazole treated group (Table 1 and Fig 1). Administration of Arumuga chendooram along with methimazole treated in the curative groups helped in restoring the creatinine, urea, sodium and potassium concentration to near normal levels. This probably points towards the nephroprotective property of Arumuga chendooram.

Table 1: Effect of Arumuga chendooram on kidney markers in experimental rats

Parameters	Group I	Group II	Group III	Group IV
Urea (mg/dl)	31.42±2.19 ^a	48.57±3.39 ^b	34.28±2.39 ^a	35.71±2.49
Creatinine (mg/dl)	0.69±0.04 ^a	1.11±0.07 ^b	0.57±0.039 ^a	0.80±0.05 ^a
Sodium (Meq/dl)	142.56±9.97 ^a	194.32±13.60 ^b	152.78±10.69 ^a	146.56±10.25 ^a
Potassium (Meq/dl)	4.89±0.34 ^a	3.25±0.22 ^b	4.65±0.32 ^a	4.70±0.32 ^a

Each value is expressed as mean ± SD for six rats in each group.

^aAs compared with group II, ^bAs compared with group I, III and IV. *p<0.05.



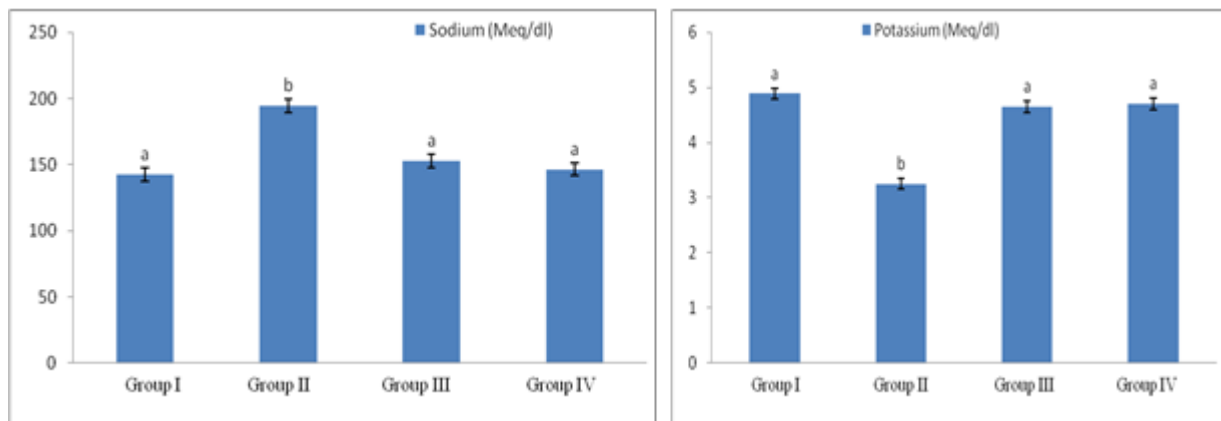


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Primarily the liver synthesizes urea, with dietary protein intake as the principal determinant of urea generation. Variation in urea generation can cause alterations in the blood urea. The excretion of urea was recognized as an estimate of kidney function even before the elaboration of the concept of the glomerular filtration rate. The factors influencing both the excretion of urea by the kidney and its generation are complex and vary widely among individuals and over time. As a result, neither the urea clearance nor the serum urea level is used today as an index of kidney function (Andrew and Levey, 2005). Urea is an end product of protein catabolism. It is freely filtered by the glomerulus, passively reabsorbed in both the proximal and distal nephron and excreted in high concentration in urine. The excretion of urea was recognized as an estimate of kidney function. The serum urea level is used as an index of kidney function (Lesley and Lvey, 2005). In the present study, we observed the increased level of urea in methimazole treated rats as compared with control rats, shows the impairment of kidney function. Administration of Arumuga chendooram significantly decreased the level of urea in group III rats.

Creatinine is an end product of muscle catabolism, which is removed at a constant rate by the kidneys. The concentration of creatinine in serum is the most widely used and commonly accepted measure of renal function in clinical medicine. The clinical utility of the serum creatinine concentration centers on its relation to the glomerular filtration rate (GFR) (Perrone *et al.*, 1992). The serum creatinine concentration is the most commonly used index of the kidney function. The level of creatinine in the blood rises if the kidney does not function properly (Lesley and Levey, 2005). In the present study, we observed the increased level of creatinine in methimazole treated rats as compared with control rats, shows the impairment of kidney function. Administration of Arumuga chendooram significantly decreased the level of creatinine in group III rats.

The composition of ICF and ECF is different. The principal intracellular cation is potassium and the main extracellular cation is sodium. ICF has high protein content, whereas the protein content of ECF is almost zero. Proteins have

multiple charges on each molecule; at body pH the net charge is negative. After protein, the principal intracellular anions are organic phosphates (e.g. creatine phosphate, ATP) (Atherton, 2006).

In a healthy individual, sodium intake and sodium excretion are equal over time. In normal salt intake is 6–18 g (100–300 mmol)/day. Sodium loss occurs via the skin (in sweat) and the gastrointestinal tract, but the principal site of sodium regulation is the kidney, which normally accounts for 95% of sodium output. Sweat is a hypotonic solution containing 5–80 mmol/litre of sodium. Sodium balance is closely related to ECF volume because sodium is the main extracellular cation. Sodium retention is associated with fluid retention and oedema, and sodium depletion with shrinkage of the ECF volume and hypovolaemia. The regulation of sodium balance in the healthy individual is determined via ECF volume, detected by receptors in the arterial (Atherton, 2006).

The renal mechanisms that affect sodium excretion are glomerular filtration rate (GFR), plasma aldosterone levels, renal tubular mechanisms and renal sympathetic activity, and atrial natriuretic peptide. A spontaneous increase in GFR leads to an increase in sodium load presented to the proximal tubule. Sodium excretion not increased markedly because of 'glomerulotubular balance' whereby the proximal tubule and the loop of Henle increase their rates of sodium reabsorption so that excess losses do not occur. Plasma potassium levels are influenced by insulin, aldosterone and the catecholamines (sympathetic stimulation). Insulin and the catecholamines both stimulate the Na⁺/K⁺-ATPase pump in the cell membrane, and potassium is pumped into the cells, resulting in a fall in plasma potassium (Iain Campbell, 2006)

Acid, bases and salts are collectively called electrolytes. Electrolyte imbalance can lead to serious consequences as it affects the homeostasis of the body. Homeostasis is the process by which the body cells maintain their internal balance in spite of changes in the external environment commonly measured electrolytes are sodium, potassium, calcium, chloride bicarbonate etc., which are good indicators of kidney function (Cohen and Lemann, 1991). In the present study, we observed the increased level of sodium and decreased level of potassium in methimazole treated rats as compared with control rats. This due to antiport transport

system of sodium and potassium i.e. the increased excretion of potassium is promoted the reabsorption of sodium. Administration of Arumuga chendooram restored in the level of sodium and potassium in group III rats.

It can be concluded that in this study methimazole induced a model of hypothyroid associated with renal dysfunction in rats were observed. The hypothyroid and its associated problems in this study could be ameliorated by supplementation of Arumuga chendooram. The study showed that herbo-mineral drug significantly restored the kidney markers. Thus, the Arumuga chendooram possesses potential renoprotective effects.

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