Toxicodynamics of Lead, Cadmium, Mercury and Arsenic- induced kidney toxicity and treatment strategy: A mini review

Mohammad Nasiruddin Rana\textsuperscript{a,b,⁎}, Jitbanjong Tangpong\textsuperscript{a}, Md. Masudur Rahman\textsuperscript{b}

\textsuperscript{a} Biomedical Sciences, School of Allied Health Sciences, Walailak University, Thasala, Nakhon Si Thammarat, Thailand
\textsuperscript{b} Department of Pharmacy, Faculty of Science and Engineering, International Islamic University Chittagong, Kumira, Chittagong-4318, Bangladesh

A R T I C L E   I N F O

Keywords:
Heavy metals
Oxidative stress
Proteinuria
Kidney toxicity
Antioxidant

A B S T R A C T

Environmental pollution has become a concerning matter to human beings. Flint water crisis in the USA pointed out that pollution by heavy metal is getting worse day by day, predominantly by Lead, Cadmium, Mercury and Arsenic. Despite of not having any biological role in flora and fauna, they exhibit detrimental effect following exposure (acute or chronic). Even at low dose, they affect brain, kidney and heart. Oxidative stress has been termed as cause and effect in heavy metal-induced kidney toxicity. In treatment strategy, different chelating agent, vitamins and minerals are included, though chelating agents has been showed different fatal drawbacks. Interestingly, plants and plants derived compounds had shown possible effectiveness against heavy metals induced kidney toxicity. This review will provide detail information on toxicodynamics of Pb, Cd, Hg and As, treatment strategy along with the possible beneficiary role of plant derived compound to protect kidney.

1. Introduction

Heavy metals are ubiquitous in various forms in the environment. Primarily, human beings and animals are intoxicated by means of consumption of contaminated foods, contaminated water, mining, battery recycling and plastics. Due to the major route of excretion from the body, kidneys are more vulnerable to heavy metal toxicity, mostly to Lead (Pb), Cadmium (Cd), Mercury (Hg), Arsenic (As)\textsuperscript{[1–4]}. Depending on the duration and dose size (low to high), numerous fatal effects have been reported in blood composition, lung, and brain [5]. In general, removal of the patient from the site is the provision to treat toxicity. Depending on dose size and severity of the condition, different antidotes and chelating agents are prescribed. But, these agents intervene with essential metal ion like Ca\textsuperscript{2+}, Cu\textsuperscript{2+}, Zn\textsuperscript{2+}, and results in aberrant physiologic function [6]. In addition, unbroken heavy metals are redistributed by these agents to potentiate toxicity at intracellular sites of liver and kidney [7]. To overcome these drawbacks, different nutrients and vitamins are suggested [8], whereas vitamins (antioxidants) at a same time could serves as chelating agent and reactive oxygen/nitrogen species (ROS/RNS) scavenger. Within few decades, numerous studies have been conducted on plants and plants derived compound against heavy metals, particularly on the kidney and reported the probable beneficial effect in \textit{in vitro} & \textit{in vivo} studies. Therefore, our current review was aimed to discuss the toxicodynamics and treatment of Pb, Cd, Hg and As toxicity on kidney and possible beneficiary role of plants & plant derived isolated compounds.

2. Lead (Pb) and kidney

Lead (Pb) is a toxic xenobiotic which causes different critical health conditions at the fatal stage [9,10]. Though it is toxic, it has been found or incorporated in different products including paints, water tape, cosmetics, fuel etc. for its different properties like low melting point, resistance to corrosion [11,12]. As a result, gastrointestinal, hematological, reproductive, immunomodulogical disorder have been recorded [13–16]. Kidney is one of targeted site of Pb-toxicity for being major route of excretion from body and facilitates kidney damage via oxidative stress and lipid peroxidation [17–19].

2.1. Pb and proteinuria

Aminoaciduria, glycosuria, and phosphaturia were reported in acute Pb toxicity as marker for proximal tubule dysfunction [20].

2.2. Toxicodynamics of renal toxicity by Pb

Lead (Pb) can readily be absorbed by intestine, lung, less commonly through the skin and almost 90% of it binds to erythrocyte proteins (albumin) [21]. Through endocytosis and/or Erythrophagocytosis [22], it locates into different tissues and organs including liver, kidney where...
2.3. Treatment strategy against Pb

The first step of treatment strategy is the removal of the patient from the site of exposure. If the patient is adult and blood Pb-level is > 70 mg/dL, then chelation therapy with dimercaprol or succimer, meso-2,3-dimercaptosuccinic acid (DMSA) and CaNa2EDTA could be considered. Conversely, if Pb-level ranges in between 45 and 69 mg/dL for children, then oral chelation therapy with DMSA might be suggested. Among the cells, proximal tubules are more susceptible to Pb-induced cellular damage followed by apoptosis. Studies on primary cultures of rat proximal tubular (rPT) cell suggested that Pb2+ elevates cytosolic, mitochondrial calcium concentration, [Ca2+] and depletes endoplasmic reticulum’s (ER) [Ca2+] via acting on inositol 1,4,5-trisphosphate receptor (IP3Rs) [26]. Interestingly, study on HEK293 cells also ensured the involvement of Ca2+, where Canonical transient receptor potential TRPC1 actively participates in the cytotoxicity and entry of Pb2+ [27]. Besides, it also displaces essential metal ion like Zn2+ and Ca2+ in proteins and inhibits Cys2His2 zinc finger transcription factors [21].

From the different point of view, Pb also hinders the integrity of cell–cell junctions (tight junction) and modify cellular structure [28]. Altered polarity and vectorial transport of epithelial cells could also be a possible consequence of atypical cell–cell junction structure following reduced renal proximal tubule lumen and microvilli loss (Fig. 1).

3. Cadmium (Cd) and kidney

The Cd pollution was first recognized by its complication named “Itai-itai”, following the second world war in Japan [40]. A few decades later, the experimental study revealed the harmful consequences of Cd depicting severe damages and histological changes in kidney along with renal dysfunction [41,42].

3.1. Cd and proteinuria

Proteinuria had been reported in workers belongs to Zn and Cd industry [43,44] and confirmed by different experimental study whereas Cd secretion was increased to 50-fold with proteinuria [45].

3.2. Toxicodynamic of renal toxicity by Cd

Following exposure, Cd is transported either from GI or lungs to blood plasma where it binds to albumin and a little of it secretes into the bile from liver. In addition to albumin, large amount of Cd make a complex with metallothionein (MT) that can easily be filtered by glomerulus, reabsorbed at proximal tubule and distal tubule by adsorptive endocytosis with the help of ZIP8 transporter situated on the apical surface of renal tubular cells [46,47]. Following entry into tubular cell, lysosome breaks the complex to free Cd; initiates the damage to kidneys through perturbing [Ca2+] homeostasis, electrochemical gradient [41], inducing oxidative stress, inflammatory cell infiltration and down-regulating mitochondrial coenzymes Q (e.g. Q9 and Q10) [48–53,54]. Regarding Cd-induced programed cell death of kidney, free radicals and ER-stress attribute separately depending on the types of cell. For example, increasing intracellular Ca2+ overload and depolarizing the mitochondrial membrane potential ER stress activates caspases (9 and

Fig. 1. Toxicodynamic of Pb–induced kidney toxicity.
3) to initiate apoptosis via ERK pathway, while excessive ROS activate glycogen synthase kinase (GSK-3β) to carry out either phagocytosis or apoptosis of mesangial cell [55]. Moreover, entrance of Cd into proximal tubules reduces cadherin-dependent (Ca2+ dependent) cell-cell junctions [56]. According to Prozialeck and Edwards, 2007, Cd also targets on cell-adhesion molecule possibly through regulating protein kinase C activation and MAPK signaling pathway prior to mitochondrial injury (Fig. 2) [56].

### 3.3. Treatment strategy against Cd

According to Agency for Toxic Substances and Disease Registry (ATSDR), for acute high dose toxicity of Cd, fluid replacement, mechanical ventilation, and oxygen supply are recommended [57]. Likewise to Pb toxicity for the chronic exposure, removal of the patient is the first step; proper clothing and eating habit are also considered. But no chelation therapy is recommended. Regarding long time chelation therapy, Nordberg, 1984 doubted about effectiveness [58].

Various studies on plants dictated the possible effective role against Cd-induced kidney toxicity (Table 2). This effectiveness might be due to the free radical quenching activity of phytoconstituents of plants, together with possible capabilities to reduce Cd absorption and accumulation, oxidative stress, and to increase the endogenous antioxidant activity, kidney function protecting nephron [48–53].

#### 4. Mercury (Hg) and kidney

Mercury is ubiquitous in nature and available in three forms: elemental mercury, organic mercury like methyl mercury and ethyl mercury, and finally inorganic mercury i.e. mercuric mercury. All form have notorious effects on organs including kidney [78] where males are more susceptible over female [59,60]. Human being can be exposed to Hg through many ways like contaminated food, battery industry or dental amalgam [61] and mercury-containing product handling.
including mining [78]. “Minamata disease” in Japan and disaster happened in Iraq from 1955 to 1972 pointed out the detrimental effect on human [62].

4.1. Hg and proteinuria

Proteinuria was also reported in Hg toxicity. An experimental study revealed female are more vulnerable to kidney toxicity exposed to Hg and effect on pars recta tubule cells are assumed to contribute in proteinuria [63]. Besides, damages of the proximal tubular cell and freely accessible through the glomerulus filter, sensitivity of lysosome could also attribute to proteinuria [64].

4.2. Toxicodynamics of renal toxicity by Hg

Long-term exposure to both organic and inorganic mercury is deleterious for health including kidney [65]. From systemic circulation, Hg is up taken by organic anion transport 1 (Oat1) and organic anion transport 3 (Oat3) into kidney specially into proximal tubules [60,66]. Here, the cleavage of carbon-mercury bond converts organic to inorganic mercury as metabolites either by the enzymatic or non-enzymatic process [67]. At the same time, Hg deposition is closely related to ROS generation, mRNA expression of MT, apoptosis and proximal tubule damage [68–70].

Organic anion transport 1 (Oat1) and organic anion transport 3 (Oat3) localize mainly in the lysosome of in the proximal tubule [66], uptake Hg into the kidney. As Hg^{2+} has a greater affinity to bind with thiol-containing enzymes [67], it inactivates the enzymes with thiol group through irreversible oxidation [71]; results in depletion of total thiol content and oxidative stress [72]. Inactivation of sulphhydril protein (e.g. Na+/K+-ATPase) also affects the cellular integrity interrupting membrane potential and volume of cells as well as cellular organelles [71]. Therefore, its consequences were observed with free radical generation (myeloperoxidase activity and MDA), and protein urea (activities of N-acetyl-beta-D-glucosaminidase (NAG)) [59,68]. Absence of detoxifying protein [63] or reduced selenolthiol containing antioxidant activity [i.e thioredoxin reductase (TrxR)] [73] also facilitate the proximal tubules damage. Interesting to note that NF-κB also play a crucial role in apoptosis linked renal damage increasing sensitivity to apoptosis which have been found both in vitro and in vivo studies [74]. But no immunological defect or glomerular damage at low dose of inorganic Hg were evidenced in the early study of Langworth et al., 1992 [75].

Mercury also reduces the function of tight junction protein in kidney and perturbs cellular permeability. According to Kawedia et al., 2008, Hg decreases transepithelial electrical resistance (TER) and facilitates the phosphorylation of tight junction protein, occludin via a protein kinase A (PKA) dependent mechanism [76] (Fig. 3).

### Table 2

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Effect of Cd on kidney</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>Decreases enzymatic antioxidants activity and non-enzymatic status, Decreases kidney function, increases LPO, tubular necrosis, degeneration, dilation, desquamation, thickening of basement membrane and luminal cast formation</td>
<td>Attenuates alteration considering all premises</td>
<td>[48]</td>
</tr>
<tr>
<td><em>Lactobacillus plantarum</em></td>
<td>Perturbation of Ca, Fe, Mn, Zn concentration Increases MDA, decreases CAT, SOD, GPx activity and GSH level. Cloudy swelling and necrosis of tubules and dilation of glomeruli. Decreases antioxidant activity, increases NO level, MDA</td>
<td>Normalizes the pathological condition through oral route rather IP administration</td>
<td>[49]</td>
</tr>
<tr>
<td>Flax seed oil (Linum usitatissimum)</td>
<td>No observation</td>
<td>Decreases hepatic LPO, increases CAT, GPx activity, GSH level. Normalizes the pathological condition</td>
<td>[50]</td>
</tr>
</tbody>
</table>

Fig. 3. Toxicodynamic of Hg-induced kidney toxicity.
Table 3
Possible beneficial effect of plants against Hg-induced kidney toxicity.

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Effect of Hg on kidney</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ginkgo biloba</em> extract</td>
<td>Increases ROS generation, tissue collagen, Myeloperoxidase (MPO) activity, Malondialdehyde (MDA), decreases endogenous antioxidant activity</td>
<td>Restores all biochemical alteration by Hg intoxication</td>
<td>[59]</td>
</tr>
<tr>
<td><em>Tea Polyphenols and Schisandrin B</em></td>
<td>Increases activity of NAG, ALP, LDH, decreases activity of endogenous antioxidant antioxidant, increases ROS generation, LPO, and apoptosis, histological alteration</td>
<td>Restores histological alteration, decreases oxidative stress, decreases activity of NAG, ALP, LDH.</td>
<td>[68]</td>
</tr>
<tr>
<td><em>Curcumin</em></td>
<td>Increases LPO, decreases CAT, SOD, Gpx activity and glutathione level, histological alteration, mRNA expression of MT</td>
<td>Reverses the histological alteration, mRNA expression of MT, decreases oxidative stress</td>
<td>[69]</td>
</tr>
<tr>
<td><em>Vitamin E</em></td>
<td>Increases activity of ALP, LDH, increases LPO, decreases CAT, SOD, Gpx activity and glutathione level, increases creatinine, BUN, increases Hg concentration, histological alteration</td>
<td>Restores histological alteration, decreases oxidative stress, decreases activity of ALP, LDH, decreases BUN, creatinine, decreases Hg concentration</td>
<td>[70]</td>
</tr>
<tr>
<td><em>Pomegranate seed oil</em></td>
<td>Increases MDA level, decreases total thiol content, increases blood urea and creatinine, protein conc. in urine, histological alteration</td>
<td>Decreases oxidative stress (MDA), decreases blood urea, creatinine and protein in urine, restores thiol content, presence of mild lesion in kidney</td>
<td>[79]</td>
</tr>
<tr>
<td><em>Tribulus terrestris fruit extract</em></td>
<td>Increases LPO, decreases CAT, SOD, GSH level.</td>
<td>Decreases LPO, increases CAT, SOD, GSH level.</td>
<td>[80]</td>
</tr>
<tr>
<td><em>Eruca sativa seed extract</em></td>
<td>Increases BUN and creatinine, decreases activity of CAT, SOD, Gpx, GR, decreases SH group, increases thiobarbituric acid reactive substances, presence of focal necrosis, and congested glomeruli and stroma in kidney histology</td>
<td>Scavenges DPPH, hydrogen peroxide (H₂O₂), hydroxyl radical (.OH) and nitric oxide (NO), superoxide.</td>
<td>[81]</td>
</tr>
<tr>
<td><em>Arabic gum</em></td>
<td>Increases blood creatinine, blood urea nitrogen, thiobarbituric acid reactive substances, Reduces activity of glutathione peroxidase (GSH-Px) and catalase, increases NO level Glomerular and tubular necrosis, interstitial nephritis, and desquamation of the tubular epithelial cells in the renal cortex in kidney histology</td>
<td>Normalizes the pathological conditions</td>
<td>[81]</td>
</tr>
<tr>
<td><em>Juglans sinensis Dode</em> extract*</td>
<td>Decreases GFR, increases plasma creatinine, increases LPO, decreases renal p-aminohippurate uptake</td>
<td>Normalizes the pathological conditions</td>
<td>[82]</td>
</tr>
</tbody>
</table>

4.3. Treatment strategy against Hg

According to Agency for Toxic Substances and Disease Registry (ATSDR), removal of the patient from the site is essential as prehospital management. Sometime chelation therapy might be considered on the basis of dose [77]. Different chelating agent like DMSA, 2,3-dimercapto-1-propanesulfonic acid (DMPS), Dpenicillamine (DPCN), or dimercaprol (BAL) are recommended for acute inorganic Hg poisoning, whereas for children FDA approved DMSA. The physician also recommends Glutathione and N-acetylcysteine (NAC) but facilitates the deposition of Hg at brain and kidney [36].

For decades, numerous approaches have been taken to find out possible effectiveness of plants against Hg-induced kidney toxicity (Table 3). A number of plants/plant derived compound demonstrated possible kidney protective effect by reducing Hg accumulation, free radicals, oxidative stress; by increasing total thiol content & endogenous antioxidants, due to in part of antioxidant activity of phytoconstituents.

5. Arsenic (As) and kidney

Arsenic (As) is a naturally occurring toxic metalloid prevalent in the earth’s crust. Drinking water is the major source of naturally occurring inorganic As. Around the world, 200 million of people are intoxicated by drinking water [83]. Developing countries like Bangladesh are most vulnerable to As poisoning and 57 million of people are at risk. According to Peters et al., 2014, 72% of wells water does not comply with the limits of world health organization at an area named Araihazar in Bangladesh during 2000, and more than 50% of the 6–11 million tube-wells containing As concentrations above the WHO guideline value of 10 μg/L [85].

Arsenic is eliminated by urinary excretion; therefore it can accumulate in the kidneys. Chronic kidney disease (CKD) is closely associated with exposure to As, which can be characterized with decrease estimated glomerulus filtration rate (eGFR) and inflammation. Besides cardiovascular disease, respiratory illness & cancer in the urinary tract (e.g. Bladder and kidney), skin and lung have been mentioned in various studies [84,86,87].

5.1. As and proteinuria

Intoxication with As also causes proteinuria including beta(2)-microglobulin urea [88] and higher in MT-null mice than the wild-type which depicts As detoxification by MT [89].

5.2. Toxicodynamics of renal toxicity by As

A co-relation with As accumulation and depletion of endogenous antioxidant activity is established and it is believed to accelerate tissue damage introducing oxidative stress condition [90–93]. Thereafter, the deposited inorganic As in kidney could be converted into methylated metabolite by the enzyme arsenic (+3 oxidation state) methyltransferase (As3mt), in consequence hydrenephrosis of kidney [94].

Briefly, binding of trivalent As to thiol-containing antioxidant, leads to series of events: decrease antioxidant activity [95], changes fatty acid composition [96], renal DNA damage and cell death modulating [Ca²⁺] concentration [97] and downregulates Nef-2 expression [91]. Arsenic also interrupt the mitochondrial electron transport chain by inhibiting function or activity of Isocitrate dehydrogenase, α-Ketoglutarate dehydrogenase, Succinate dehydrogenase, Cytochrome c oxidase, increasing LPO and decreasing antioxidant activity in mitochondria [98].

Meanwhile, As decreases the reabsorption and increases kidney dysfunction decreasing BBM enzyme activity [99] and membrane-bound ATPase-like Na⁺/K⁺/ATPase, Ca²⁺/ATPase, Mg²⁺/ATPase [91]. Kidney dysfunction (i.e. increased estimate glomerulus filtration rate) is also closely associated with ROS-mediated inflammation, observed in vivo study [87]; possibly triggering TNF-α mediated apoptosis [100]. Successfully, it also modulates CpG site at -168 bases upstream of transcription start site in the IL-8 promoter and its demethylation along with CBP/P300 recruitment; increased H3 histone acetylation leads to IL-8 mediated kidney pathology [101]. Apart from above, As also possess immunosuppressive effect, whereas it suppresses Th1 (IF-γ, IL-12), Th2 (IL-4, IL-10) and complementary protein C3a in the kidney;
**Table 4** Possible beneficial effect of plants against As-induced kidney toxicity.

<table>
<thead>
<tr>
<th>Plant / agent/extract name</th>
<th>Effect on kidney by arsenic</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silibinin</td>
<td>Increases apoptosis, NADPH oxidase, iNOS and NF-κB overexpression, decreases the activity of antioxidants and ATPase</td>
<td>Decreases caspase-3 mediated tubular cell apoptosis and decreases the NADPH oxidase, iNOS and NF-κB expression, upregulates the Nrf2 expression in the renal tissue, restores the activity of antioxidants and membrane bound ATPase.</td>
<td>[91]</td>
</tr>
<tr>
<td>Astaxanthin</td>
<td>Kidney dysfunction, arsenic deposition, decreases levels of Na + K + ATPase and sulfhydryl.</td>
<td>Decreases endogenous antioxidant level, increases LPO, increases ROS generation, DNA damage, renal interstitial hemorrhage, focal necrosis, expansion and hyperemia in renal capsule, plasmolysis of epithelium, and cellular swelling of the renal tubular cell</td>
<td>[93]</td>
</tr>
<tr>
<td>Ascorbic acid and/or α-tocopherol</td>
<td>Increases LPO, decreases antioxidants and enzymes present in mitochondria.</td>
<td>Normalizes the pathological conditions</td>
<td>[98]</td>
</tr>
<tr>
<td>Naringenin</td>
<td>Increases level of TNF-α, increases apoptosis</td>
<td>Decreases TNF-α level and apoptosis</td>
<td>[100]</td>
</tr>
<tr>
<td>Quercetin and monoisooamyl 2, 3-dimercaptosuccinic acid</td>
<td>Increases TBARS, arsenic deposition and depletion of Gpx, SOD, CAT activity.</td>
<td>Increases antioxidant potential and radical quenching action, decreases oxidative stress and restores renal function.</td>
<td>[108]</td>
</tr>
<tr>
<td>Acetyl-L-Carnitine</td>
<td>Increases MDA, and decreases SH content, GST, SOD, CAT, tubulointerstitial inflammation and cytoplasmic vacuolization with necrosis of tubules</td>
<td>Increases antioxidant activity</td>
<td>[110]</td>
</tr>
<tr>
<td>Selenium lentil diets</td>
<td>Increases arsenic concentration with lower urinary excretion.</td>
<td>Decreases arsenic conc., increases blood GSH level and urinary excretion.</td>
<td>[111]</td>
</tr>
<tr>
<td>Resveratrol (pretreatment)</td>
<td>Increases oxidative stress, decreases endogenous antioxidant, thiol content, selenium content and increases kidney arsenic accumulation, BUN, creatinine, cortex edema, tubular cell swelling, interstitial edema, glomeruli dilution and hyperemia, pyknotic nuclei and severe necrosis, and denudation of the tubular cells</td>
<td>Normalizes the pathological conditions</td>
<td>[112]</td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>Perturbation of carbohydrate metabolism, decreases enzyme activity of BBM, kidney dysfunction, decreases activity of endogenous antioxidant with oxidative stress and histopathological condition</td>
<td>Restores carbohydrate metabolism, activities of BBM, kidney function and antioxidant along with architecture</td>
<td>[113]</td>
</tr>
<tr>
<td>Biochanin A</td>
<td>Increases BUN, creatinine and urea, increases MDA, phospholipid, free fatty acid, decreases SOD, CAT, GSH level, degenerated renal tubules, elongation of urinary space and mild infiltration of inflammatory cells</td>
<td>Decreases BUN, creatinine and urea, decreases free fatty acid, increases antioxidant level, presence of mild degeneration of renal tubules.</td>
<td>[114]</td>
</tr>
<tr>
<td>Trichosanthes dioica root</td>
<td>Increases LPO, decreases GSH, and increases GSSG, decreases activity of Gpx and GR, CAT, SOD and increases % of DNA fragmentation.</td>
<td>Normalizes the pathological conditions</td>
<td>[115]</td>
</tr>
<tr>
<td>Folate and/or Vitamin B12</td>
<td>Increases urea and creatinine in blood, shrinkage of glomerular capsule, tubular lumen and tissue degradation</td>
<td>Decreases urea and creatinine in blood, increases the integrity of cellular structure</td>
<td>[116]</td>
</tr>
<tr>
<td>Hesperidin and Lipoic Acid</td>
<td>Tubular epithelium vacuolation, interstitial blood.</td>
<td>Restores the histopathology about to normal</td>
<td>[117]</td>
</tr>
</tbody>
</table>
makes it susceptible to pathogenic attack [102]. Interestingly, acute As toxicity causes decrease of mitochondrial function and up-regulates the expression of multidrug resistance-associated protein 2 (MRP2) which helps to excrete into urine and generate tolerance of kidney against As [103].

The metabolomic study suggested that altered energy metabolism (e.g. glycolysis, Krebs cycle), amino acid metabolism, choline metabolism, methionine cycle (transmethylation), purine metabolism and degradation of membrane phospholipids contributes to cell apoptosis in As toxicity [104]. In this context, attribution of profound damages to brush border membrane (BBM), mitochondria of renal proximal tubule could be, due to, perturbed carbohydrate metabolism, decreased TCA cycle, gluconeogenesis and or HMP-shunt pathway alteration [105]. Moreover, As also regulates the expression of various phase I and phase II aryl hydrocarbon receptors (AhR)-regulated metabolizing enzymes [phase I enzymes (cytochrome P450 1A1 (CYP1A1), CYP1A2) and phase II enzymes (NAD(P)H: quinone oxidoreductase-1 (NQO1), glutathione-S-transferase A1 (GSTA1))] [106] (Fig. 4).

5.3. Treatment strategy against Arsenic

Agency for Toxic Substances and Disease Registry (ATSDR) recommended aggressive intravenous fluid replacement therapy, gastric lavage, activated charcoal with a cathartic (e.g. sorbitol) for acute high dose As poisoning. Hemodialysis and chelation therapy with (2-3-dimercapto-1-propanesulfonate (DMPS), meso 2, 3-dimer-captosuccinic acid (DMSA) are also suggested. Nutrient and vitamins like Se, retinol could also be effective for promoting excretion of As from kidney [107].

List of plants and plant derived compounds which could be beneficial against As-mediated kidney toxicity is presented in Table 4. These plants and plant derived compounds exhibited their possible beneficial effects by increasing antioxidant activity, reducing oxidative stress, specially free radical quenching activity [108-110], increasing anti-oxidant enzyme activity regulating Nr-2 [91] and chelating activity against As [111]. Moreover, few of them might be effective to protect kidney in different ways: decreasing As accumulation [112], protecting mitochondria [98] & altered carbohydrate metabolism [113], increasing enzyme activity of BBM & membrane protein decreasing free fatty acid [114], DNA damage [93,115] and NF-kb, TNF-mediated apoptosis [91,100].

6. Conclusion

This comprehensive review on heavy metals and kidney toxicity dictates that we can easily be exposed to heavy metals from surroundings until proper management has been implied throughout the world to reduce environmental pollution by heavy metals. Following toxicity, they exhibits their notorious effect especially on kidney by facilitating oxidative stress, competing with essential metals like Selenium (Se), Zn and Ca, mitochondrial dysfunction, Ca²⁺ and ROS-mediated apoptosis. In the kidney, Cell-cell junction serves as the permeability and absorption of epithelial cells. Alteration by heavy metal was also evidenced except arsenic (no available data), which results in proteinuria and kidney dysfunction. Due to the fatal side effect of chelation therapy, concurrent treatment of combined therapy is more preferred than monotherapy, even at lower doses. Besides, vitamins and minerals together with potent antioxidant derived from plants might be used to treat acute exposure after thorough investigation and clinical trial. To sum up, antioxidants from plants and different supplements might play a crucial role in settling new approach to treat heavy metal poisoning.

Conflict of interest

Authors have declared no conflict of interest.

Source of funding

This work was financially supported by Walailak University (WU59122), Thailand.

Acknowledgment

Thankful to Walailak University for financial assistance.

References


