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Effect of Coriander (*Coriandrum sativum L.*) and Fennel (*Foeniculum vulgare M.*) on lead nephrotoxicity in rats

Thesis

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Introduction

Nephrotoxicity is a major complication based on functional changes including inhibition of protein synthesis, lipid peroxidation, mitochondrial damage and reduced glutathione depletion. Oxidative damage is considered as one of the main mechanisms involved in approximately all chronic renal diseases ***(Abd El-Ghany et al., 2012).*** Exposure to chemical reagents like carbon tetra chloride, ethylene glycol, sodium oxalate and heavy metals like lead, mercury, arsenic and cadmium also leads to nephrotoxicity ***(Pydi, 2011).***

Lead (Pb) is a well-known multi-organ toxicant and it damages liver and kidney ***(Manoj Kumar et al., 2013)***. It is a divalent cation with a tendency to settle in the proximal tubule of the nephron, leading to nephrotoxicity, lead accumulation in the proximal tubule leads to hyperuricaemia and gout, especially by inhibiting secretion of uric acid and reduced glomerular filteration rate ***(Gonick, 2008).***

Lead is found in many industrial sources. Chief among these are the accumulator battery industry, lead smelters, lead or silver ore mining and lead refining. Non-industrial sources are air-borne lead from leaded gasoline fumes and lead-based paints ***(Patrick, 2006a)***. It has been used in paintings, pipes, ammunition and in more recent times in alloys for welding storage materials for chemical reagents ***(Garaza et al., 2006)***. Exposure to lead usually occurs through the respiratory and gastrointestinal systems ***(Ibrahim et al., 2012).***

Lead is known to cause oxidative damage in many tissues by inducing an imbalance in the production and removal of reactive oxygen species (ROS) ***(Hamadouche et al., 2009).*** Lead is known to cause free radical damage in tissues by two mechanisms: Increased production of ROS, including hydroperoxides, singlet oxygen and hydrogen peroxides, and by causing direct depletion of antioxidant reserves ***(Ercal et al., 2001).***

Many herbs have been used for the treatment of kidney diseases in traditional system of medicine throughout the world due to their strong antioxidant activities, without side effects and of their economic viability. Several herbs are recommended for ameliorating renal damage and to prevent kidney related complications. These can be immense value in combating renal damage ***(Peesa, 2013).***

Coriander *(Coriandrum Sativum L.)* is belonging to the family *Umbelliferae* which is highly reputed medicinal herb and widely distributed and mainly cultivated for seeds. The seeds contain an essential oil and the monotrepenoid, linalool, is the main component ***(Eikani et al., 2007).*** It has been used as a flavouring agent in food products, perfumes and cosmetics ***(Emamghoreishi et al., 2005).***

Coriander has been reported to possess many pharmacological effects such as antifertility ***(Al-Said et al., 1987),*** antiproliferative (***Nakano et al., 1998***), anti-hyperlipidemic ***(Chithra and Leelamma, 1999),*** digestive stimulant ***(Platel and Srinivasan, 2000),*** hypotensive (***Burdock and Carabin, 2008***) and antihyperglycemic ***(Eidi et al., 2009).*** *Coriandrum sativum* showed excretion of heavy metal in the urine of patients and also augmented the efficacy of antibiotics ***(Manoj Kumar et al., 2013).***

Fennel *(Foeniculum Vulgare M.)* is belonging to the family *Apiaceae* (*Umbelliferae*) with a characteristic aromatic odor. Fennel is one of the most essential medicinal plants grown within the Mediterranean region, in Europe and in Egypt ***(Aboelsoud, 2010).*** Fennel seeds are generally eaten for the taste but also very healthy due to the nutrition value attached to it. Fennel is also used for many health benefits that are derived from its antioxidants ***(Alexandrovich et al., 2003)***. Fennel contains its own unique combination of phytonutrients including the flavonoids quercitin, rutin and various kaempferol glycosides that give it potent antioxidant activity ***(Shaffie et al., 2010).***

Fennel is commonly known as culinary herb but it is a mainly used household remedy for several medicinal purposes such as anticancer, anti-inflammatory and antioxidant agent ***(Chatterjee et al., 2012)***. Fennel used as carminative, lactogogue, digestive, diuretic and in treating respiratory and gastrointestinal diseases. Fennel has been shown to possess anti-diabetic, anti-bacterial, anti-fungal, analgesic, estrogenic, hepatoprotective activities. In addition, it is used as herbal medicine for kidney diseases (***Koppula and Kumar, 2013).***

Aim of the work

The present study has been designed to examine the possible nephroprotective role of coriander and fennel seeds water extracts at different doses against lead-induced nephrotoxicity in rats.

This was evaluated through induction of nephrotoxicity by administration of lead acetate and determination of the following indices:

1- Feed intake and feed efficiency ratio.

2- Body weight change.

3- Relative and absolute weights of kidneys.

4- Serum delta amino-levulinic acid dehydratase activity.

5- Serum and renal lead concentration.

6- Serum creatinine, urea, uric acid, sodium and potassium concetrations.

7- Urinary protein, creatinine clearance, sodium and potassium concentrations.

8- Renal content of lipid peroxidation (MDA), nitric oxide (NO), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and glutathione-S-transferase (GST) activities.

9- Plasma GST and CAT activities.

Review of Literature

1. Kidneys

The kidneys are paired organs that lie on the posterior wall of the abdomen behind the peritoneum on either side of the vertebral column. In the adult human, each kidney weighs between 115 and 170 g and is approximately 11 cm long, 6 cm wide and 3 cm thick ***(Tonelli et al., 2006).***

The kidneys are organs that serve a number of essential regulatory roles. Kidneys are functioning as filters, removing metabolic wastes and toxins from the blood and excreting them through the urine. But the kidneys also serve other vital functions. The kidneys produce or activate hormones that are involved in erythrogenesis, calcium metabolism and the adjustment of blood pressure and blood flow. Most mammalian kidneys have three main sections: the cortex, the outer medulla and the inner medulla ***(Sands and Layton, 2000).***

The kidneys of a normal adult human filter about 180 liters of blood daily, and 99% of filtered electrolytes, solutes and fluid are reabsorbed and returned to the circulation. Only 1% of the filtered load is eventually excreted in urine. The kidneys have the unique capacity to precisely adjust the urinary excretion of electrolytes and fluid in order to match spontaneous variations in their intake to sustain body electrolyte and fluid homeostasis, acid-base balance and normal blood pressure ***(Candido et al., 2007).***

The functional unit of the kidney is the nephron. Each human kidney consists of about a million nephrons. Each rat kidney (which is the well-studied mammalian kidney) is populated by about 38, 000 nephrons; Each nephron consists of a renal corpuscle including the glomeular tuft, which contains a network of capillaries and Bowman's capsule and a tubule unit including proximal tubule, loop of Henle, distal

tubule, connecting tubule and the collecting duct ***(Kriz and Kaissling, 2008)***.

In the physiological context, a nephron represents a functional unit that filters blood, reabsorbs the filtered electrolytes, solutes and fluid and excretes wastes and excessive electrolytes and water. The glomerulus is exclusively responsible for filtering blood up to 25% of a normal cardiac output. The tubules of the nephron have an important role in reabsorbing 99% of glomerular filtered electrolytes and water and returning them to the circulation ***(McDonough, 2010).***

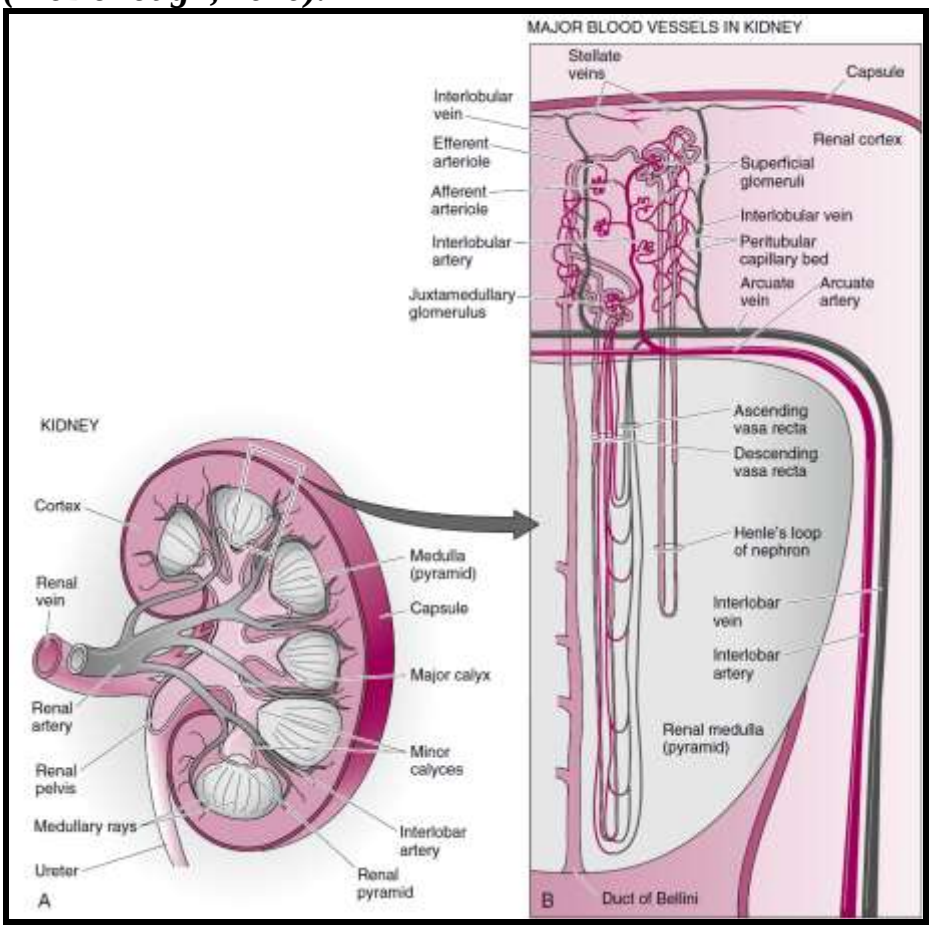

Figure (1): Structure of a human kidney, cut open to show the internal structures ***(Boron and Baulpaep, 2009).***

It is well known that proximal tubular segments exert a more prominent role. Proximal tubules are responsible for reabsorbing about 65% of filtered load and most, if not all, of filtered amino acids, solutes and low molecular weight proteins ***(Weinstein, 2008).***

Proximal tubules also play an important role in the maintenance of body acid-base balance by reabsorbing 80% of the filtered bicarbonates and glucose metabolism by reabsorbing all filtered glucose and regulating gluconeogenesis ***(Bevensee and Boron, 2008).*** The distal convoluted tubules and collecting tubules are also important sites for the reabsorption of water ***(Marsenic, 2009).***

2. Assessment of renal dysfunction

The mammalian kidney is a morphologically and functionally complex organ that plays an important role in control and regulation of homeostasis with several reabsorptive, secretory, metabolic and endocrine functions ***(Sabolić, 2006).***

Failure to perform these functions is revealed in reabsorptive and secretory defects along the nephron, which in cases of restricted malfunctions a small molecular weight proteinuria is resulted; in more severe cases exhibit also polyuria, glucosuria, aminoaciduria, phosphaturia and raised excretion of electrolytes, as well as an elevated blood urea nitrogen and creatinine (***Dock and Vahter, 1999)***.

While in most severe forms, a generalized damage to the kidney functions manifests as the Fanconi's syndrome which is a generalized proximal tubule defect leading to urinary wasting of many solutes such as bicarbonates, amino-acids, phosphates and glucose that results in polyuria, growth failure and resistant rickets. It is an uncommon tubulopathy and is commonly secondary to a systemic

disease, metabolic disorder or drug toxicity ***(Bergeron et al., 2000).***

Though some of the functional defects of the nephron are related to the inherited malfunctions of specific genes, a significant number of such cases, particularly in the adult human population, are induced by toxic damages to the nephron following acute or chronic exposure to various environmental and/or occupational (toxic metals, mycotoxins, pesticides, herbicides, etc.) or chemotherapeutic substances (some toxic metals, various drugs used in medicine) (***Sabolić, 2006***).

Adequate measurement of kidney function is important for the management of all children and adolescents ***(Filler, 2011***). Accurate measurement of kidney function is also important for drugs excreted by the kidneys across all other ages. With many kidney disorders, intervention often depends on whether kidney function is normal or abnormal. Further, when there is an impaired kidney function, accurate assessment of kidney function is important for initiation of renal replacement therapy (***Abbink et al., 2008)***, listing for renal transplant (***Herget-Rosenthal et al., 2007***), evaluating interventions and monitoring changes of function over time (***Bokenkamp et al., 2006).***

The markers of renal function test assess the normal functioning of kidneys. If there is an increase or decrease in the valves of these markers it indicates dysfunction of kidney. These markers are creatinine, urea, uric acid and electrolytes are for routine analysis while many studies have confirmed and consolidated the usefulness of markers such as cystatin C, β-Trace protein ***(Laura et al., 2007*** *and* ***Gowda et al., 2010).***

3. Renal function tests

3.1. Serum creatinine

Creatinine is a breakdown product of creatine phosphate in muscle and is usually produced at a fairly constant rate by the body depending on muscle mass**.** It is commonly used as a measure of kidney function ***(Zuo et al., 2008 and Corbett, 2008).***

Creatinine values may alter as its generation may not be simply a product of muscle mass but influenced by muscle function, muscle composition, activity, health status and diet (***Banfi and Del, 2006***). The increased excretion of creatinine in some patients with kidney dysfunction could give false negative value ***(Branten et al., 2005).***

The elevated creatinine values are also seen in muscular dystrophy paralysis, anemia, leukemia and hyperthyroidism. The decreased creatinine values are observed with glomerulonephritis, congestive heart failure, acute tubular necrosis, shock, polycystic kidney disease and dehydration ***(Edmund and David, 2006***).

3.1.1. Creatinine as a measure of glomerular filtration rate (GFR)

The concept of renal clearance was known as a way of expressing the relation between the excretion per unit time and the concentration in the plasma which is definitely an index of kidneys ability to clear the blood of any substance. Measurements of GFR are commonly based on the renal clearance of a marker in plasma, expressed as the volume of plasma completely cleared of the marker per unit time. The ideal marker should be endogenous, freely filtered by glomerulus, neither reabsorbed nor secreted by the renal tubule and eliminated only by the kidney. Various markers

used to measure GFR include exogenous such as inulin and iothalamate or endogenous such as urea and creatinine substances ***(Sirwal et al., 2004).***

Clinically, GFR is often obtained from plasma creatinine concentration alone albeit with limited accuracy. Determination of GFR from plasma creatinine may give unreliable results because plasma creatinine is not only dependent on GFR but also on muscle mass which varies with gender, weight and age. In cirrhosis and diseases with reduced muscle mass, plasma creatinine is low. On the other hand, a high protein intake can lead to 10% increase in plasma creatinine ***(Perrone et al., 1992).*** To enhance the estimation of GFR from plasma creatinine concentration, formulas which incorporate variables like gender, weight, height and age can be used ***(Salzar and Corcoran, 1988).***

GFR is considered as the best overall measure of kidney function. In day to day clinical practice an estimation of GFR is required for various reasons: (a) renal function assessment (b) severity of renal disease (c) calculation of proper drug dosage and (d) evaluation of renal involvement in systemic diseases ***(Hock et al., 2003).***

3.2. Serum urea

Urea is the major nitrogenous end product of protein and amino acid catabolism, produced by liver and distributed throughout intracellular and extracellular fluid. In kidneys urea is filtered out of blood by glomerulli and is partially being reabsorbed with water ***(Corbett, 2008).*** The most frequently determined clinical indices for estimating renal function depends upon urea concentration in the serum. It is useful in differential diagnosis of acute renal failure and pre renal condition where blood urea nitrogen–creatinine ratio is elevated ***(Mitchell and Kline, 2006).***

Urea clearance is considered as a poor indicator of glomerular filtration rate as its overproduction rate depends on several non-renal factors, including urea cycle enzymes and diet. Increased blood urea nitrogen (BUN) is seen associated with kidney disease or failure, kidney stone causing blockage of urinary tract, congestive heart failure, dehydration, fever and shock and bleeding in the digestive tract (***Gowda et al., 2010).***

3.3. Proteinuria

The presence of albuminuria or proteinuria establishes a sign of kidney damage and together with the determination of glomerular filtration rate are used for evaluation of chronic kidney disease. Proteinuria is an important marker for progression of chronic kidney disease as well as a marker of increased cardiovascular morbi-mortality ***(Gorriz and Martinez-Castelao, 2012).***

The glomerulus produces the primary urine by filtering blood and retains larger proteins including most serum albumin which its molecular weight is greater than 67 kd. Proteins with a molecular weight less than 60 kd usually pass easily through the glomerular basement membrane and are actively reabsorbed within the tubular system. The renal tubule reabsorbs the small molecules along with a small amount of albumin that passes freely through the glomerulus ***(Halbesma et al., 2006).***

Clinically the appearance of significant amount of protein in urine is one of the earliest sign of almost all renal diseases. Assessment of proteinuria helps in differentiating between tubulointerstitial and glomerular diseases and also to monitor the progress of renal disease and to evaluate the response to therapy. Normally execretion of protein in urine over 24 hrs is between 20-150 mg in most healthy adults. Proteinuria more than 3.5 gm/day is taken to be an indication of nephrotic syndrome. Panels of protein

measurement including α_2-macroglobulin, albumin, immunoglobulin G (IgG) and α_2- microglobulin have been used in differential diagnosis of prerenal and postrenal disease ***(Sandeep et al., 2004).***

Types of proteinuria

Urine protein concentration may be the result of various mechanisms, being that the quantity and quality of the proteinuria are very different.

1- Pre renal proteinuria: caused by over production. This can be observed in paroxysmal nocturnal haemoglobinuria rhabdomyolysis (myoglobinuria), mielomonocític leukemia (lysozimuria) and myeloma (free light chain disease).

2- Glomerular proteinuria: caused by functional or structural alterations of the electronic glomerular basemembrane charge, producing a disturbance of the filtration barrier. This can be observed in glomerulonephritis, infections, hypertension, diabetes, systemic erythematous lupus, neoplasia and congenital diseases.

3- Tubular proteinuria: decreased reabsorption of the proteins commonly filtered by the glomerulus caused by changes of the tubular reabsorption mechanisms. Low-molecular-weight proteins appear in the urine, such as retinol-binding protein, α_1-microglobulin or β_2-microglobulin. This kind of proteinuria is found in congenital or systemic diseases and in cases of toxicity induced by drugs and toxins.

4- Post renal proteinuria: as a consequence of hemorrhage, inflammatory or infectious processes, epithelial tubular cells can add proteins to the tubular fluid affecting the lower urinary tract ***(Kashif et al., 2003).***

3.4. Serum and urinary electrolytes

Serum electrolytes, sodium and potassium are vital macronutrient to the human and it is supplied to the body in the solid and liquid food materials. These electrolytes have various roles in the body and these functions are critical for life. Its rate of consumption and excretion may differ to the different geographical region, and this may cause the variable medical fitness ***(Tripathi et al., 2011).***

3.4.1.Sodium

Sodium is the most abundant cation in the extracellular fluid and is the major regulating factor for body water balance. Extracellular (i.e., intravascular and interstitial) and intracellular sodium contents are closely influenced by the body fluid status. Thus, an accurate explanation of serum sodium concentration must include an understanding of body water homeostasis and the inter-relationship between the regulation of sodium and water ***(Guyton and Hall, 2001).***

The kidneys are the primary organ essential for the retention and excretion of body sodium and water. While almost 100% of the plasma sodium is filtered through the glomeruli, less than 1% is excreted in the urine under normal conditions. The proximal tubule and the Loop of Henle each are responsible for approximately 45% of sodium reabsorption ***(Rose, 2001).***

Hyponatremia can be defined as a serum sodium concentration less than 136 mEq/L (<136 mmol/L) ***(Halperin and Goldstein, 1994).***

The most common causes of hyponatremia can be broken down into two types: sodium depletion in excess of total body water loss (e.g. severe dehydration with true reduction of total body sodium) and dilutional hyponatremia