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Mechanistic impact of medicinal plants affecting cisplatin-induced nephrotoxicity; an overview

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Abstract

Cisplatin is a powerful chemotherapy drug that is administered to treat a wide range of cancers. However, its clinical use is limited due to kidney damage and the reduction in glomerular filtration rate that occurs in 15% to 30% of patients. Several mechanisms lead to renal dysfunction after cisplatin administration, including direct damage to proximal tubular epithelial cells that causes necrosis and apoptosis. Cisplatin administration is accompanied by the production of reactive oxygen species (ROS), which causes lipid peroxidation, proteins and nucleic acids oxidation, cell membrane degradation, and finally reduction in glomerular filtration. The most prominent effect of cisplatin-induced nephrotoxicity (CIN), which can be progressive, is hypomagnesemia, Fanconi syndrome and anemia. Cisplatin nephrotoxicity is more prominent in individuals who received higher doses of this drug, or in patients who had previous chemotherapy regimen and presence of renal dysfunction. This paper is sought to describe cisplatin nephrotoxicity and the protective role of medicinal plants in preventing the renal toxicity. In this regard, the role of antioxidants will be specifically addressed.

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Introduction

Cisplatin, with the full name of cis-dichlorodiammine-platinum, is a synthetic and anti-tumor compound commonly used in clinics as an anticancer drug for treating tumors such as head and neck, bladder, lung, esophageal, cervical, metastatic breast, testicular and ovarian cancers. Cisplatin-induced nephrotoxicity (CIN) is the most important reason for reducing the dose of this drug. A large number of acute kidney failure cases in hospitalized patients are due to the unavoidable prescription of this drug. Despite the use of hydration to reduce CIN, in approximately one-third of patients receiving cisplatin, occurs irreversible kidney damage. Today, the incidence of CIN is a limiting factor which prevents the administration of higher doses of this agent.

Key point

Several mechanisms lead to renal dysfunction after cisplatin administration, including direct damage to proximal tubular epithelial cells that causes necrosis and apoptosis of tubular cells.

In addition to destroying cancer cells, this drug also has destructive effects on healthy tissues (1). Cisplatin inhibits mitosis and induces apoptosis by stimulating oxidative stress and creating crosslinking of DNA strands in cancer cells (2). Dysfunction of renal tubules leads to acute and chronic renal failure, which is one of the complications of this drug that occurs in 15%-30% of patients (3). The incidence of this complication was more pronounced in the early years of using this drug (4). Today, cisplatin is used in

various chemotherapy protocols, despite its high incidence of acute renal failure. However, due to the potency of this drug, its administration is not limited, since this drug is still one of the main agents of chemotherapy protocols. Medicinal plants have been used for a long time as a safe remedy to treat various diseases and prevention of drug-induced toxicity (5).

This paper is sought to describe cisplatin nephrotoxicity and the protective role of medicinal plants to prevent renal toxicity. Since free oxygen radicals play a major role in the development of CIN, therefore antioxidants can be effective in reducing the kidney injury.

Materials and Methods

To conduct this review paper, articles published between 1975 and 2018 and indexed in databases Scientific Information Database, PubMed, Institute for Scientific Information and Scopus were searched. Attempts were made to use the articles published within the past 30 years. Keywords used include cisplatin, nephrotoxic, antioxidant, chemotherapy, and the names of medicinal plants below. After reviewing the articles retrieved, relevant articles were used. This review article mainly sought to investigate and introduce the plant compounds and their potential antioxidant, antioxidant enzyme-increasing, lipid peroxidation-decreasing, and kidney tissue damage-reducing properties.

Mechanisms of cisplatin action

Cisplatin damage proximal tubular epithelial cells cause necrosis and apoptosis. The process started with increasing and releasing pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6, interferon-gamma and caspase, which cause renal leukocyte infiltration, DNA destruction and induction of cell death (6). It is thought that free radical production and lipid oxidation are the main causes of progression of CIN (7). The mechanism of anticancer impact of cisplatin is an interaction with purine base DNA function, which leads to stopping the proliferation of tumor cells and inducing apoptosis (8). Free oxidant radicals reduce glomerular filtration and cause acute nephrotoxicity in the tubules, particularly S3 segment of proximal tubules (9)

The complications of cisplatin

Cisplatin has numerous side effects, one of them is nephrotoxicity by inflammation in the interstitial tissue (10). Hypomagnesemia is another complication which is due to loss of magnesium through the urine because of damage to the thick, ascending part of Henle loop and distal tubules. This complication may develop hypokalemia, which exacerbates renal injury and increases the mortality due to cisplatin (11). A Fanconi like a syndrome, due to damage to proximal tubule cells, was also reported. This syndrome is caracterized by increased urinary excretion of glucose and amino acids. However, classic Fanconi syndrome has not been reported (12). Anemia is also commonly seen in patients receiving cisplatin, while the severity of this anemia is more than cisplatin suppressive effect on bone marrow. This condition might be due to renal failure. In human and animal studies, it has been pointed out that cisplatin may lead to erythropoietin deficiency by inducing damage to the renal tubules. This mechanism also causes anemia, and therefore administration of erythropoietin stimulating agents is effective in treating the anemia (13). Other parameters that may increase CIN include; female gender, elderly, smoking, hypoalbuminemia, and history of kidney disease (14). Cisplatin nephrotoxicity is more prominent in individuals who received higher doses of this drug, or in patients who had previous chemotherapy regimen and presence of renal dysfunction (15). Other side effects of cisplatin include alopecia, hiccups, seizure, loss of appetite, nausea, vomiting, and digestive discomfort (16).

Diagnosis

To diagnose CIN determination of serum urea and creatinine levels, glomerular filtration rate and renal histological findings and some biomarkers are useful (17).

Antioxidant therapy to reduce cisplatin renal toxicity

Turin

As an endogenous antioxidant agent, turin is produced from the amino acids cysteine and methionine in the liver. It has beneficial effects on a variety of inflammation models, including puromycin amino nucleoside-induced nephropathy (18), and streptozocin-induced diabetic nephropathy. According to recent studies, it was thought that co-injection of turin and cisplatin in male rats leads to protection against cisplatin's degrading effects and significantly reduced cisplatin-induced kidney damage. Improvement in renal function is due to the regulation of the osmotic activity of the kidney is the protective mechanism of Turin. The amounts of urea and creatinine and lipid peroxidation level significantly decreased, and catalase increased in pre-treated animals with turin (19).

Crocin

Crocin is a carotenoid compound in saffron that is water-soluble and has various pharmacological effects. A study showed that crocin has nephroprotective effects and prevents renal ischemia(20). Crocin is also effective to prevent aflatoxin B1 which induced acute hepatic injury. In addition, crocin has inhibitory effects on the growth of cancer cells *in vitro* (21), and also prevents genetic damage induced oxidative stress in the mouse model (22). In another study, it has been shown that crocin increases the synthesis of glutathione and prevents oxidative stress in the PC-12 brain cells. Considering the above-mentioned effects and the mechanism of cisplatin cytotoxicity, the process of inhibiting, free radicals and reactive oxygen species (ROS)-induced oxidative stress, and also increasing

the synthesis of glutathione, crocin can reduce tubular injury and, as a result, prevent acute CIN. Accordingly, it is anticipated that crocin can be used as an agent to reduce the renal side effects of cisplatin (21).

Olive (Olea europaea)

Olea europaea is a shrub from the *Olea* genus with evergreen leaves. The plant is used in traditional medicine as a laxative, refrigerant, and tonic agent, and is effective in treating urinary tract infections and relieving headache (23). *O. europaea* leaf has been detected to exhibit a variety of properties including antibacterial and antiviral (24), and hypotensive activities through blocking L-type calcium channels (25). Some compounds of *O. europaea* leaf also have antioxidant properties, including phenolic compounds such as oleuropein, tyrosol, hydroxytyrosol and caffeic acid (26). It seems that increasing the dose of *O. europaea* and the duration of its administration, can increase plasma levels of oleuropein and other antioxidant substances that lead to increase in the efficacy of the extract in reducing CIN. By inhibiting free radicals and ROS-induced oxidative stress, and by increasing the synthesis of glutathione, crocin can reduce tubular injury and, as a result, prevent acute CIN (27).

Quercetin

Oral administration of quercetin, as a bioflavonoid and a polyphenolic compound with potent antioxidant properties, before and after cisplatin treatment, significantly reduced the side effects of cisplatin, including acute renal failure, indicated by an ameliorated effect on function and morphology of the kidney (28).

Flavonoids, silibinin, Phellinus rimosus

Administration of some other active ingredients, as well as plant extracts, such as flavonoids, silibinin, and the ethyl acetate extract of *Phellinus rimosus*, also reduced the severity of cisplatin-induced renal injury (29).

Milk grass (Galium aparine)

Galium aparine, commonly called butcher in English, belongs to the Ronose family, which acts as a diuretic due to the presence of glycosides anthraquinone and flavonoids. The positive effect of the plant extract is conducted through the reduction of renal hypertrophy and glomerulomegaly (10).

Tribulus terrestris

Tribulus terrestris, commonly called puncture, is an annual plant growing in many tropical regions of the world, including the United States, Mexico, the Mediterranean region and throughout Asia (30). Studies have shown that this plant contains steroids, saponins, flavonoids, alkaloids, unsaturated fatty acids, vitamins, tannins, resins, potassium, nitrates, aspartic acid and glutamic acid (31). Tribulus terrestris has various beneficial effects, including improvement of sexual function, preventing of urinary tract infection, anesthetic, relieving of pain, antimicrobial appetizer (32). It has been shown that the consumption of *T. terrestris* extract increases total serum antioxidant capacity. The extract increases the activity of superoxide dismutase, glutathione peroxidase and catalase in cells (33). Oral consumption of this plant as a supplement to chemotherapy regimen, particularly cisplatin, produces a supporting effect, also prevents and eliminates the toxic metabolite of cisplatin (34).

Boiss taraxacum

Boiss *taraxacum* is originated from the *Taraxacum syriacum officinalis* species and is used in traditional medicine for the treatment of jaundice, liver disease, and gallstones. The plant species have polyphenolic compounds and antioxidant properties that can inhibit the production of free radicals by cytochrome P450 (35). Therefore, the protective effect of Boiss *taraxacum* may be due to its antioxidant effects, which are possibly exerted through increasing renal glutathione. The effectiveness of Boiss *taraxacum* extract in protecting the kidney against nephrotoxicity is due to phenolic compounds and flavonoids, can increase creatinine excretion and decrease serum creatinine levels (36).

Raspberry

Raspberry (*Rubus idaeus*) is a perennial shrub from the Rosaceae family, which has dense thorns and blackish red fruits (37). This plant is a significant source of phenolic compounds, including anthocyanins, flavonoids, chlorogenic acid, tannins, and procyanidins, which have high biological activities and protect the body against cardiovascular disease, cancer, inflammation, obesity and other chronic diseases (38).

Satureja khuzestanica

Satureja khuzestanica is an aromatic and perennial plant from the Lamiace family. *S. Khuzestanica* has a lot of medicinal properties and has been investigated in various studies. This plant has antiviral and antioxidant properties. In previous studies, administration of *S. Khuzestanica* extract containing phenolic compounds was observed to reduce the serum creatinine concentration. Polyphenolic compounds and flavonoids can also protect the cell by increasing the capacity of antioxidant enzymes (glutathione reductase, glutathione peroxidase and catalase), and reduce the effects of cisplatin-induced toxicity (39).

Silybum marianum and silymarin

Silybum marianum is commonly known as the milk thistle. This medicinal plant is recommended to digestive disorders, hepatotoxicity, liver cirrhosis, and also as an adjuvant drug for liver inflammation. Silibinin is the most active ingredient in silymarin, which is known

as an antioxidant and hepatoprotective agent, and its concentration in bile is 60 times more than that in the blood (40). The seed extract of this plant has numerous compounds, including silybin A and B, silidianin, silichristine, apigenin, dihydrosilybin, dioxysilichristine, and dioxysilidianine, which have antioxidant efficacy. Administration of standard silymarin and methanolic extract of *S. marianum* L two hours before administration of cisplatin inhibited renal tubular necrosis and also decreased blood urea and creatinine levels. The generation of free radical oxygen is the main factor resulting in renal complications and is reduced by the silymarin's flavonoids (41).

Turnip (Brassica napus)

Brassica napus is a plant from the Brassicaceae family that is useful for treating kidney disease, bladder inflammation, gout, and joint pains due to its pharmacological properties. It has also been reported that its antioxidants properties reduce the risk of developing certain diseases such as hypertension and rheumatoid arthritis (42). This plant is expected to be effective in the treatment of diabetes. A study conducted by Amouoghli-Tabrizi et al about the protective effects of *B. napus* root hydroalcoholic extract on CIN showed that the extract plays a protective role against cisplatin by reducing stress oxidative. This herb reduces malondialdehyde level and increases glutathione reductase and superoxide dismutase, catalase, and glutathione peroxidase (43).

Mulberry

The preventive effect of hydroalcoholic extract and flavonoid fractions (polyphenolic extracts) of the Morus Alba L's leaves against CIN in rats has been studied. In two groups receiving flavonoid fractions at 50 and 100 mg/kg, creatinine and BUN were ameliorated ($P<0.05$). The pathological examinations of the kidneys also showed less renal damage in these two groups than other groups ($P<0.05$). Analysis of the results showed that the compounds present in the polyphenolic extract could be effective to prevent CIN. Mulberry has antioxidant potential, due to flavonoids, polyphenols, alkaloids, and terpenoids (44).

Lagenaria siceraria

Lagenaria siceraria is a plant from the gourd family. The family has approximately 118 genera and 825 species. *L. siceraria* is originally native to India and Africa (45). The extract of *L. siceraria* has numerous compounds, such as cucurbitacin, licorice (lagenin), polysaccharide, flavonoids. This plant has antioxidant, cardioprotective, hepatoprotective, anti-inflammatory, antihyperlipidemic and antihyperglycaemic properties (46).

Nigella sativa

Nigella *sativa* is a herb belongs to the Ranunculaceae family (7). Its seeds have been traditionally used in India, Europe, the Middle East, the Far East, and Southeast Asia as a spice and a natural remedy for diseases such as asthma, headache, fever, dizziness, hypertension, infections, obesity, influenza and coughing (47). The beneficial effect of *N. sativa* to improve certain renal parameters such as serum urea and creatinine in CIN was studied previously (48). *N. sativa* could improve dose-dependently cisplatin-induced renal toxicity in rats. The effects of this plant's extract on renal parameters were due to its antioxidant, anti-inflammatory, immunoregulatory, anti-cancer and anti-apoptotic features (49).

Zingiber officinale L.

Zingiber officinale is a plant of East Asia, especially India. The most famous species of this genus is common ginger, which has a height of 100-120 cm. The special odor and taste of *Z. officinale* are due to a mixture of chemical compounds gingerols, zingerone, shogalo, and volatile oils that account for 3% of its weight. *Z. officinale* consumption increases the activity of antioxidant enzymes and eliminates free radicals. *Z. officinale* extract has anti-inflammatory effects (50). It has been shown that its hydroalcoholic extract has protective effects on the kidney cells of poisoned immature mice, while its protective effect is mainly related to its phenolic and ethanol compounds. These compounds neutralize free radicals and stimulate the repair of kidney cells due to antioxidant properties (51).

Fenugreek (Trigonella foenum-graecum)

Trigonella foenum-graecum belongs to Rose family and from the *Trigonella* L genus. The main ingredients of *T. foenum-graecum's* seed include saponins, alkaloids and mucilage fibers (50%). An interesting point of *T. foenum-graecum* is its wide range of therapeutic effects, such as analgesic, antiatherosclerotic, anti-inflammatory, antispasmodic, anticancer, hypoglycemic, cardiotonic and hypocholesterolemic efficacy (52). *T. foenum-graecum* has been reported to exhibit protective effects against cisplatin-induced toxicity in treated mice. Blood glucose, creatinine, urea, 24-hour urine protein, and creatinine clearance were significantly lower than these parameters in the untreated group (53).

Ferula asafoetida

Ferula asafoetida belongs to Apiaceae family and is prepared by cutting off the root or bottom of the stems of the plant to produce oleoresin gum or the syrup. Its English names are *stinking gum* and *devils dung*. It has a sharp, sulfur-like odor, which resembles stinking garlic, or a nasty flavor (54). In traditional medicine, *F. asafoetida* is reported to have anticonvulsive effects, treat neurological diseases, relieve kidney pain, enhance memory and has an anti-rheumatism effect. This medicinal plant eliminates the harmful effects of fatty foods, exert antispasmodic

effects, and affect blood pressure (55). High-quality type of *F. asafoetida* contains 62% resin, 25% gum, 3%-7% essential oil, 28.1% free ferulic acid and a little amount of vanillin (56). The study conducted by Changizi-Ashtiyani et al showed the positive effects of the plant on CIN. In most studies, the protective effect of drugs in renal tissue has been attributed to their antioxidant effect (57).

Glycine

The protective effect of some drugs, such as glycine against cisplatin-induced renal damage, depends on the NO production (58). Reduction of NO is at least partly effective to develop cisplatin-induced renal damage. In a few experimental studies, it has been pointed out that the administration of glycine amino acid may reduce the risk of developing cisplatin renal toxicity (59).

Discussion

CIN occurs in 15% to 30% of patients and is commonly associated with acute and chronic renal failure (4). Cisplatin is an effective drug to treat neoplasms and other diseases. This drug can be a major cause of CIN. Major risk factors for cisplatin-induced kidney damage include administration of higher dose and higher serum concentrations. Other factors increasing cisplatin renal toxicity are its recent administration, the history of underlying kidney damage and co-administration of other nephrotoxic drugs, such as aminoglycosides. Studies on CIN suggest that cisplatin toxicity is due to the production of free radicals of oxygen, in particular, radical hydroxyl, which causes lipid peroxidation. It has also been shown that flavonoids and phenolic compounds in plants have several biological effects including antioxidant, free radical-scavenging and anti-lipid peroxidation properties (60).

According to the study of Naghizadeh et al, the presence of carotenoid compounds (crocin) can reduce tubular damage, and therefore prevent acute CIN by inhibiting free radicals, inhibiting ROS-induced oxidative stress, and enhancing the synthesis of glutathione (61).

According to the study of Behling et al, oral administration of quercetin, as a bioflavonoid and a polyphenolic compound, at 50 mg/kg/d before and after cisplatin treatment, substantially decreased the side effects of cisplatin, including acute kidney injury (28). Flavonoid and glycoside compounds with antioxidant activity eliminate free radicals and improve renal function (62).

The study by Hu and Kitts showed that the protective effect of *Taraxacum syriacum* could inhibit the activity of free radicals produced by cytochrome P450 due to polyphenols ingredients and their antioxidant properties (63). Accordingly, Johari et al reported phenolic and ethanolic compounds of *Zingiber officinale* could neutralize free radicals, stimulate the repair of kidney cells and reduce creatinine clearance due to antioxidant properties (64). Likewise, the study by Hart et al showed that herbs can increase the activity of superoxide dismutase, glutathione peroxidase and catalase in cells against the side effects of chemotherapy regimen (35). According to the study of Saad et al, administration of the NO precursor molecule could also reduce the oxidative stress and the toxicity and mortality due to cisplatin (65).

Conclusion

Administration of certain drugs such as n-acetylcysteine and glycine, herbal medicines, phenolic, flavonoid and antioxidant compounds can reduce the risk of cisplatin-induced renal damage; however, it is better to avoid cisplatin administration in patients who have contraindications for cisplatin or are at increased risk for renal failure.

Conflicts of interest

There are no conflicts of interest.

Authors' contribution

MS, NH and MRKF prepared the first draft. RV, BG, NN, SE, PN and MH completed it. MH and SE edited the last version. MRKF finalized the paper. All authors read and signed the final manuscript.

Ethical considerations

Ethical issues which include plagiarism, data fabrication, double publication have been completely observed by the authors.

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