Possible Mechanism Of Mercuric Chloride Induced Nephrotoxicity and Protective Effect of Herbs

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***Abstract*- Mercury (Hg) is a hazardous environmental and industrial pollutant which induces the severe changes in the tissues of the body in both humans and the animals. Mercury can cause biochemical destruction to tissues and genes through various mechanisms, such as intervention intracellular calcium homeostasis, disrupting membrane potential, altering protein synthesis. Mercury is primarily accumulated on kidney and expresses toxicity to the kidney. Mercury promotes the formation of reactive oxygen species (ROS) in animals. Various herbal plants have protective effect against mercuric chloride induced nephrotoxicity.**

Keywords- Mercuric chloride

I. INTRODUCTION

Nephrotoxicity is a condition of renal injury which was caused by the some chemicals, poisonous substances, drugs etc[10]. The nephrotoxicity is caused by some drugs: Amphotericin B,Gentamycin (Antifungal agents), Acyclovir, Ganciclovir (Antiviral agents) etc. some Heavy metals are also used to cause nephrotoxicity: mercury, cadmium, lead, arsenic etc.[17,22,20]

Mercury (Hg) is a hazardous environmental and industrial pollutant which induces the severe changes in the tissues of the body in both humans and the animals[19] . The widespread peoples are exposed to methyl mercury through the diet i.e; the main source is fish consumption[5]. Mercury is primarily accumulated on kidney and expresses toxicity to the kidney. Acute exposure of mercury included damage to the kidney and the gastrointestinal, cardiovascular, and nervous systems.

The Sources of exposure to mercury are as:

Occupational exposure:

Workplace environments presenting the largest potential sources of occupational exposure to mercury include chlorine-alkali production facilities, cinnabar mining and processing operations and the manufactures and the use of instruments containing liquid mercury[6].

Experimental exposure:

Potential sources of mercury exposure for the general population include inhalation from ambient air, ingestion in water and food stuffs and dental and medical treatments. The dietary exposure is the main exposure.
(Public health guidance note 2002)
Mercuric chloride (HgCl2) is a vigorous nephrotoxic agent that has been widely used in animal models for studying acute renal failure because it trigger oxidative stress and renal damage. The animals exposed to mercuric compounds induces an oxidative stress, production of reactive oxygen species and decreases in antioxidant enzymes[22], reduced ATP content[14]. Mercury promotes the formation of reactive oxygen species (ROS) in animals [8].
The primary mechanism in the luminal uptake of inorganic mercury involves the actions of the brush-border enzyme, g-glutamyltranspeptidase (g-GT) by catalytic cleavage of the g-glutamylcysteine bond on molecules of GSH bonded to mercuric ion. The mercuric conjugate of cysteinylglycine has obtained after the cleavage of g-GT [26].

II. MECHANISM OF MERCURIC CHLORIDE NEPHROTOXICITY

Mercury compounds have toxic health effects by different mechanisms such as: intervention in formation of microtubule, altering intracellular calcium balance and membrane potential, changing cell membrane integrity, disturbing or obstruction of enzymes, inducing oxidative stress, obstruction of protein and DNA synthesis and disturbing immune functions[13] .

Mercury can cause biochemical destruction to tissues and genes through various mechanisms, such as intervention intracellular calcium homeostasis, disrupting membrane potential, altering protein synthesis[26] .

Mercuric chloride enter in the proximal tubular cells both through re-absorption as a cysteine conjugate from the lumen and by transport across basolateral cells, again as a conjugate. Mercuric chloride does not attack the transport process, but rather utilize it to reach intracellular sites where they exert their nephrotoxic effects [24]

The mechanism of mercuric chloride nephrotoxicity is as:

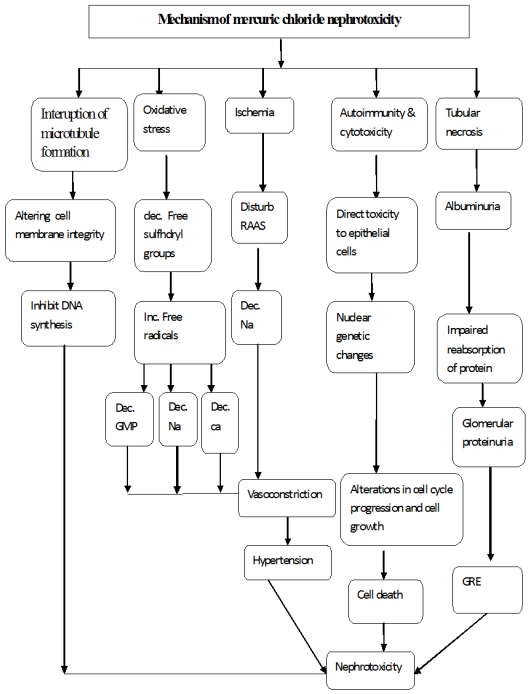

Fig.1.1:Mechanism of mercuric chloride induced nephrotoxicity

Oxidative stress: The toxicity of mercury and its ability to react with and deplete free sulffydryl groups . The decrease in free sulffydryl groups can cause to the formation of an oxidative stress, resulting in increase in concentration of free redicals that produced vasoconstriction by increasing the Nitric oxide (NO)[17], cGMP and also calcium level [26]

Ischemia: Inadequate blood flow and oxygen to a kidney caused by mercuric chloride which decreases tubular reabsorption of sodium and a decrease of circulating sodium can cause vasoconstriction through rennin angiotensin system. Renal blood flow decreases through vasoconstriction

Cytotoxicity: Mercury has high affiliation to sulfhydryl groups of proteins, and results in alterations in many renal enzyme activities, such as in glutathione peroxidase, glutathione reductase, superoxidase, alkaline phosphatase, 5'- nucleotidase, acid phosphatase, alpha-glycerophosphate, malic dehydrogenase (Wang 2000).

Autoimmune Reaction: Another possible mechanism may involve autoimmunity. Chronic exposure to foreign toxicants can induce an autoimmune response that produces antibodies targeting the basement membrane of the glomerulus[5].

The cytotoxicity and autoimmune reactions leads to nuclear and genetic changes such as a decrease in DNA synthesis, production of DNA fragmentation, impairment in DNA replication, DNA single strand breaks, and an inhibitionin repair of DNA strand breaks. Many of these alterations may interfere with cell cycle progression and cell growth. Both inorganic and organic mercury decreases cell growth and cell proliferation which leads to cell death.

Nitrosative and oxidative stress: Mercury exposure produces an elevated in reactive oxygen species (ROS) and reactive nitrogen species (RNS) activating signaling pathways, such as NFκB(nuclear factor kappa), and JNK(c-Jun N-terminal kinase) generating the activation of antioxidant response and as well as swelling. This reaction induce oxidative and nitrosative stress, which damages DNA, lipids and proteins. One of the main result of oxidative stress is the interference of the tight junction proteins that may cause renal dysfunction[11].

Tubular necrosis: Tubular necrosis involving the death of tubular epithelial cells that form the renal tubules of the kidneys. The death of tubular epithelial cell induced albuminurea. Imbalance in reabsorption of protein produce to decline the glomerulus filtration rate[11].

III.PROTECTIVE EFFECT OF HERBS ON MERCURIC CHLORIDE NEPHROTOXICITY

Herbs are the wide source of a secondary metabolites, nowadays which are used as pharmaceuticals, agrochemicals, flavors, fragrances, colors, biopesticides and food additives. Herbs have been used as drugs by humans since thousands of years ago[21].

Various plants have been used for the treatment of kidney damage in traditional system of medicine throughout the world. Knowledge of traditionally used herbs will serve as a most importantly search engine and provide safe natural products for the research to rediscover the drug discovery process[21].

Herbal plants have protective effect on mercuric chloride induced nephrotoxicity. The herbs have different mechanism to treat the nephrotoxicity and are as:

Herbs are potent antioxidant which suppress the oxidative stress produced by mercuric chloride nephrotoxicity.

Herbs have many chemical constituents like glycosides, alkaloids, flavonoids which have strong reducing ability.

Herbs with a large amount of polyphenols have high reducing ability.

Herbs have strong antioxidant property which reduce the serum creatinine and blood urea nitrogen which was elevated by the mercuric chloride.

Herbs are also have saponins which act as surface lowering agents and plays major role to treat the nephrotoxicity induce by the mercuric chloride[21].

Table 1.1: Protective effect of herbs on mercuric chloride induced nephrotoxicity

Botanical name	Common name	Family	Part used	Nephrotoxic agent	Animal used	References
Acacia senegal	Arabic gum	Leguminosae	Stems & branches	HgCl2 (5 mg/kg IP) for 1 week	Male Swiss albino rats,	Gado and Aldahmash; 2013
Ajuga iva	Chendgoura	Lamiaceae	Whole plant	Mercuric chloride (1mg/kg IP) for 4 weeks	Albino wistar female rat	Ahlem and Yusuf; 2014
Allium sativum	Garlic	Amaryllidaceae	Clove	Mercuric chloride (100mg/kg IP) for 30 days	Albino wistar rats	Abirami and Jagdeesswari;2006
Allium cepa	Onion	Alliaceae	Fruit	Mercuric chloride (1mg/kg IP) for 7 days	Albino wistar rats	Langeswaran *et al; 2013*
Aloe berbedensis	Aloevera	Asphodilaceae	Plant	Mercuric chloride (1mg/kg IP) for 7 days	Albino wistar rats	Kumar *et al;* 2013
Boerhaavia diffusa	Punarnava	Nyctaginaceae	Leaves	Mercuric chloride (200mg/kg IP) for 5 days	Albino wistar rats	Indhumathi *et al; 2011*

Ginkgo biloba	Ginkgo	Ginkgoaceae	Leave	Mercuric chloride (5mg/kg orally) for 5 days	Albino wistar rats	Sener *et al;2007*
Juglans sinensis	Walnut	Juglandaceae	Fruits	Mercuric chloride(10mg/kg s.c)	Rabbit	Ahn 2002
Kaempferia galangal	Kencur	Zingiberaceae	Rhizome	Mercuric chloride(1mg/kg IP) for 30 days	Albino wistar rats	Vijyaprakash et al; 2013
Myrciaria dubia	Camucamu	Myrtaceae	Fruit	Mercuric chloride (1.2 mg/kg orally) for 28 days	Albino wistar rats	Hounkpatin *et al; 2012*
Rosa rugosa	Rose hips	Rosaceae	Seeds	Mercuric chloride (1.2 mg/kg orally) for 28 days	Albino wistar rats	Johnson *et al;* 2012
Solanum lycopersicm	Tomato	Solanaceae	Fruits	Mercuric chloride (5mg/kg s.c) for 10 days	Albino wistar rats	Augusti *et al; 2007*

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