REVIEW

Cisplatin-Induced Nephrotoxicity; Protective Supplements and Gender Differences

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Abstract

Cisplatin (CDDP) has been widely used as a chemotherapeutic agent for solid tumors. The most common side effect of CDDP is nephrotoxicity, and many efforts have been made in the laboratory and the clinic to employ candidate adjuvants to CDDP to minimize this adverse influence. Many synthetic and herbal antioxidants as well as trace elements have been investigated for this purpose in recent years and a variety of positive and negative results have been yielded. However, no definitive supplement has so far been proposed to prevent CDDP-induced nephrotoxicity; however, this condition is gender related and the sex hormone estrogen may protect the kidney against CDDP damage. In this review, the results of research related to the effect of different synthetic and herbal antioxidants supplements are presented and discussed with suggestions included for future work.

Keywords: Cisplatin- nephrotoxicity- antioxidant- trace elements- herbal agents- gender

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Introduction

The molecular structure of many therapeutic agents that are used in the clinic contain metals (Chen et al., 2009; Frezza et al., 2010). Cisplatin (CDDP); cis-[PtII(NH3)2Cl2] as an anticancer agent (Frezza et al. 2010; Weiss et al., 1993) is known with the full name of cis-diamminedichloroplatinum(II). (Reedijk et al., 1985). CDDP was synthesized in 1845 and was named as Peyrone's chloride, and later its structure was provided (Alderden et al., 2006; Desoize et al., 2002; Florea et al., 2011; Kauffman et al., 2010). CDDP has undergone several improvements; including transplatin that was first synthesized by Reiset in 1844 (Natile et al., 2001), and finally, the Kurnakow method detected trace quantities of transplatin contaminant (Woollins et al., 1983).

Subsequent experiments made clear the biological effect and inhibition of cell division for platinum (Rosenberg, 1971; Rosenberg et al., 1967; Rosenberg et al., 1965). It was also reported that the cis form of the platinum (IV) complex, [PtCl4(NH3)2], was the agent responsible for inhibition of tumors (Pizarro et al., 2009). Accordingly, platinum (II) complex, cis-[PtCl2 (NH3)2], and platinum (IV) complex, cis-[PtCl4 (NH3)2], were tested against sarcoma tumors in mice, and it was shown to have a remarkable anti-tumor activity and shrinking large solid tumors accompanied with improved mice survival (Rosenberg et al., 1970; Wang et al., 2005). Based on these findings, CDDP as Palatinol® (Bristol-Myers Squibb) became available for clinical practice in 1978 (Florea et al. 2010; Jamieson et al., 1999; Kelland, 2007). The successful results for CDDP in testicular cancer, ovarian and bladder cancers, osteogenic sarcoma, head and neck tumors, endometrial and cervical cancers, and non-small cell lung cancer were documented (Jamieson et al., 1999; Reedijk, 1987; Reedijk et al., 1985). Understanding of drug mechanism is extremely important for a better application of the therapeutic agents in clinic. In this regard, it is clear that CDDP reacts with various cellular components including proteins, DNA, RNA, membrane phospholipids, microfilaments, and thiol-containing molecules (Jamieson et al., 1999; Rebillard et al., 2008; Speelmans et al., 1996; Speelmans et al., 1997). CDDP maintains a relatively stable neutral state in blood (Alderden et al., 2006; Jamieson et al., 1999; Jung, 2005; Reedijk, 1987; Reedijk et al., 1985) and binds to blood proteins while this binding is hampered by high concentration of chloride in blood; so one day after CDDP administration, 65–98% of the platinum in blood is protein-bound (Alderden et al., 2006; Barnham et al., 1996; Ivanov et al., 1998; Keppler,

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1993). The CDDP component that remains intact can enter tumor cells (Mellish et al., 1994; Wiltshaw, 1979). In addition, due to the lower chloride concentration inside the cell, chloride ions are replaced with water molecules, and this platinum compounds; cis-[Pt (NH3)2(H20) CI]+ is an active form of CDDP bound to DNA (Alderden et al., 2006; Chu, 1994; Jamieson et al., 1999; Jung, 2005; Reedijk, 1987; Reedijk et al., 1985). Generally, it is accepted that cell death occurs due to inhibition of DNA synthesis (S phase arrest) (Harder et al., 1970; Howle et al., 1970; Jamieson et al., 1999; Salles et al., 1983; Weiss et al., 1993). However, some studies indicated that cells treated with CDDP progressed through the S phase, where DNA synthesis occurs, and were arrested in the G2 phase (Sorenson et al., 1988a; Sorenson et al., 1988b). Finally, the analysis of apoptosis induced by CDDP reveals DNA fragmentation followed by loss of membrane integrity and cell shrinkage (Sorenson et al., 1990).

Renin angiotensin system (RAS) and CDDP-induced nephrotoxicity

The renin angiotensin system (RAS) has been involved in the pathogenesis of kidney diseases and drug-induced nephrotoxicity. CDDP-induced acute renal failure in rats indicates structural alteration in the renal tubular epithelia, which is associated with changes of renal functions. CDDP alters renal hemodynamics (Hye Khan et al., 2007), attenuates glomerular filtration rate (GFR) and renal blood flow (RBF), and increases plasma renin activity and renal vascular resistance (RVR); this is while it does not affect mean arterial pressure (MAP) (Cornelison et al., 1993; Hutchison et al., 1988; Hye Khan et al., 2007; Matsushima et al., 1998; Winston et al., 1985). Hemodynamic changes may be related to RVR induced by tubular-glomerular feedback (Cornelison et al., 1993). RAS receptors may also involve in CDDP-induced nephrotoxicity, and in this regard, it is reported that angiotensin type 1 receptor (AT1R) blocker protects the kidney against CDDP in male rats (Haghighi et al., 2012).

Immediately after CDDP administration, although RBF and GFR do not undergo alterations, the rate of proximal reabsorption decreased significantly; so destructive effect of CDDP initiates from proximal tubule before changes in renal hemodynamics occur (Daugaard, 1990; Daugaard et al., 1989). CDDP also decreases sodium transporters including Na-K-ATPase and Na-K-2CL co-transporters and Na-H exchanger (Daugaard et al., 1989). The effect of CDDP on sodium and water transport represents an early change in kidney to induce tissue toxicity (Daugaard et al., 1989; Lajer et al., 2005a). CDDP also causes abnormities in the renin-aldosterone system (Bosl et al., 1986; Iida et al., 2000). Treatment with CDDP reduces mineralocorticoid receptor binding (Iida et al., 2000) as the genes for amiloride-sensitive epithelial sodium channel and Na-k-ATPase are regulated by aldosterone positively (Masilamani et al., 1999; Wang et al., 1994).

Plasma levels of aldosterone and angiotensin II increase after CDDP therapy (Okui et al., 2012) whereas administration of angiotensin converting enzyme (ACE) inhibitor and AT1R blockers fails to reduce the elevation of plasma aldosterone level induced by CDDP (Okui et al., 2012). This finding suggested that ACE-mediated AngII/AT1R signaling system may not be involved in acute renal failure induced by CDDP (Daemen et al., 1999). ACE inhibitors either synthetic such as captopril or herbal have protective effects against CDDP-induced nephrotoxicity. Another group of ACE inhibitors is flavonoids that can improve renal function in CDDP-treated rats (Balasuriya et al., 2011). Losartan is an AT1R blocker and antioxidant agent, and it has been the target of treatment to protect against CDDP-induced nephrotoxicity (Saleh et al., 2009) while different responses have been reported in acute or chronic administration of AT1R blocker (Deegan et al., 1995; Haghighi et al., 2012). It is accepted that CDDP may disturb renal hemodynamics parameters including RAS; however, the induced nephrotoxicity is not due to hemodynamics disturbance alone. AT1R blocker or ACE inhibitors may attenuate renal toxicity in CDDP therapy, but it is hard to accept these agents as the optimal protective agents against CDDP-induced nephrotoxicity.

Synthetic antioxidants supplementation on CDDP-induced nephrotoxicity

Vitamins C and E are essential nutrients that act as non-enzymatic factors in cytosol and membrane cells. These vitamins have protective role against CDDP-induced nephrotoxicity (Ajith et al., 2009; Ajith et al., 2007). Vitamin C is involved in many biological processes, and acts as a protective agent against neoplasms and the damage involved in oxidative stress (Greggi Antunes et al., 2000) and renal glutathione (GSH) depletion (Meister, 1992). Under conditions such as low iron level, low concentration of vitamin C causes lipid peroxidation (Halliwell B, 1989). Vitamin C also inhibits glomerular damages by preventing production of free radicals (Appenroth et al., 1997).

Vitamin E as an antioxidant and membrane stabilizer has protective effect against CDDP-induced nephrotoxicity (Fang et al., 2002; Wang et al., 1999) while CDDP decreases vitamin E in kidney tissue (Nazıroğlu et al., 2004). Ajith et al. have shown that the use of CDDP increases serum creatinine (Cr) and blood urea nitrogen (BUN) levels while supplementation of vitamins C and E reduces serum Cr and BUN levels (Ajith et al., 2007). Administration of a single dose of vitamins C, E and combination of vitamins C and E decrease the serum level of malondialdehyde (MDA) after CDDP treatment (Ajith et al., 2009). Twenty four hours after CDDP administration, 55% increase in GSH concentration was detected while vitamin C induced a slight decrease in GSH (Greggi Antunes et al., 2000). Naziroglu et al. showed that administration of CDDP increases MDA and decreases GSH peroxidase (GSH-Px) levels in serum (Nazıroğlu et al., 2004).

The glycoside derivatives of vitamin C are more stable, and are able to act as free radicals scavengers (Fujinami et al., 2001) and antioxidant agents (Mathew et al., 2007), which reduce DNA lipid membrane injuries (Claycombe et al., 2001). Monoglycoside tocophrol is a water-soluble derivative (Kapoor et al., 2002) and its combination with vitamin C could prevent the CDDP-induced antioxidant depletion (Maliakel et al., 2008). It is also suggested that

pretreatment with vitamin E compensates CDDP-induced nephrotoxicity, and this effect is not enhanced by a second vitamin E administration, while simultaneous administration of vitamin C and E twelve hours prior to CDDP intensifies the protective effect of vitamin E (Appenroth et al., 1997). GSH has protective effect against CDDP nephrotoxicity, and its depletion leads to lipid peroxidation; so treatment with vitamins C and E improves GSH concentration and enhances protection against CDDP side effects (Abraham, 2005; Babu et al., 1995). This is while decrease in GSH concentration leads to enhance susceptibility to chemical damage and oxidative stress, because GSH as a non-protein thiol plays an important role in formation of the metabolite drug conjugate compounds (Rana et al., 2002). CDDP causes a reduction of 64% in zinc (Zn) and 55% in copper (Cu) content of cytosol, and decreases superoxide dismutase (SOD) activity. This activity is related to reduced content of Cu and Zn as essential elements for SOD activity (Sharma, 1985).

AT1R blockers such as losartan also act as an antioxidant. Actually, losartan acts via inhibiting vasoconstriction and increasing renal blood flow (Ullman et al., 2001a; Ullman et al., 2001b). It is reported that co-administration of vitamin C and losartan do not have protective effect for kidney tissue; in contrast to losartan alone that shows protective effect. Co-administration of vitamin C and losartan may lead to drug interaction that limits the effectiveness of losartan (Ashrafi et al., 2012b). Similarly, co-administration of losartan and vitamin E do not protect against CDDP-induced nephrotoxicity (Nematbakhsh et al 2012a) while estradiol may abolish the losartan effect against CDDP-induced nephrotoxicity (Ghadirian et al., 2015).

Erythropoietin (EPO) is another antioxidant studied in this regard. It belongs to the large family of cytokine-1. Hypoxia releases EPO from fibroblast-like cells in the cortex of the kidney (Jacobson et al., 1957). EPO initially was identified as a glycoprotein hormone produced mainly in the liver and kidney (Fisher, 2003). It is more than 30 years that kidney is recognized as the primary site of EPO production (Jacobson et al., 1957) and bone marrow as its target organ (Nagai et al., 1995b). EPO also has anti-apoptotic (Bartesaghi et al., 2005; Mohamed et al., 2013), antioxidant (Katavetin et al., 2007), and anti-inflammatory (Marti, 2004; Mohamed et al., 2013) activities. EPO has been used as a nephroprotective against various kidney injuries such as kidney damage induced by ischemia-reperfusion (Sharples et al., 2004; Vesey et al., 2004), CDDP-induced nephrotoxicity (Bagnis et al., 2001; Kong et al., 2013; Rjiba-Touati et al., 2011; Yalcin et al., 2003; Zafirov et al., 2008), and gentamicin-induced kidney toxicity (Rafieian-Kopaei et al., 2012). The results obtained by Zafirov et al. showed that increase in BUN and Cr as well as proteinuria induced by CDDP are improved after EPO administration, and they suggested that recombinant human EPO significantly reduces renal failure and renal damage induced by CDDP (Zafirov et al., 2008). In a study, it was reported that RBF and GFR significantly reduced on the fourth day after CDDP administration while on the ninth day after EPO administration, both RBF and GFR increased, and tubular cell regeneration on the fourth day after EPO injection enhanced significantly (Bagnis et al., 2001). EPO administration reduces the serum level of Cr induced by CDDP; and also cell death induced by CDDP terminated by EPO. In addition, EPO suppresses the increased expression of endoplasmic reticulum stress markers (CHOP and GRP78) and attenuates the suppression of phosphatidylinositol-3kinase/akt signaling induced by CDDP (Kong et al., 2013). Based on our laboratory data, EPO improved CDDP-induced nephrotoxicity while female sex hormones inhibits this effect (Pezeshki et al., 2012).

A study has shown that administration of EPO in animals treated with CDDP improves GSH level and decreases MDA level in the serum while increased expression of inducible nitric oxide (NO) synthase (iNOS) and serum nitrite level are attenuated by EPO (Mohamed et al., 2013). EPO by several mechanisms including reduction of oxidative and nitrosative stress, decreased expression of vascular endothelial growth factor (VEGF), and improvement of Bc12 immunoreactions in tubular cell can improve renal function (Mohamed et al., 2013).

Alpha lipoic acid (ALA), a necessary cofactor for mitochondrial enzymes, is introduced as a new antioxidant and acts as free radical scavenger (Biewenga et al., 1997; Packer et al., 1995). This agent is used for neurodegenerative disorders, heavy metal toxicity, and oxidative tissue injury (Nagamatsu et al., 1995; Panigrahi et al., 1996). It also has therapeutic effects on diabetes, polyneuropathy, cataract, neurodegeneration, and nephropathies (Alegre et al., 2010; Amudha et al., 2007). It serves similar to lipoamid as a cofactor in the multi-enzyme system for catalysis of oxidative decarboxylation of α-keto acids (Marangon et al., 1999). ALA chelates platinum and prevents its accumulation in renal tissue in CDDP-induced nephrotoxicity (Nagamatsu et al., 1995; Panigrahi et al., 1996). Somani et al. have reported that increased Cr level induced by CDDP is improved after administration of graded doses of ALA (12, 50, 100 mg/kg) (Somani et al., 2000). Furthermore, CDDP administration reduces GSH, GSH-Px, and GSH-reductase; which increase after treatment with different doses of ALA (50, 100 mg/kg), decreases SOD activation, and increases MDA concentration that is corrected by ALA (Somani et al., 2000). ALA is a thiol containing nucleophile that reacts with free radicals and heavy metals. Thereby, it might act as scavenger of reactive oxygen species free radicals, chelator of platinum in renal tissue that inhibits lipid peroxidation, and increases glutamine (Somani et al., 2000). Treatment of mice with CDDP elevates MDA level and decreases GSH while ALA administration decreases MDA and increases GSH levels. In addition, CDDP treatment leads to decline in catalase, SOD, and GSH-Px activities, all of which improve after ALA administration. ALA also ameliorates oxidative stress and enhances gene expression of antioxidant enzymes (El-Beshbishy et al., 2011). Moreover, ALA reduces the depletion of GSH level in the kidney of rats treated with CDDP and provides nephroprotection (Mistry et al., 1991; Somani et al., 1995). The recovery of renal SOD, catalase, GSH-Px, and GSH

reductase with lipoic acid pretreatment suggests that this factor can protect these enzymes three days after CDDP administration (Mistry et al., 1991; Somani et al., 1995).

N-acetylcysteine (NAC) is a thiol-containing antioxidant, which was originally introduced as a mucolytic drug (Dickey et al., 2005a; Mishima et al., 2006). The results have shown that NAC is able to inhibit activation of P38 mitogen-activated protein kinases (p38MAPK), biosynthesis of tumor necrosis factor alfa (TNF-α), and activation of nuclear factor-κB (NF-κB) (Li YQ, 2006). It is also able to inhibit CDDP-induced apoptosis and it is shown to be the precursor of GSH (Wu et al., 2005). NAC is the compensator for cellular GSH resources and also acts as scavenger of oxygen free radicals (Nisar et al., 2002). The effect of NAC is due to a direct effect of the drug (e.g., inactivation of hydroxyl radicals) or it is related to induction of GSH production (Fishbane et al., 2004). Previous studies have shown that NAC improves CDDP nephrotoxicity in humans and rats (Appenroth et al., 1993; Dickey et al., 2008; Dickey et al., 2005a; Somani et al., 2000). It should be considered that the route of NAC administration is important in protection of CDDP nephrotoxicity; for instance, intravenous infusion leads to better results in comparison with oral or intraperitoneal administration (Dickey et al., 2008). In a case study, Hanad et al. have reported that in 52-year-old female who developed acute renal failure after administration of 150 mg CDDP for treatment of squamous cell cancer of the esophagus, the serum levels of BUN and Cr increased from 12 and 0.7 mg/dL to 24 and 1.8 mg/dL, respectively, on day 5 after CDDP administration. She was subjected to treate with NAC (140-mg/kg-body weight followed by 70 mg/kg every 4 h for 4 days), and two days later, renal function began to improve, and after 10 days, her serum Cr reduced to 0.8 mg/dL (Nisar et al., 2002). Another study indicated that NAC may reverse CDDP-induced nephrotoxicity (Sheikh-Hamad et al., 1997). NAC (500 mg kg-1 per day for 9 days) restored the renal hemodynamics, as well as the biochemical and histopathological changes induced by CDDP (Abdelrahman et al., 2010). Luo et al. have demonstrated that NAC suppresses oxidative stress, p38 MAPK activation, caspase-3 cleavage, tissue apoptosis, renal dysfunction, and morphological damage induced by CDDP. They suggested that at least in part, oxidative stress and cell death pathways related to p38 MAPK are involved in the pathogenesis of CDDP-induced acute renal failure (ARF) (Luo et al., 2008). It seems that inhibition of p38 MAPK activity inhibits oxidative stress and therefore improves renal function.

Deferoxamine (DFX) is a natural trihydroxamate that has antioxidant properties (Freedman et al., 1989). Possibly its antioxidant property is independent of its capability to bind iron (Shimoni et al., 1994). It is an iron chelator and is used to treat iron overload (Maxwell, 1995). It has been reported to be useful in treatment of Alzheimer's (Cuajungco et al., 1998), stroke (Hurn et al., 1995), encephalomyelitis (Bowern et al., 1984), acute renal failure (Paller et al., 1988; Shah et al., 1988; Walker et al., 1988), and CDDP-induced nephrotoxicity (Baliga et al., 1998a). Iron plays an important role in tissue damage caused by oxidative stress (Halliwell et al., 1989). Increased iron level catalyzes free radical reactions involved in ischemia/reperfusion-induced acute renal failure (Baliga et al., 1993), glycerol-induced acute renal failure (Baliga et al., 1996), and CDDP-induced nephrotoxicity (Baliga et al., 1998a). Iron chelators, including DFX and 2,3-dihydroxybenzoic acid, have protective effect in several models of acute renal failure (Paller et al., 1988; Shah et al., 1988; Walker et al., 1988) and oxidant-induced damage (Paller et al., 1991; Walker et al., 1991) including CDDP nephrotoxicity. Similarly, CDDP-induced acute renal failure is improved by DFX administration in rats (Baliga et al., 1998a). It is nice to know that hydroxyl radical scavengers, dimethyl sulfoxide, mannitol, and benzoic acid significantly decrease CDDP-induced toxicity; and treatment with dimethyl sulfoxide or dimethylthiourea causes significant protection against CDDP-induced ARF; taken together, these data support critical role of iron in mediating tissue injury via hydroxyl radical in this model of nephrotoxicity (Baliga et al., 1998a). DFX pretreatment reduces renal dysfunction and lipid peroxidation induced by CDDP; while at the same time increases non-protein sulfhydryl (-SH) concentrations in the kidney tissue (Özdemir et al., 2002), which involved ROS system (Guelman et al., 2004).

Glutamine is one of the most abundant amino acids in the body (Bergstrom et al., 1974). One of its most important roles is to participate in the metabolism of GSH (Wu et al., 2004). GSH is a potent antioxidant and plays an important role in the metabolism of exogenous and endogenous substances (Wu et al., 2004). GSH participates in many cellular reactions. It directly scavenges free radicals and other reactive oxygen species (hydroxyl radical, lipid peroxyl radical, peroxynitrite, and H2O2), and is indirectly related to enzymatic reactions (Fang et al., 2002). Mora et al. have reported that CDDP injection increases renal GSH level (Mora et al., 2003), and the level returned to normal by glutamine administration. In addition, 24 hours after glutamine administration, the increased lipid peroxidation induced by CDDP came back to the normal level; however, glutamine does not inhibit the increase in renal GSH 7 days after treatment (Mora et al., 2003). Salicylates are anti-inflammatory, analgesic, antipyretic and antithrombotic agents. Aspirin is the most common form that is metabolized in the serum within 15 to 30 minutes, and its anti-inflammatory effect is related to inhibition of cyclohexane-oxygenase 2 (Chernov et al., 1997). Aspirin also acts as hydroxyl radical scavenger (Ghiselli et al., 1992). Li G et al. have demonstrated that administration of salicylate reduces BUN and serum Cr levels induced by CDDP (Li et al., 2002). It seems that antioxidant agents, in general have some protective effect against CDDP-induced nephrotoxicity. However, selection of the most appropriate antioxidant supplement is of great importance. Fighting the CDDP-induced oxidative stress via antioxidants is only one side of the coin, while special attention should be paid to the other side of the coin including renal hemodynamics and kidney processes and reduction of CDDP effect on target tumor. In addition, it should be mentioned that

some others protective approaches against CDDP induced nephrotoxicity like oxygen pretreatment have been studied by others (Rasoulian et al., 2010; Kaeidi et al., 2013; Rasoulian et al., 2014; Saadat et al., 2014;).

Mineral elements and CDDP-induced nephrotoxicity

Mineral elements such as magnesium (Mg), Zn, Cu, sodium (Na), and selenium (Se) are necessary in biological and physiological processes (Bray et al., 1990; Fawcett et al., 1999; Rayman, 2000; Soetan et al., 2010). Mg as the most common cation in the body plays an essential role in enzymatic reactions (Fawcett et al., 1999). Advantages of Mg supplementation in diabetes (Soltani et al., 2005) and endothelial function (Barbagallo et al., 2010) have been documented. Hypomagnesaemia is one of the most important disturbances in cancer patients (Anvari et al., 2010; Arunkumar et al., 2011; Hodgkinson et al., 2006; Lajer et al., 2005b; Stewart et al., 1985; Zumkley et al., 1982). In addition, hypomagnesaemia may induce hypocalcaemia (Lyman et al., 1980) via three mechanisms of inhibiting parathyroid hormone secretion, reducing responses of tissue to parathyroid hormone (Anast et al., 1976; Estep et al., 1969), and impairing the release of calcium from bone (Johannesson et al.,1983 et al., 1983). Clinical studies indicate that Mg supplements could ameliorate CDDP-induced nephrotoxicity (Anvari et al., 2010; Hirai et al., 2013; Hodgkinson et al., 2006; Kidera et al., 2014; Muraki et al., 2012; Wcislo et al., 2008; Willox et al., 1986; Yoshida et al., 2014). Recently, experimental studies have shown that administration of Mg supplementation did not reduce CDDP-induced nephrotoxicity, rather intensified it. Ashrafi et al., (2012a) examined intraperitoneal administration of various doses of Mg sulphate (20, 80, and 200 mg/kg) against CDDP-induced nephrotoxicity in rat model. Noteworthy the low dose of Mg supplementation aggravated renal dysfunction, while high doses of Mg sulphate did not protect the kidney against CDDP. In addition, Soltani et al., (2013) demonstrated that oral administration of Mg sulphate (10 g/l) exacerbated nephrotoxicity in diabetic and normoglycemic rats (Soltani et al., 2005). There is a correlation between Mg level and OCT2, and up-regulation of OCT2 in Mg-deficient diet enhances renal accumulation of CDDP (Yokoo et al., 2009). In another study mice were exposed to Mg-deficient diets for two weeks, and after CDDP administration, the animals received 0.3% MgCl2 and MgSO4 (100 mg/kg/day) through drinking water and subcutaneous injection, respectively, and Mg supplementation ameliorated renal failure and apoptosis induced by CDDP (Solanki et al., 2014). Oral administration of Mg sulphate (3 and 10 g/l) alone do not protect the kidney against CDDP-induced nephrotoxicity while the combination of AT1R blocker; losartan and Mg sulphate (3 g/l) ameliorate the nephrotoxicity induced (Razmjoo et al., 2014). Some studies, however, have shown positive effects of various doses of Mg (0.6% in diet, 2% and 0.6% in drinking water) on renal failure induced by cyclosporine (Asai et al., 2002; Burdmann et al., 1994; Kimura, 2000; Mervaala et al., 1997; Pere et al., 2000; Yuan et al., 2005). The combination of Mg supplementations with potassium (Pere et al., 2000) or NAC (de Araujo et al., 2005; Malek, 2013) are efficient to attenuate renal function against various failure models in the kidney.

Se is another necessary element which participates in biological processes (Rayman, 2000). A clinical study showed cancerous patients under CDDP chemotherapy that received Se supplementation did not exhibit ARF (Ghorbani et al., 2013), while similar results were reported by Hu et al. study (Hu et al., 1997). Francescato et al. administered Se (2 mg/kg, by gavage) 24 h and 1 h prior to administration of CDDP and continued for the next seven days. They observed that Se treatment ameliorated serum level of Cr and renal level of MDA as well as kidney damage, but not other parameters such as renal GSH and Cr clearance (Francescato et al., 2001). Se reduces nephrotoxicity induced by CDDP (Baldew et al., 1988; Berry et al., 1984) without direct effect on tumor cells or antitumor activity of CDDP (Berry et al., 1984). In addition, depletion of Se itself induces oxidative stress, which results in progression of CDDP-induced nephrotoxicity (Araya, 1990; Fujieda et al., 2006). This is while Se treatment decreases such renal damage (Araya, 1990; Fujieda et al., 2006) with no effect on blood cells and liver (Araya, 1990; Araya et al., 1990). Baldew et al. examined the effect of sodium selenite (2 mg/kg) before and after CDDP administration and suggested protective effect of Se on nephrotoxicity when it was administered before CDDP (Baldew et al., 1989). They also concluded that selenite protect kidney against CDDP toxicity through reaction of selenite metabolite with CDDP in the presence of GSH without reducing CDDP antitumor activity (Baldew et al., 1991). The combination of Se with a high dose of vitamin E also improves antioxidant state in CDDP-induced nephrotoxicity animal model (Naziroglu et al., 2004). This was confirmed by Hemati et al. in a clinical study (Hemati et al., 2012). In contrast with previous reports, it was demonstrated that Se orally has no protective effect against nephrotoxicity induced by CDDP (Antunes et al., 2001). Also, oral single dose of Se could ameliorate proximal tubular injury, but not renal dysfunction (Camargo et al., 2001). In another study, Se nanoparticles inhibited generation of ROS induced by CDDP in cell culture and blocked apoptosis in a dose-dependent manner (Li et al., 2011). Different supplementation regimens of Se ameliorate renal toxicity induced by CDDP and decrease mortality rate (Naganuma et al., 1984; Naganuma et al., 1983; Satoh et al., 1992; Satoh et al., 1989; Vermeulen et al., 1993; Yokoyama et al., 1985; Zhang et al., 2008a). Pretreatment with Se could inhibit CDDP-induced kidney and liver damage (Imaga et al., 2014). Furthermore, short-term administration of sodium selenosulfate reduces gastrointestinal disturbances induced by CDDP while long-term administration of sodium selenosulfate is more efficient in reducing side effects of CDDP in comparison with sodium selenite (Li et al., 2012).

Daley-Yates et al., (1985) examined the effect of chloride salts on nephrotoxicity induced by CDDP, and reported that administration of sodium chloride (NaC1) or NH4C1 90 min before CDDP could prevent nephrotoxicity in rats, although NaC1 had no protective effect when

given 3 or 24 hr after CDDP administration. Another study showed that NaCl loading has lower protective effect than acetazolamide, although it decreases the rate of mortality induced by CDDP (Heidemann et al., 1990). The patients who received sodium loading alone or sodium loading with forced diuresis showed no difference in incidence of nephrotoxicity induced by CDDP (Leu et al., 2010).

Sodium thiosulfate (ST) suppresses the nephrotoxicity induced by CDDP in human gastric cancer transplanted in nude mice, although reduces antitumor effect of CDDP (Saito et al., 1989; Wagner et al., 1988). Therefore, it is suggested to use low dose of ST in CDDP chemotherapy (Fujii et al., 1988). Intraperitoneal or intravenous injections of ST attenuate the CDDP-induced hypomagnesemia and nephrotoxicity (Wong et al., 1988). ST is also known as effective agent to decrease level of total kidney platinum (Nagai et al., 1995a), and administration of ST increases antitumor effects of CDDP in bladder tumor (Sagiyama et al., 1983), while it also decreases nephrotoxicity in the patients treated with CDDP (Vance et al., 1986). In a clinical trial, simultaneous administration of ST and CDDP permits higher dose of CDDP (at least two folds) in patients under chemotherapy (Pfeifle et al., 1985) without raising the Cr level (Howell et al., 1982). In addition, ST protection increases survival in guinea pigs treated by CDDP and could enhance animal tolerance against doses three times higher than the toxic dose of CDDP (Leitao et al., 2003). It should be emphasized that the time of ST administration is very important to exhibit anti-cytotoxic and anti-apoptotic effects against CDDP (Dickey et al., 2005b). ST is found to block CDDP-induced nephrotoxicity, although platinum concentration in subcellular fractions indicates that ST cannot fully protect against nephrotoxicity (Uozumi et al., 1986). Different routes of sodium malate administration; e.g., intravenous, intraperitoneal, subcutaneous, and oral are shown to reduce nephrotoxicity induced by CDDP through binding to CDDP and converting into diammino-platinum (II) malate (Ueda et al., 1998a; Ueda et al., 1998b).

Zn has protective and antioxidant effects (Bray et al., 1990). Zn sulphate pretreatment is shown to increase survival in CDDP-induced nephrotoxicity and reduce iNOS activity (Joshi et al., 2004). Also, Zn supplementation could ameliorate nephrotoxicity induced by CDDP through preventing lipid peroxidation (Huang et al., 1997; Srivastava et al., 1995; Tuzcu et al., 2010) and inflammation (Tuzcu et al., 2010).

Máthé et al., (2013) reported that chronic administration of CV247 (an aqueous mixture of Cu gluconate, manganese (Mn) gluconate, vitamin C, and sodium salicylate) can reduce renal histological damage induced by CDDP through decreasing reactive oxidants, but it does not prevent increasing the levels of BUN and Cr. Another study has shown that metalloporphyrins such as iron(III) tetrakis (N-methyl-4'-pyridyl) porphyrin (FeTMPyP) and Mn(III) tetrakis (4-benzoic acid) porphyrin (MnTBAP) as peroxynitrite scavengers attenuate nephrotoxicity induced by CDDP via decreasing DNA fragmentation, apoptosis and nitrative stress, and this protection effect is observed 12 h after CDDP administration (Pan et al., 2014). An in vivo study reported that, combination of iron and aminolevulinic acid (a precursor of tetrapyrrole compounds) can prevent mitochondrial structural changes and ameliorate decreasing in mitochondrial enzymes, while it decreases apoptosis and increases heme concentration in CDDP toxicity (Terada et al., 2013). However, in vivo and in vitro studies indicate that CDDP increases catalytic iron that results in elevating BUN and Cr levels (Baliga et al., 1998a; Baliga et al., 1998b) and iron chelators ameliorate renal dysfunction (Baliga et al., 1998a; Özdemir et al., 2002). Accordingly, it is clear that CDDP therapy disturbs the levels of some trace elements; however, the correlation between CDDP-induced nephrotoxicity and disturbance of a specific trace element is not completely known. Therefore, it is hard to suggest a specific trace element as a supplement to fully protect the kidney against CDDP-induced toxicity.

Diseases and CDDP-induced nephrotoxicity

In clinic, patients that undergo chemotherapy may suffer from other medical conditions such as hypertension, ischemic heart disease and diabetes mellitus (Mathe et al., 2011). Here, a question is proposed "Could the diseases affect nephrotoxicity induced by CDDP?" A study showed that nephrotoxicity is aggravated by diabetes mellitus plus ischemic heart disease in lung cancer patients (Mathe et al., 2011). In another study, it is reported that nephrotoxicity develops similarly in diabetic and non-diabetic patients treated by CDDP (Weese et al., 2009). Animal experiments have shown that diabetic kidney is resistance against CDDP-induced nephrotoxicity (Sarangarajan et al., 2004; Sarangarajan et al., 1996; Sarangarajan et al., 1999; Scott et al., 1989; Scott et al., 1990; Valentovic et al., 1991), and administration of insulin reverses this protection (Sarangarajan et al., 2004) but normalization of high glucose in diabetic animal model by oral vanadyl sulphate have no effect on diabetes-induced protection against CDDP nephrotoxicity (Sarangarajan et al., 1999). Various mechanisms have been proposed to be responsible for protection induced by diabetes against CDDP in rats. Firstly, urinary platinum excretion is greater in diabetic group than that in non-diabetic group for 48 h after CDDP injection (Valentovic et al., 1991). Secondly, diuresis induced by high levels of glucose is not responsible for attenuation of nephrotoxicity in diabetic model (Scott et al., 1990). Thirdly, diabetic state decreases renal platinum accumulation (Cacini et al., 1991; Sarangarajan et al., 1997; Sarangarajan et al., 2004). OCT2 system is responsible for transportation of CDDP into the proximal tubule cells, and this system is impaired in the kidneys of streptozotocin (STZ)-diabetic rats (Grover et al., 2002) and this in turn disturbs renal platinum accumulation in the diabetic kidneys (Sarangarajan et al., 1997). However, diabetes has no protective effect in patients against CDDP-induced nephrotoxicity. The involved mechanisms are not known and further investigations are required to determine the underlying cause. In this regard, Mathe et al., (2011) reported that both hypertension plus ischemic heart disease and diabetes mellitus plus ischemic heart disease predispose lung cancer patients to nephrotoxicity induced by CDDP.

Herbal agents in CDDP-induced nephrotoxicity

Today, herbal medicine provides an opportunity for treatment of some diseases and prevention of abnormal side effects induced by synthetic drugs (Sohn et al., 2009). Patients who are not satisfied with chemical medicine may focus on herbal medicine. Different studies have documented antioxidant effect of herbal agents (Ekor et al., 2010; Elmhdwi, 2013; Gulec et al., 2006; Hadjzadeh et al., 2013; Sohn et al., 2009); so, many researches have been performed to determine the role of herbal medicine in CDDP-induced nephrotoxicity (Table 1).

Oxidative stress in renal tubules is caused by different free oxygen radicals such as superoxide anion, hydrogen peroxide, and hydroxyl radicals (Baek et al., 2003). It seems that phenolic components, especially flavonoids, are powerful sources of antioxidant. This is while many plants contain flavonoids, and these components exert protective effect against CDDP-induced nephrotoxicity (Karimi et al., 2005; Öztürk et al., 2007). Silymarin has a mixture of three flavonolignans that can scavenge free radicals and increase GSH level (DerMarderosian et al., 2002; Thomas, 2000). Ginkgo biloba is a source of flavonoids and considering its quercetin content is considered as an antioxidant herb (Inselmann et al., 1995; Song et al., 2013; Trompezinski et al., 2010).

Carob and Morus alba L. leaves are rich in flavonoids (Elmhdwi, 2013; Nematbakhsh et al., 2013b). Other studies have shown that grape seed proanthocyanidin extract (GSPE) has antioxidant effect that could downregulate oxidative stress proteins, while its antioxidant effect is 50 times higher than vitamin E and 20 times that of vitamin C (Chacón et al., 2009; Gao et al., 2014; Li et al., 2008; Terra et al., 2009). Lipid peroxidation caused by oxidative stress and thiobarbituric acid reactive substances (TBARS) is the final product of lipid peroxidation that increases when CDDP is administrated (Karthikeyan et al., 2007; Saad et al., 2009). Free radicals exert wide tissue damage due to their reaction with macromolecules such as membrane lipids, proteins, and nucleic acids (Conklin et al., 2008; Satoh et al., 2003). GSH is one of the critical compounds to maintain cell integrity, regulate cell function, and protect cells from oxidative stress and free radicals. It is shown that thiol portion of GSH reacts with alkylating agents such as CDDP (Atessahin et al., 2005), and CDDP decreases the level of GSH in the kidneys (Yilmaz et al., 2004). Other antioxidant enzymes are GSH S-transferase (GST) and GSH peroxidase (GSH-Px) that are GSH-depended antioxidant enzymes (Karthikeyan et al., 2007). GSH-Px is an essential endogenous antioxidant enzyme that can delete hydrogen peroxide and lipid

Table 1. Different Effects of Some Herbal Extracts in Different Studies on CDDP-Induced Nephrotoxicity Models

Herbal extract	Observation
Paeonia suffruticosa (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Curcumal longa (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Centipeda minima (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Loranthus parasiticus (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Pulsatilla dahurica (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Sinapis alba (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Scutellaria barbata (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Rheum ribes (Hadjzadeh et al., 2013)	Decreasing BUN, No effect on Cr and kidney tissue damage score (KTDS)
Milk thistle (Karimi et al., 2005)	Decreasing BUN, Cr, and KTDS
Grape seed (GSPE) proanthocyanidin extract (Gao et al., 2014; Saad et al., 2009)	Decreasing BUN, Cr, apoptosis, inflammatory and oxidative stress, and DNA degradation
Polyphenolic extract of soybean (PESB) (Ekor et al., 2010)	Decreasing BUN, Cr, KTDS, and oxidative stress
Rubia cordifolia (RCE) (Joy et al., 2008)	Decreasing BUN, Cr, oxidative stress and MDA
Ginkgo biloba (Song et al., 2013)	Decreasing KTDS, BUN, Cr, oxidative stress
Curcuma comosa (Jariyawat et al., 2009)	Decreasing BUN, Cr, oxidative stress
Morchella esculenta (Nitha et al., 2008)	Decreasing BUN, Cr, oxidative stress
Ceratonia siliqua L. (Elmhdwi, 2013)	Decreasing BUN, Cr, MDA, oxidative stress
Pomegranate flower (Motamedi et al., 2014)	Decreasing BUN, Cr, KTDS
Fennel essential oil (Mazaheri et al., 2013)	No effect on BUN, Cr, MDA and KTDS
Morus alba (Nematbakhsh et al., 2013b)	Decreasing BUN, Cr, KTDS
Prunus persica flesh (Lee et al., 2009)	Decreasing BUN, Cr and oxidative stress
Brassica rapa (Kim et al., 2006)	Decreasing MDA, oxidative stress, BUN, Cr, and urinary LDH
Leea asiatica (Sen et al., 2013)	Decreasing BUN, Cr, Uric acid, and MDA
Pueraria tuberosa (Nagwani et al., 2010)	Decreasing BUN, Cr, oxidative stress, KTDS
Lagerstroemia speciosa (Priya et al., 2007)	Decreasing BUN, Cr, oxidative stress
Ginger extract (Ali et al., 2013)	Decreasing BUN, Cr, KTDS, and apoptosis
Phellinus rimosus (Ajith et al., 2002)	Decreasing oxidative stress

peroxide and protect cellular membrane from peroxidative damages (Karthikeyan et al., 2007). Another enzyme is SOD that catalyzes dismutation of the superoxide anion (O_2), which is detoxified to H_2O by catalase (Valavanidis et al., 2006). It is indicated that administration of GSPE accompanied with CDDP decrease the increment of hiobarbituric acid reactive substances (TBARS), increase the activity of catalase, SOD and GSH-dependent antioxidant enzymes (Saad et al., 2009); while activity of antioxidant enzymes is related to the levels of Cu and Zn (Badary et al., 2005).

Some phytoestrogens especially isoflavones found in soybean are useful in attenuation of the oxidative stress (Nitha et al., 2008; Zhu et al., 1999). The phenolic extract of soybean is protective against nephrotoxicity induced by CDDP and gentamicin (Ekor et al., 2006). Polyphenolic extract of soybean (PESB) inhibits renal xanthine oxidase activity (Ekor et al., 2010) and protects against kidney toxicity (Gulec et al., 2006). The extract of Rubia cordifolia has antioxidant effects and plays a protective role against loss of antioxidant enzymes such as GSH-dependent enzymes, catalase and SOD caused by CDDP administration (Joy et al., 2008). Large amounts of antioxidant components have been isolated from roots of Rubia and Curcuma comosa Roxb. These components include several types of anthraquinones such as 1-hydroxy-2-methylanthraquinone, nordamnacanthal, and diarylheptanoid that scavenge free radicals and decrease oxidative stress (Jariyawat et al., 2009; Tessier et al., 1981). In another study, low dose of pomegranate flower extract could ameliorate CDDP-induced nephrotoxicity via its antioxidant properties (Motamedi et al., 2014). It has been demonstrated that some plants containing phytoestrogens also have antioxidant effect because of their components such as isoflavonoids and trans-anethole (Mazaheri et al., 2013; Setchell, 1998). In addition, it has been demonstrated that phytoestrogens are beneficial for renal diseases (Velasquez et al., 2001). Trans-anethole as an agent with estrogenic activity could be found in high amounts in fennel essential oil (Devi et al., 1985; Farook et al., 1991). Although trans-anethole is also an antioxidant, it is seems that estrogen and trans-anethole do not affect the CDDP-induced nephrotoxicity (Devi et al., 1985).

It is clear that CDDP causes inflammation and genotoxicity (Jung et al., 2007; Pabla et al., 2008). Degradation of DNA is one of the most important reasons for cell death in renal tubules (Basnakian et al., 2005). It is demonstrated that CDDP polymorphonuclear leukocyte infiltration, which is indicated by increment of myeloperoxidase (MPO) activity (Pan et al., 2009). Previous researches have shown that Paeonia suffruticosa, grape seed, soybean, and Ginkgo biloba extracts have anti-inflammatory effect (Chacón et al., 2009; Ekor et al., 2010; Sohn et al., 2009; Song et al., 2013), and the extracts of grape seed, mushrooms, and carob could protect DNA from CDDP-induced injury (Elmhdwi, 2013; Gao et al., 2014; Nitha et al., 2008). CDDP can also increase inducible NO synthase (iNOS). In this regard, Song et al. reported that Ginkgo biloba can diminish NO production by inhibiting both gene expression and enzymatic activity of iNOS (Abd-Elhady et al., 2013; Song et al., 2013). Nigella sativa (Hadjzadeh et al., 2012), Garlic (Anusuya et al., 2013), Olive leaf (Kaeidi et al., 2016; Jafaipour et al., 2016) and Corcin (Naghizadel et al., 2008) also were studied by others to find their protective role against CDDP induced nephrotoxicity. Most herbal antioxidants that were subjected to use as supplement to protect the kidney against CDDP-induced toxicity have been demonstrated to have positive results. However, until now, there is no single acceptable herbal agent that is able to prevent CDDP nephrotoxicity to be recommended clinically.

NO on CDDP-induced nephrotoxicity

NO has been suggested to play an important role in CDDP-induced nephrotoxicity (Saad et al., 2001). NO is a key cellular factor synthesized by NO synthase from L-arginine (Nathan et al., 1994). NO possess both pro-apoptotic and anti-apoptotic functions; depending on the cell type and concentration of NO (Kolb, 2000). NO induces apoptosis by its ability to produce oxidative stress and activate caspase (Klein et al., 2003). In contrast, It has been reported that endogenous NO production or presence of appropriate amount of NO inhibits apoptosis both in in vivo and in vitro experimental models (Chung et al., 2001). It was previously reported that NO plays role in CDDP nephrotoxicity and usage of 2 - amino -4 - methylpyridin as a NOS inhibitor aggravates CDDP - induced nephrotoxicity (Saad et al., 2001).

Srivastava et al. showed that L-NG-nitroarginine methyl ester (L-NAME) as a nonselective NOS inhibitor attenuates CDDP-nephrotoxicity by reduction of BUN and Cr levels and lipid peroxidation (Srivastava et al., 1996). According to their report, CDDP increases the level of lipid peroxidation as well as NO and NOS activity, while L-NAME decreases amount of NO production in the kidney and liver. Thus, NOS inhibition may be helpful in prevention of developing toxic side effect of CDDP. This is while, it has been demonstrated that administration of L-arginine as the NO donor in rats treated with CDDP resulted in amelioration of indexes of CDDP-induced nephrotoxicity (Saleh et al., 2005). Also, intravenous injection of L-arginine accompanied by CDDP was demonstrated to lead to significant protection of kidney function (Quan et al., 1994). L-arginine also induces protective effects via increment of RBF, GFR, and vasodilator effect; so, L-arginine exerts its protective effects against CDDP-induced nephrotoxicity via hemodynamic and non-hemodynamic mechanisms (Quan et al., 1994). So far, the role of NO in experimental models remains controversial; non-protective role (Srivastava et al., 1996) or protective role (Mansour et al., 2002; Quan et al., 1994) against CDDP nephrotoxicity. It showed that mRNA and iNOS levels are increased in rats treated by CDDP and selective inhibitor of iNOS reduces CDDP-induced nephrotoxicity (Chirino et al., 2004; Chirino et al., 2008). They proposed that NO production is toxic and the main source of NO is iNOS (Chirino et al., 2008). NO produced under oxidative stress condition reacts with superoxide (O2-) and modifies biological molecules such as amino acids. It is demonstrated that there is enhancement of peroxynitrite (ONOO) production in CDDP-induced nephrotoxicity (Chirino et al., 2004).

It observed increment in mRNA levels of iNOS in the kidney 4 h after CDDP injection, and administration of iNOS inhibitor 3 days after CDDP injection prevented enhancement of Cr and BUN levels; decreased kidney tubules injury, and was protective against CDDP-induced oxidative stress and nitrosative (Deng et al., 2001). However, Saad indicated that inhibition of NOS aggravates kidney injury (Saad et al., 2001). This controversy may be related to the type of inhibitors. In addition, it is reported that the effect of L-arginine in CDDP-induced nephrotoxicity is gender-related (Eshraghi-Jazi et al., 2011) while L-arginine decreases the serum levels of BUN and Cr in male but not in female. Another study indicated that L-NAME promotes CDDP-induced nephrotoxicity in male rats (Moslemi et al., 2013).

Furthermore, it is demonstrated that aminoguanidine (AG) has protective effect against nephrotoxicity induced by CDDP (Mansour et al., 2002). AG is a compound structurally similar to L-arginine and inhibits iNOS (Misko et al., 1993). Administration of AG 5 days before and after single injection of CDDP reduces the rise in the serum levels of urea and Cr. AG also normalizes the decreased level of albumin (Misko et al., 1993). AG administration before and after CDDP normalizes urine volume, and pretreatment with AG decreases kidney mass and lipid peroxide. AG does not ameliorate the depletion of GSH content or the decrease in catalase activity induced by CDDP. They concluded that overproduction of iNOS might be the cause of several toxicities induced by CDDP. They proposed that the protective effect of AG may be related to its antioxidant effects and AG may be helpful as a protective agent against CDDP nephrotoxicity (Misko et al., 1993).

Gender difference in CDDP-induced toxicity

Gender difference in tumor growth process is one of the important subjects that is highlighted in clinical and experimental researches. A sex dimorphism in antitumor response to CDDP is observed in the growth of the Dalton's lymphoma where female mice show an accelerated tumor growth compared with male mice (Gupta et al., 2008). In CDDP therapy, the severity of weight loss, prolonged heat latency, sciatic motor nerve conduction velocity, and atrophy of nucleus and neuronal cell body were higher in males than females; while decrease in myelinated fiber diameter, myelin thickness, and myelinated fiber density were more significant in females (Wongtawatchai et al., 2009). Nephrotoxicity as a major side effect of CDDP found to be gender-related (Nematbakhsh et al., 2013a; Nematbakhsh et al., 2012c). CDDP increases the serum levels of BUN and Cr, kidney MDA levels, KTDS, kidney weight, and weight loss more in males than in females (Nematbakhsh et al., 2013a; Nematbakhsh et al., 2012c). In the study of Stakisaitis et al., male rats excreted more sodium after CDDP administration, and the Na/Cl ratio was significantly higher in male than female rats, which may be related to higher tubular toxicity in males (Stakisaitis et al., 2010). However, when CDDP is accompanied with different supplements, different results may observe in males and females. L-arginine shows protective effects against CDDP-induced nephrotoxicity in male rats; however, it promotes kidney injury in female rats (Eshraghi-Jazi et al., 2011). Losartan as an AT1R blockade has higher protective effects against CDDP-induced nephrotoxicity in males than females (Haghighi et al., 2012). Moreover, EPO in CDDP-treated animals fail to improve kidney damage in female rats, while it has protective effect against CDDP-induced nephrotoxicity in male rats (Eshraghi-Jazi et al., 2013). Furthermore, administration of vitamin E in CDDP-induced nephrotoxicity model decreases kidney injury and kidney dysfunction biomarkers to normal values in male rats but it does not have ameliorative effect on CDDP-induced toxicity in female rats (Jilanchi et al., 2013). Dexamethasone induces CDDP resistance in lung cancer cells in a gender dependent manner, and lung cancer cells in females show higher resistance to CDDP by dexamethasone as compared to those in males (Zhang et al., 2008b). It has been documented that serum nitrite concentration increases after CDDP administration in males but not in females, and co-administration of vitamin E and CDDP decreases the serum nitrite level in males while this was not the case in females (Nematbakhsh M, 2013a). Accordingly, CDDP-induced nephrotoxicity must be considered as a gender-related condition, and the exact underlying mechanisms should be determined. The most common organic cation transporter in kidney is organic transporter 2 (OCT2), which is expressed prominently in the basolateral membranes of proximal tubules. The action of OCT2 leads to accumulation of various cationic drugs as well as CDDP into proximal tubular epithelial cells, and stimulates CDDP-sensitive cells (Yonezawa et al., 2005). It is found that the expression level of renal OCT2 is higher in male rats (Urakami et al., 1999). It is indicated that up to 3 min after CDDP administration, the total clearance of CDDP is higher in male than female rats and the renal tissue uptake clearance of CDDP is greater in male than female rats (Yonezawa et al., 2005). Moreover, renal OCT2 expression decreases in castrated rats (Yonezawa et al., 2005), and it is reported that testosterone recovers renal OCT2 expression (Urakami et al., 2000). Administration of CDDP in tumor-bearing mice with Dalton's lymphoma indicated higher inhibition of tumor growth due to increased apoptosis and DNA fragmentation in male than female mice; while in vitro study indicated lower survival rate for male tumor cells in the proximity of CDDP (Gupta et al., 2008). In addition, the expression of p53 in the Dalton's lymphoma cell was higher in CDDP-treated male than that in female mice (Gupta et al., 2008). It is interesting that carboplatin toxicity can be affected by population and gender. It was shown that female Yoruban population (African descent) cell lines has lower sensitivity to carboplatin in comparison with male cell lines whereas in a European descent population gender difference was not seen (Huang et al., 2007), Also carboplatin IC50 (inhibition 50% cell growth) was higher in the African descent versus the European descent but this different was observed only in females of two strains (Huang et al., 2007). A study on the effect of CDDP-induced cytotoxicity on renal proximal tubular cells with different age, sex, and species (monkey and rat) indicated renal proximal tubular cells of the rats

have higher susceptibility to CDDP compared with those in monkeys; however, this study indicated sex and age are not associated with CDDP-induced renal proximal tubular cell injury in Sprague-Dawly rat (Lu et al., 2005). Furthermore, the different aspects of CDDP-induced toxicity in both genders may contribute to the phenotypic difference observed among the populations while gender difference has been shown in some populations and male gender is more susceptible to CDDP toxicity compared to female. Moreover, the probability of CDDP-induced nephrotoxicity is higher in male rats than females. This may be because of higher contribution of cationic transporter OCT2 in male gender than female or may be related to sex hormone alteration after CDDP injection.

CDDP therapy reduces testosterone levels (Imamura et al., 1996; Kinkead et al., 1992; Longo et al., 2011; Salem et al., 2012). Men in complete remission of testicular cancer for over two years show lowered testosterone levels (Wiechno et al., 2007). Also, 25-48% decrease in testosterone synthesis is reported in CDDP-therapy patients (Carreau et al., 1988). Decrease in testosterone level is accompanied with elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in CDDP treatment (Aydiner et al., 1997; Malarvizhi et al., 1996a; Strumberg et al., 2002). Decreased activity of renal beta-glucuronidase during CDDP-treatment reflects the decreased availability of testosterone (Malarvizhi et al., 1996b). It is reported that CDDP suppresses the spermatogenesis and steroidogenesis by inhibiting the steroidogenic marker enzyme activity (Reddy et al., 2010). CDDP generates ROS that may inhibit testosterone production (Masubuchi et al., 2006; Mori Sequeiros GarcÃa et al., 2012). Testosterone supplementation was stated to reduce the side effects of CDDP (Vawda, 1994). Also, activity of renal beta-glucuronidase increases in rats supplemented with testosterone propionate (Malarvizhi et al., 1996b). The decreased microsomal enzyme activity is nearly restored when testosterone propionate is given once a day for 7 days after CDDP-treatment (Imamura et al., 1996). However, high dose of testosterone damages spermatogenesis in animals treated with low dose of CDDP (Aminsharifi et al., 2010). A recent study indicated that testosterone in low dose (physiologic dose) protects the kidneys against CDDP-induced nephrotoxicity; while high dose promotes nephrotoxicity (Rostami et al., 2014).

The effect of tamoxifen, as an estrogen antagonist receptor, on CDDP sensitivity has not indicated any correlation between tamoxifen effect on CDDP sensitivity and estrogen receptors, and this conception reveal that CDDP sensitivity of ovarian cancer cells are not linked with expression of estrogen receptors (Nowak-Markwitz et al., 2010). CDDP increases the level of FSH and decreases estradiol concentration in mice (LiNing, 2011). Also CDDP decreases ovarian and uterus weights, reduces the number of follicles and causes structural damage in the ovary; however, use of gonadotropin-releasing hormone (GnRH) combined with estrogen protects ovary against CDDP damage in mice (LiNing, 2011). CDDP and estrogen receptors bind with DNA, but CDDP decreases estrogen receptor affinity for DNA (Massaad-Massade et al., 2000). Effects of estrogen and CDDP on growth of human ovarian cancer cell line HO-8910 shows that 17-β estradiol does not inhibit the apoptosis but enhances proliferation of human ovarian cancer cell line HO-8910 (Grott et al., 2013). Vitamins E and C, and losartan have antioxidant and nephroprotective effects against CDDP, but this effect is abolished in the presence of pharmacological doses of estrogen (Nematbakhsh et al., 2012a). In addition, EPO has antioxidant, anti-apoptotic, and anti-inflammatory effects that result in nephroprotectant effect; however, it could not protect kidney against CDDP in the presence of estrogen (Pezeshki et al., 2012). Evaluation of estrogen role in CDDP-induced nephrotoxicity could not confirm the nephroprotective role of estrogen against CDDP although its cardioprotective effects is highlighted (Pezeshki et al., 2013). In addition, progesterone reduces the effect of CDDP in ovcar3 cells via progesterone receptor membrane component-1 (PGRMC1), because overexpression of PGRMC1 increases the cellular binding sites for progesterone and attenuates the killing effects of CDDP by about 50% while depleting PGRMC1 enhances the killing effect of CDDP in the presence of progesterone by 50%, and using PGRMC1 antibody in the presence of progesterone sensitizes the cells to CDDP (Peluso et al., 2008). It is also demonstrated that progesterone attenuates CDDP-induced toxicity in ovarian cancer cells via progesterone receptor (Zhu et al., 2013), and co-administration of high dose of progesterone (25 mg) (sustained-release pallet) and CDDP (2 mg/kg/week) increases platinum effect and facilitates CDDP toxicity in the two cell lines ovcar-3 and SKOV-3 in epithelial ovarian cancer cells and tumor genesis is suppressed by combination of CDDP and progesterone (Murdoch et al., 2008). Both estrogen and progesterone pretreatments result in resistance of A549 non-small cell lung cancer cells in vitro to CDDP and thus decrease CDDP-induced apoptosis, while this phenomenon is not antagonized by estrogen and progesterone antagonists such as ICI 182,780 and RU486 (Grott et al., 2013). Evaluation of oxytocin effect on CDDP-induced nephrotoxicity shows that oxytocin has a protective effect against CDDP-induced nephrotoxicity (Elberry et al., 2012).

It seems that interaction between CDDP and female sex hormones indicates that estrogen enhances CDDP sensitivity in tumor cells. At high pharmacological dose, it promotes kidney toxicity, but at low pharmacological dose has no effect on CDDP-induced kidney injury. Progesterone reduces the effect of CDDP in ovarian cancer cells and protects ovarian cancer cells from CDDP by progesterone receptor whereas co-administration of high dose progesterone and CP increases platinum effect and facilitates CDDP toxicity. Combination of estrogen and progesterone results in CDDP resistance and decreases apoptosis. Based on this result, the physiological or low pharmacological dose of progesterone and combination dose of estrogen and progesterone may protect kidney against CDDP. It also seems that keeping the sex hormone testosterone at the physiological level after CDDP therapy can help prevent CDDP side effects.

The results of many different researches in the laboratories and clinics were documented in the literature to show how the renal side effect of CDDP can be reduced.

Moreover, there are still many running researches to examine or to develop agents against CDDP-induced nephrotoxicity. Nevertheless, most experimental researches are designed in normal animals rather than in tumor models. The research on CDDP-induced nephrotoxicity cannot be stopped; however, It is the time to test the suggested supplements in real animal cancer models to make sure that the supplements do not reduce the direct effect of CDDP on tumors. In other words, an optimal candidate supplement should have two characteristics; protect the kidney against CDDP-induced toxicity, does not attenuate the direct effect of CDDP on the tumor (Wang et al., 2014).

Finally, according to this review several suggestions may provide to reduce CDDP induced nephrotoxicity:

1. CDDP induced nephrotoxicity is gender related. It seems female gender involves with the lower risk of nephrotoxicity after CDDP therapy.

2. Estrogen may increase the risk of renal toxicity after CDDP therapy, so CDDP therapy in women is recommended when the serum level of sex hormone estrogen in not high in the body.

3. To use the antioxidant as a supplementation to protect the kidney against CDDP induced nephrotoxicity, special care is needed. Some antioxidants have protective role to prevent CDDP induced nephrotoxicity in male, however the same antioxidants have not protective role against CDDP induced nephrotoxicity in female.

4. CDDP therapy has not only increased stress oxidative in the kidney as well as in the body, but also it disturbs renal hemodynamics, trace elements levels, RAS component, etc., Therefore and logically there is no expect to solve all the disturbances by one antioxidant supplementation. However, a suitable supplementation could reduce the progress of kidney toxicity after CDDP therapy.

5. According to previous studies, it is the time to select the few best protective agents which have the best laboratory evidences related to CDDP induced nephrotoxicity, and examine their protective role against CDDP induced nephrotoxicity in animals tumor models and design clinical trial studies to test the protective role of these agents in patients subjected to CDDP therapy.

Conflict of interest

The authors declare no conflict of interest.

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