Jundishapur J Nat Pharm Prod. 2019 August; 14(3):e61527. doi: 10.5812/jjnpp.61527.

Published online 2019 July 29. **Review Article**

Efficacy of Antioxidant Supplements on Prevention and Amelioration of Cisplatin-Induced Nephrotoxicity: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Received 2017 September 10; **Accepted** 2018 April 22.

Abstract

Context: Cisplatin is a widely used antineoplastic agent in the treatment of a wide range of malignancies although it is associated with nephrotoxicity. Much clinical evidence supports the use of antioxidant supplements in the prevention of cisplatin-induced nephrotoxicity (CIN). However, conflicting evidence makes us unable to provide any robust results for antioxidants use against CIN.
Objectives: The study aimed to investigate the efficacy of antioxidant supplements on CIN through a comprehensive meta-analysis of randomized controlled trials.
Data Sources: A systematic literature search was conducted in PubMed, EMBASE, Cochrane Library, CPCI-S (Conference Proceedings Citation Index-Science), ICTRP (International Clinical Trials Registry Platform), and Google Scholar until February 2017 by two independent researchers. Various outcomes such as serum creatinine, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), creatinine clearance, and incidence of CIN were assessed. All statistical analyses were performed using RevMan V.5.3
Results: Overall, 672 patients were identified from 10 studies of whom 330 (49.10%) patients received antioxidant treatment. Antioxidant treatment showed a significant reduction in serum creatinine (SMD: -3.40, 95% CI: -5.47 to -1.33, P = 0.001), BUN (SMD = -5.96, 95% CI: -10.07 to -1.86, P = 0.004), and eGFR (SMD = -3.77, 95% CI: -6.16 to -1.38; P = 0.002) when compared to the control group.
Conclusions: Antioxidant treatment is associated with a reduced risk of CIN. It also has important clinical implications for CIN patients who are not responding to other therapies such as hydration, diuresis, or magnesium supplementation.

Keywords: Antioxidant, Cisplatin, Meta-Analysis, Nephrotoxicity, Systematic Review

1. Context

Cisplatin (cis-diamminedichloroplatinum [II]; CDDP; Platinol) is a platinum-based antineoplastic agent that serves a highly effective treatment regimen for an array of malignancies such as head and neck cancer, cervical cancer, soft-tissue neoplasms, squamous cell cancer, non-small cell lung cancer, gastric cancer, testicular cancer, bladder cancer, and ovarian cancer (1, 2). Despite its effectiveness, the clinical use of cisplatin is compromised in up to 85% of cases due to severe side effects including ototoxicity, nephrotoxicity, bone marrow toxicity, gastrointestinal toxicity, and peripheral neuropathy (3). The prevalence of cisplatin nephrotoxicity was reported as 34.1% among various cancer patients in a study (4) and the incidence of cisplatin-induced nephrotoxicity was around 30% - 40% in another study (5), which was dose-dependent and usually reversible. It has been reported that CDDP, as a platinum-based alkylating compound, has an ability to interact with DNA to form interstrand cross-links and intrastrand bifunctional N-7 DNA adducts at d(GpG) and d(ApG) (6). The formation of these adducts can result in DNA damage, oxidative stress, protein synthesis inhibition, and mitochondrial dysfunction (7).

The current treatment strategy for cisplatin-induced nephrotoxicity (CIN) manifestations primarily includes supportive care with sodium chloride or bicarbonate volume expansion, metformin withdrawal, administration of various agents such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers and statins, and reduced volume of contrast media (8). CIN can be ameliorated using oral hydration therapy (9) or magnesium supplementation (7); however, it is reversible and does not completely prevent CIN. Dialysis has been successfully implicated in the management of various features of CIN

including uremia, metabolic disturbances, and hypervolemia; however, it does not play any role in the removal of accumulated cisplatin from renal tissue (10). Despite these various strategies, the treatment of CIN still poses limitations.

The accumulation of toxins causes the elevation of reactive oxygen species (ROS), which, in turn, leads to a variety of consequences (11, 12). The decreased levels of antioxidant enzymes including superoxide dismutase (SOD), glutathione reductase (GSH-R), and catalase (CAT) can lead to the structural alteration in the cell membrane, which, in turn, causes apoptosis and cell death (13, 14). Some compounds with antioxidant potential such as vitamin E, selenium, glutathione, N-acetyl-L-cysteine, and lipoic acid have an ability to bind with ROS and inhibit the damage produced by ROS (15, 16). Numerous randomized controlled trials have been carried out over the past few decades and have shown the potential of these antioxidant moieties against CIN in various cancer patients (17-22). However, conflicting evidence makes us unable to provide any robust results for the use of antioxidants against CIN.

2. Objectives

To the best of our knowledge, no meta-analysis has been carried out to determine the efficacy of antioxidants against CIN. Hence, the aim of the present study was to investigate the efficacy of antioxidant supplements on CIN through a comprehensive meta-analysis of randomized controlled trials.

3. Methods

3.1. Data Sources and Selection Criteria

This systematic review and meta-analysis study was conducted as per the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (23) (Appendix 1 in Supplementary File).

3.2. Quality Assessment of the Articles

The quality of each study included in the analysis was assessed using the Cochrane risk of bias tool for systematic reviews of interventions (version 5.0.1) (24) and the Downs and Black critical appraisal tool. Two independent reviewers performed the quality assessment and disagreements on scores were resolved through discussion.

3.3. Data Analysis

The standardized mean difference (SMD) was used with a 95% confidence interval (CI) and standard deviation (SD). A meta-analysis was conducted with the simultaneous use of random-effect models. All statistical analyses were performed using RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK).

4. Results

4.1. Summary of Included Studies

Running the searches in the electronic databases yielded 1542 results in total (Figure 1). After duplicates were removed and reports were screened by title, keywords and abstract, they were assessed for inclusion and exclusion criteria. A full-article review of the remaining 17 identified articles was necessary to determine the eligibility for this review. Based on the full article review, 10 articles received a full evaluation for qualitative and quantitative analysis. The primary findings from the included studies are summarized in Table 1.

4.2. Characteristics of the Studies

4.2.1. Included Studies

Table 1 shows the study characteristics. There were 672 enrolled patients in total, of whom 330 (49.10%) patients received antioxidant treatment whereas the remaining patients were on placebo or conventional treatment. Out of 12 randomized controlled trials, five were double-blinded (19, 22, 26-28), one was single-blinded (17), and one was open-controlled (18).

The potential of various antioxidant treatments against CIN was assessed by measuring changes in BUN, eGFR, serum creatinine, creatinine clearance, and CIN incidence. The change in BUN was measured in two studies (18, 21), change in eGFR in four studies (17, 20, 25, 27), change in serum creatinine in five studies (17, 18, 21, 25, 27), change in creatinine clearance in two studies (18, 28), and the incidence of CIN in four studies (19, 22, 26, 27).

4.2.2. Excluded Studies

Seven studies were excluded from this review. Five excluded studies were non-controlled studies, one study did not report any separate outcome for CIN patients, and one study did not use any antioxidant for intervention.

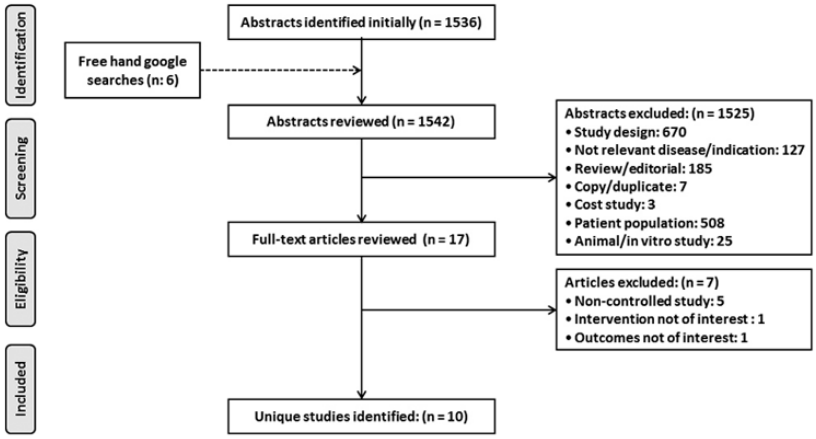

Figure 1. PRISMA flow diagram depicting the selection process of studies for the systematic review and meta-analysis

Table 1. Characteristics of Included Studies (N = 9)

Authors, Year of Publication, Country	Study Design	Characteristics of Participants		Intervention and Sample Size (Analyzed)		Study Duration, mo	Measured Outcome (P Values)	Authors' Conclusions
		Sample Size	Cisplatin Dose	Antioxidant Group	Placebo Group			
Benoehr et al., 2005, Germany (17)	R, P, SB, PC	36	50 mg/m^2	Theophylline (350 mg, three times daily), 4 days	Placebo	-	S. Cr ($P < 0.001$), eGFR	Prophylactic application of theophylline as i.v. loading dose and oral maintenance regimen may preserve kidney function in CIN
El-Ghiaty et al., 2014, Egypt (18)	R, P, O	49	70 mg/m^2	Cystone (225 mg, two tablets thrice daily), 18 weeks	Placebo	23	S. Cr ($P < 0.001$), Cr. Cl ($P < 0.001$)	Cystone could protect from CIN
Ghorbani et al., 2013, Iran (19)	R, DB	122	203.72 mg	Selenium (400 mcg tablet), 1 week	Placebo	-	ICIN ($P = 0.013$)	Selenium could probably prevent CIN along with hydration therapy
Hemati et al., 2012, Iran (20)	R, PC	46	76 mg/m^2	Vitamin E (400 IU) + Selenium (200 μg)	Placebo	16	eGFR ($P < 0.001$)	Vitamin E and selenium could be used to reduce CIN
Karademir et al., 2016 (25)	R, PC	64	50 mg/m^2	Theophylline (400 mg, oral), 5 days	Placebo	36	SCr ($P = 0.965$), GFR ($P = 0.149$)	Less nephrotoxicity developed in theophylline as compared to placebo
Momeni et al., 2015, Iran (21)	R, PC	60	-	Silymarin (140 mg/bid tablet), 7 days	Placebo	-	S. Cr ($P = 0.001$), BUN	Silymarin could decrease CIN
Mousavi et al., 2014, Iran (26)	R, P, DB, PC	76	50 mg/m^2	Aminophylline (4 mg/kg, i.v.) + theophylline (200 mg, three times daily, p.o.), 4 days	Placebo	4	ICIN	Prophylactic application of aminophylline and theophylline did not have a protective effect against CIN
Shahbazi et al., 2015, Iran (27)	R, DB, PC	30	185 - 220 mg	Silymarin (420 mg)	Placebo	12	eGFR ($P = 0.01$), S. Cr	Prophylactic silymarin treatment could not prevent CIN
Smyth et al., 1997, Multi-country (22)	R, DB, PC	151	100 mg/m^2	Glutathione (3 g/m^2), 3 weeks for 6 courses	Placebo	-	ICIN ($P = 0.006$)	Glutathione improved CIN patient's quality of life
Weijl et al., 2004, The Netherlands (28)	R, DB, PC	50	70 mg/m^2	Antioxidant micronutrients (Vitamin C (1000 mg) + Vitamin E (400 mg) + Selenium (100 μg))	Placebo	30	Cr. Cl ($P < 0.05$)	Antioxidant treatment could not prevent CIN due to poor compliance and/or inadequate supplementation

Abbreviations: BUN, blood urea nitrogen; CIN, cisplatin-induced nephrotoxicity; Cr. Cl, creatinine clearance; DB, double-blind; eGFR, estimated glomerular filtration rate; ICIN, incidence of cisplatin-induced nephrotoxicity; O, open-label; P, prospective; P-2, phase 2 trial; PC, placebo-controlled trial; R, randomized controlled trial; S. Cr, serum creatinine; SB, single-blind.

4.3. Risk of Bias

The results of the risk of bias (ROB) assessment for the included studies are presented in Figure 2. The included studies showed high variations in overall quality. The randomized studies included in this review varied in their study design, structure, and methodology. Of 10 studies

identified for analysis in this study, five were classified as high-quality (17, 19, 22, 27, 28) and five as low-quality (18, 20, 21, 25, 26).

Downs and Black scoring was used to evaluate the quality of the studies. The quality of the studies was variable. The overall quality of study reporting was good, external validity was low, and internal validity was good amongst studies (Table 2). The heat map of the overview of the quality of studies determined using Downs and Black scoring system is provided in Appendix 1 in Supplementary File.

4.4. Heterogeneity

There was significant heterogeneity between the studies in the patient population, nephrotoxicity definition, and duration of antioxidant treatment. Therefore, the random-effects model was required in all analyses.

Individual and cumulative cisplatin dose varied considerably among the studies (Table 1). In the studies on human participants, individual cisplatin dose ranged from 50 to 100 mg/m^2 of the body surface area.

4.5. Conflicting Evidence

An array of research studies evaluated the efficacy and safety of antioxidants for the treatment of CIN, but with conflicting results. Studies by Benoehr et al. (2005) and Karademir et al. (2016) found that theophylline treatment preserved kidney function in CIN (17, 25) whereas Mousavi et al. (2014) reported that theophylline did not have a protective effect against CIN (26). Momeni et al. (2015) reported that silymarin could decrease the progression of CIN (21); however, Shahbazi et al. (2015) reported that silymarin treatment could not prevent CIN (27). As low statistical power may limit the interpretability of the findings, the results of these trials should be interpreted with caution.

4.6. Outcomes

Because of heterogeneity in the studies, we used a random-effects model for the analysis of changes (Δ) in BUN, eGFR, serum creatinine, and creatinine clearance whereas a fixed-effects model was used for the analysis of the incidence of CIN (Table 3).

Antioxidant treatment showed a significant reduction in serum creatinine (Z = 3.21; P = 0.001) and there was heterogeneity between the studies (I^2 = 96%; P < 0.00001) (Figure 3A).

As shown in Figure 3B, antioxidant treatment resulted in a significant change in BUN, with an overall effect size (Z) of 2.85; however, there was heterogeneity between the studies (I^2 = 94%; P < 0.0001). The change in BUN was significantly higher in the antioxidant group than in the control group (SMD = -5.96, 95% CI: -10.07 to -1.86, P = 0.004).

The intervention with antioxidants was associated with a non-significant change in creatinine clearance levels (Z = 0.95; P = 0.34), with substantial heterogeneity between the studies (I^2 = 98%; P < 0.00001). The change in creatinine clearance levels was more in the antioxidant group than in the control group (SMD = -2.50, 95% CI: -7.67 to 2.67; P = 0.05) (Figure 3C). However, the meta-analysis was considered inappropriate because of the small number of studies.

Antioxidant combination resulted in a significant change in eGFR, with an overall effect size (Z) of 3.09 (P = 0.002) and with substantial heterogeneity (I^2 = 96%; P = 0.00001). The change in eGFR was significantly more in the antioxidant group than in the control group (SMD = -3.77, 95% CI: -6.16 to -1.38; P = 0.002) (Figure 4A).

The efficacy of antioxidant treatment in the reduction of CIN incidence lost its statistical significance (Z = 1.56; P = 0.12). There was no heterogeneity between the studies (I^2 = 0%; P = 0.43). There was no statistically significant difference in the incidence of CIN between the antioxidant group and the control group (SMD = 0.37, 95% CI: 0.11 to 1.29; P = 0.12) (Figure 4B).

5. Discussion

Nowadays, cisplatin (CDDP) is a well-known and widely used antineoplastic agent in the treatment of a wide range of malignancies. However, it causes renal impairment and induces toxicity in approximately 30% - 40% of treated patients (5). The cisplatin-induced nephrotoxicity (CIN) leads to decreased glomerular filtration rate (GFR), altered creatinine clearance, impaired urinary albumin excretion ratio, increased serum creatinine (S. Cr), and elevated blood urea nitrogen (BUN) level (29, 30). Thus, it is essential to attenuate the acute manifestations and renal failure along with subclinical reduced kidney function. A recent systematic review was conducted to examine the efficacy of hydration therapy in the prevention or amelioration of CIN (9). However, the findings of the reviewed studies showed that hydration therapy was useful only in patients receiving high-dose CDDP and in some patients, over-diuresis resulted in dehydration (9). Thus, currently, no ideal nephroprotective agent exists in clinical use for CIN treatment.

Some clinical evidence supports the use of antioxidant supplements in the prevention of CIN (17-22). Furthermore, in most countries, many herbal supplements with antioxidant potential are used under the name of functional food, medicinal food, or food supplement for the treatment of various diseases including CIN. However, we need to determine the efficacy and safety of these herbal supplements used in the treatment of CIN. Hence, the current systematic review and meta-analysis study was undertaken to ex-

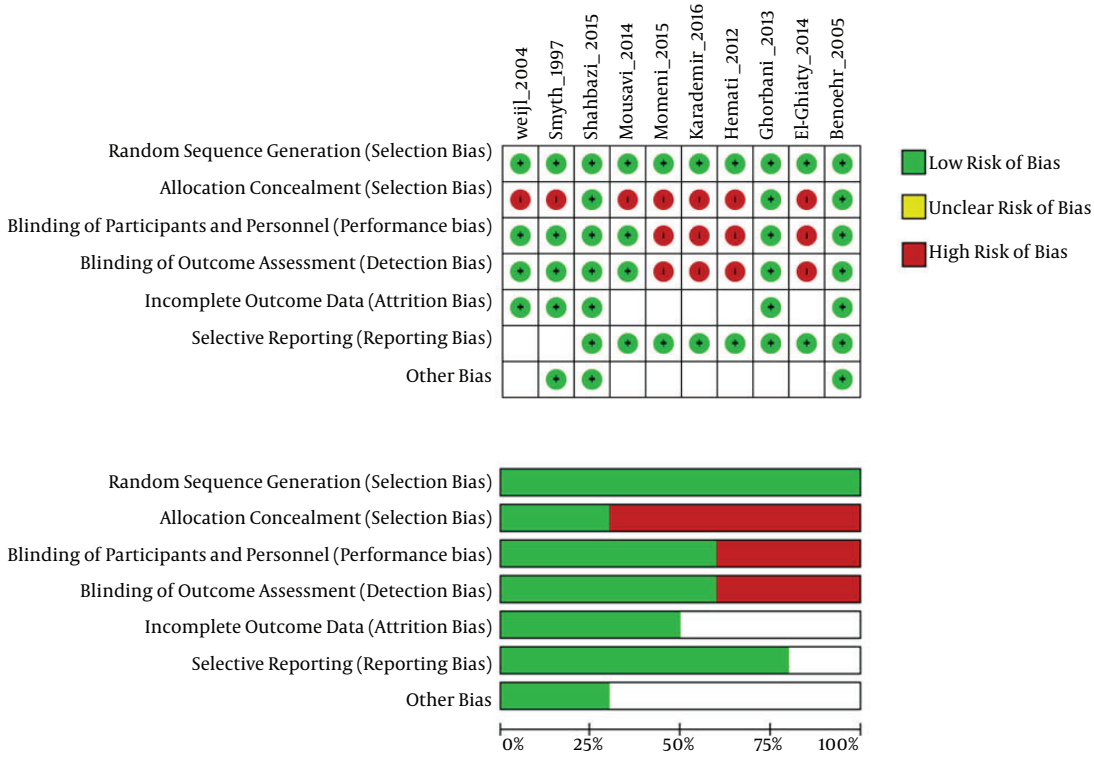

Figure 2. Risk of bias graph of included trials: review authors' judgments about each item of risk of bias for each included study (A) and review authors' judgments about each item of risk of bias presented as a percentage across all included studies (B)

Table 2. Quality of Studies Based on the Downs and Black Scoring System

Authors, Year of Publication	Reporting (Max: 11)	External Validity (Max: 3)	Internal Validity-Bias (Max: 7)	Internal Validity-Confounding (Selection Bias) (Max: 6)	Total (27)
Benoehr et al., 2005 (17)	10	3	5	5	23
El-Ghiaty et al., 2014 (18)	9	3	3	4	19
Ghorbani et al., 2013 (19)	8	3	5	5	21
Hemati et al., 2012 (20)	8	3	3	4	18
Karademir et al., 2016 (25)	8	3	3	4	18
Momeni et al., 2015 (21)	8	3	3	4	18
Mousavi et al., 2014, Iran (26)	8	3	5	3	19
Shahbazi et al., 2015 (27)	11	3	6	6	26
Smyth et al., 1997 (22)	8	3	5	4	20
Weijl et al., 2004 (28)	9	3	7	5	24

amine the randomized controlled trials that directly evaluated the role of various antioxidants against CIN.

A good number of the popularly used cisplatin for its efficacy against various malignancies and it has been well documented that its use is associated with a significantly higher risk of acute renal injury (31). Various clinical studies suggested that the administration of antioxidants significantly decreases the incidence of CIN (19, 22, 26, 27). We identified 10 eligible studies, including 672 participants, and found that antioxidant treatment was effec-

Table 3. Clinical Outcomes of Antioxidant Groups Compared to Control Groups

Outcomes	Heterogeneity		Analysis Model	Summary Statistics	Overall Effect		No. Trials
	I^2 (%)	P Value			SMD/OR [95% CI]	P Value	
Serum creatinine, mg/dL	96	< 0.00001	Random	SMD	-3.40 [-5.47, -1.33]	0.001	5
BUN, mg/dL	94	< 0.0001	Random	SMD	-5.96 [-10.07, -1.86]	0.004	2
Creatinine clearance, mL/min	98	< 0.00001	Random	SMD	-2.50 [-7.67, 2.67]	0.34	2
eGFR, mL/min	96	< 0.00001	Random	SMD	-3.77 [-6.16, -1.38]	0.002	4
Incidence of CIN	0	0.43	Fixed	OR	0.37 [0.11, 1.29]	0.12	4

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; OR, odds ratio; SMD, standardized mean difference.

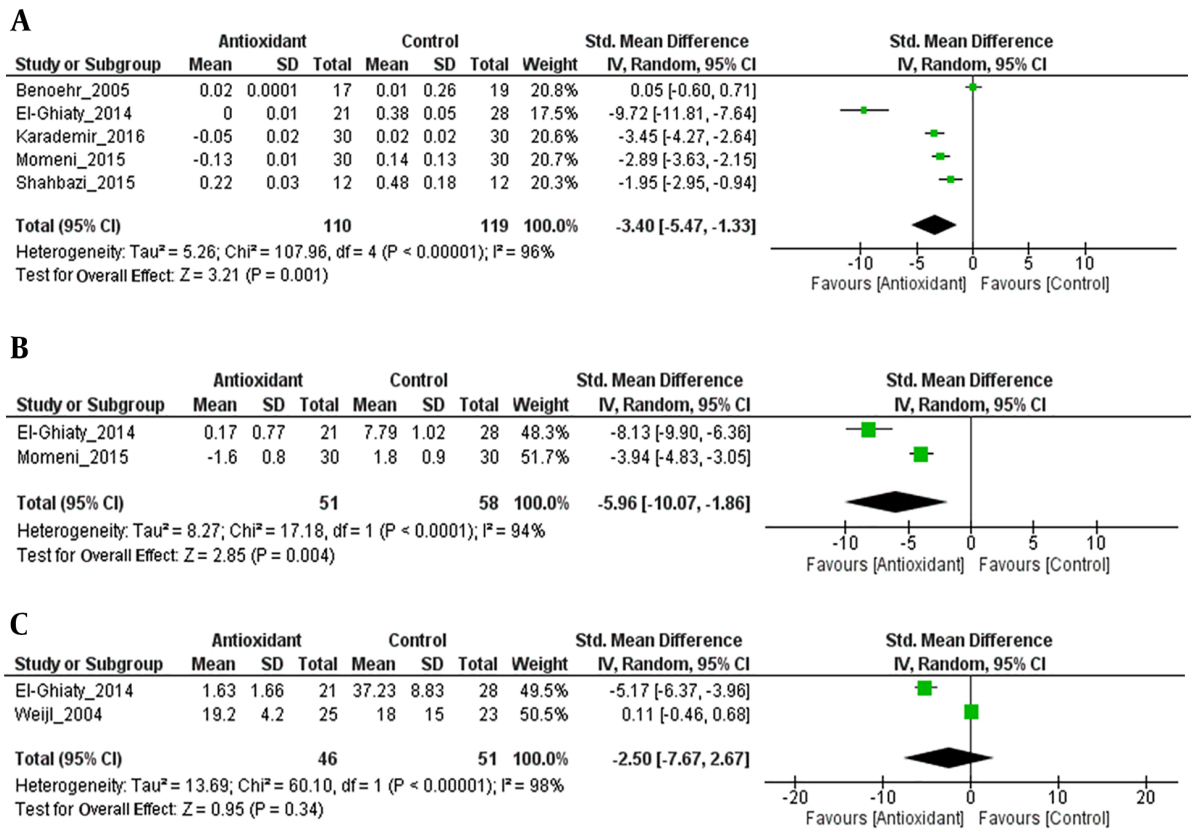

Figure 3. Forest plot evaluating the effects of antioxidants on changes in serum creatinine (A), BUN (B), and creatinine clearance (C) compared to the control group using a random-effects model

tive in the amelioration of kidney function altered by the administration of cisplatin in cancer patients. The results of the present meta-analysis also showed similar findings indicating that antioxidant treatment ameliorates the incidence of CIN (OR: 0.37 [0.11, 1.29], P = 0.12).

The altered serum creatinine level is one of the important clinical features of CIN that has been consistently observed in the available body of evidence (18, 32). It has been well documented that the increased level of ROS induces mesangial cells contraction and modifies the filtration surface area, resulting in an increased serum creatinine level (33, 34). Previous preclinical studies suggested that antioxidant supplementation inhibits free radical damage and thereby decreases GFR and finally inhibits CIN-induced el-

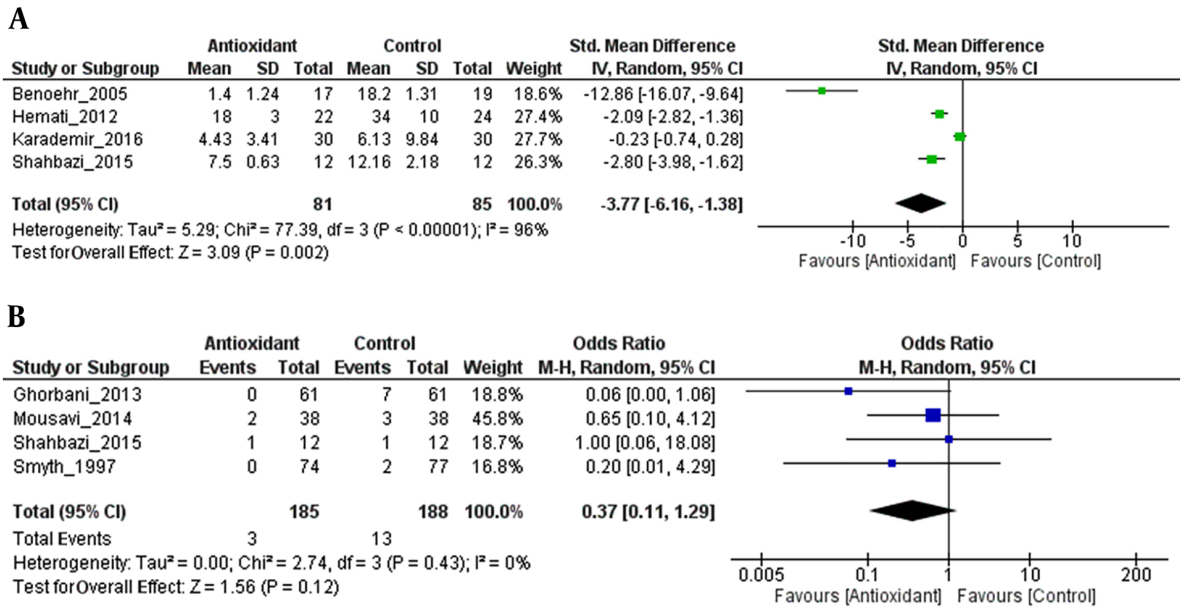

Figure 4. Forest plot evaluating the effects of antioxidants on eGFR (A) and incidence of CIN (B) compared to control groups using a random-effects model

evated serum creatinine (35, 36). Our meta-analysis indicated that the administration of antioxidants significantly decreased the cisplatin-induced increase in GFR (SMD = -3.77, 95% CI: -6.16 to -1.38; P = 0.002) and serum creatinine (SMD = -3.40, 95% CI: -5.47 to -1.33; P = 0.001). The findings of the present meta-analysis are in line with those of in-vivo animal studies where antioxidant treatment decreased serum creatinine levels (37). Contrary to the findings of our review, limited clinical evidence shows that the administration of antioxidants such as silymarin does not produce any significant change in GFR and serum creatinine concentration (27). However, this conflicting result could be explained based on several factors. First, preclinical studies might not represent the biological processes clinically (38). Second, the duration of treatment might be insufficient to exert its effect, as Shahbazi et al. (2015) reported no significant effect of silymarin when administered 48 h before the initiation of cisplatin infusion (27) whereas a report by Momeni et al. (2015) showed that the prophylactic administration of silymarin for seven days prevented CIN (21). Thus, the beneficial effects of antioxidant supplements against CIN might be related to the timing of their administration.

Earlier studies suggested that creatinine clearance and BUN are important clinical factors that usually predict nephrotoxicity (39) and serve as confounding factors for the selection of dose and schedule of cisplatin during treatment of malignancies in cancer patients (40, 41). In most trials, patients treated with cisplatin showed increased creatinine clearance, which is a major concern regarding CIN (41). Antioxidants have shown beneficial effects against CIN in preclinical studies (35, 36); however, they have failed to show benefits under clinical circumstances (28). The results of the present meta-analysis indicate that there is a discrepancy in the results of animal studies and those of randomized controlled trials concerning the association between antioxidants and amelioration in creatinine clearance. The non-significant decrease in creatinine clearance by antioxidant treatment in CIN may be related to poor compliance (28). However, our findings are similar to those of a previous meta-analysis where hydration therapy showed significant attenuation in creatinine clearance, which is essential for patients to prevent CIN (9).

5.1. Limitation

Although our meta-analysis suggested a possible clinical benefit for the antioxidant treatment of CIN, it had important limitations, the comparators varied too much, and the effects were inconsistent and imprecise. As limitations, first, we determined the efficacy of antioxidant supplements that were synthetic in nature (except for that used by El-Ghiaty et al. (2004)); thus, the findings of the present meta-analysis cannot be extended to antioxidants that are derived or extracted from plants. Second, there was a large

statistical heterogeneity due to the lack of patient selection in the present study. Third, the baseline characteristics such as tumor type, CDDP dose, and nephrotoxicity definition varied largely across the studies, which limits our ability to make concrete recommendations regarding the implication of antioxidant supplements in CIN. Fourth, since the majority of the patient populations enrolled in studies were male, the findings of the present meta-analysis are applicable to male patients, which may result in gender bias. Furthermore, preclinical studies show that CIN more frequently occurs in male rats than in female rats, which may be due to the higher expression level of OCT2 (organic cation transporter 2) in males than in females (42). However, conflicting results exist possibly related to the risk factors of CIN and gender difference (31, 43). Thus, there is a need for studies that enroll populations with equal gender distribution in the future. Finally, the publication bias could not be excluded from the present meta-analysis, as six studies were published positively among the 10 included studies.

6. Conclusions

In conclusion, the findings of this systematic review and meta-analysis suggest that antioxidant treatment is associated with the reduced risk of CIN. The findings of the present investigation have important clinical implications where antioxidant treatment can be used in patients with CIN who do not respond to other therapies such as hydration, diuresis, or magnesium supplementation. However, future studies concerning the comparative effectiveness of antioxidants for preventing CIN need to stratify patients according to baseline characteristics. More research could strengthen the evidence of the efficacy of antioxidant treatment in patients with high CIN risk.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: Study concept and design: Amit D. Kandhare; acquisition of data: Amit D. Kandhare and Anwesha Mukherjee; analysis and interpretation of data: Subhash L. Bodhankar; drafting of the manuscript: Amit D. Kandhare and Subhash L. Bodhankar; critical revision of the manuscript for important intellectual content: Subhash L. Bodhankar; statistical analysis: Amit D. Kandhare; administrative, technical, and material support: Subhash L. Bodhankar; study supervision: Subhash L. Bodhankar.

Conflict of Interests: It is not declared by the authors.

Funding/Support: It is not declared by the authors.

References

1. Lee H, Nho D, Chung HS, Lee H, Shin MK, Kim SH, et al. CD4+CD25+ regulatory T cells attenuate cisplatin-induced nephrotoxicity in mice. *Kidney Int*. 2010;**78**(11):1100–9. doi: 10.1038/ki.2010.139. [PubMed: 20463654].
2. Florea AM, Busselberg D. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. *Cancers (Basel)*. 2011;**3**(1):1351–71. doi: 10.3390/cancers3011351. [PubMed: 24212665]. [PubMed Central: PMC3756417].
3. Hartmann JT, Lipp HP. Toxicity of platinum compounds. *Expert Opin Pharmacother*. 2003;**4**(6):889–901. doi: 10.1517/14656566.4.6.889. [PubMed: 12783586].
4. Prasaja Y, Sutandyo N, Andrajati R. Incidence of cisplatin-induced nephrotoxicity and associated factors among cancer patients in Indonesia. *Asian Pac J Cancer Prev*. 2015;**16**(3):1117–22. doi: 10.7314/apjcp.2015.16.3.1117. [PubMed: 25735341].
5. Kobayashi R, Suzuki A, Matsuura K, Yamada N, Nakano M, Deguchi T, et al. Risk analysis for cisplatin-induced nephrotoxicity during first cycle of chemotherapy. *Int J Clin Exp Med*. 2016;**9**(2):3635–41.
6. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol*. 1999;**17**(1):409–22. doi: 10.1200/JCO.1999.17.1.409. [PubMed: 10458260].
7. Saito Y, Kobayashi M, Yamada T, Kasashi K, Honma R, Takeuchi S, et al. Premedication with intravenous magnesium has a protective effect against cisplatin-induced nephrotoxicity. *Support Care Cancer*. 2017;**25**(2):481–7. doi: 10.1007/s00520-016-3426-5. [PubMed: 27699503].
8. Perazella MA, Moeckel GW. Nephrotoxicity from chemotherapeutic agents: Clinical manifestations, pathobiology, and prevention/therapy. *Semin Nephrol*. 2010;**30**(6):570–81. doi: 10.1016/j.semnephrol.2010.09.005. [PubMed: 21146122].
9. Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. *Oncologist*. 2017;**22**(5):609–19. doi: 10.1634/theoncologist.2016-0319. [PubMed: 28438887]. [PubMed Central: PMC5423518].
10. Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Ann Oncol*. 2010;**21**(7):1395–403. doi: 10.1093/annonc/mdp598. [PubMed: 20118214].
11. Kandhare AD, Alam J, Patil MV, Sinha A, Bodhankar SL. Wound healing potential of naringin ointment formulation via regulating the expression of inflammatory, apoptotic and growth mediators in experimental rats. *Pharm Biol*. 2016;**54**(3):419–32. doi: 10.3109/13880209.2015.1038755. [PubMed: 25894211].
12. Kandhare AD, Bodhankar SL, Mohan V, Thakurdesai PA. Acute and repeated doses (28 days) oral toxicity study of glycosides based standardized fenugreek seed extract in laboratory mice. *Regul Toxicol Pharmacol*. 2015;**72**(2):323–34. doi: 10.1016/j.yrtph.2015.05.003. [PubMed: 25979642].
13. Adil M, Kandhare AD, Visnagri A, Bodhankar SL. Naringin ameliorates sodium arsenite-induced renal and hepatic toxicity in rats: decisive role of KIM-1, Caspase-3, TGF-beta, and TNF-alpha. *Ren Fail*. 2015;**37**(8):1396–407. doi: 10.3109/0886022X.2015.1074462. [PubMed: 26337322].
14. Kandhare AD, Ghosh P, Bodhankar SL. Naringin, a flavanone glycoside, promotes angiogenesis and inhibits endothelial apoptosis through modulation of inflammatory and growth factor expression

in diabetic foot ulcer in rats. *Chem Biol Interact*. 2014;**219**:101–12. doi: 10.1016/j.cbi.2014.05.012. [PubMed: 24880026].
15. Honmore V, Kandhare A, Zanwar AA, Rojatkar S, Bodhankar S, Natu A. Artemisia pallens alleviates acetaminophen induced toxicity via modulation of endogenous biomarkers. *Pharm Biol*. 2015;**53**(4):571–81. doi: 10.3109/13880209.2014.934382. [PubMed: 25339313].
16. Kandhare AD, Ghosh P, Ghule AE, Bodhankar SL. Elucidation of molecular mechanism involved in neuroprotective effect of Coenzyme Q10 in alcohol-induced neuropathic pain. *Fundam Clin Pharmacol*. 2013;**27**(6):603–22. doi: 10.1111/fcp.12003. [PubMed: 23057828].
17. Benoehr P, Krueth P, Bokemeyer C, Grenz A, Osswald H, Hartmann JT. Nephroprotection by theophylline in patients with cisplatin chemotherapy: A randomized, single-blinded, placebo-controlled trial. *J Am Soc Nephrol*. 2005;**16**(2):452–8. doi: 10.1681/ASN.2004030225. [PubMed: 15590762].
18. El-Ghiaty MA, Ibrahim OM, Abdou SM, Hussein FZ. Evaluation of the protective effect of Cystone against cisplatin-induced nephrotoxicity in cancer patients, and its influence on cisplatin antitumor activity. *Int Urol Nephrol*. 2014;**46**(7):1367–73. doi: 10.1007/s11255-014-0644-y. [PubMed: 24448757].
19. Ghorbani A, Omidvar B, Parsi A. Protective effect of selenium on cisplatin induced nephrotoxicity: A double-blind controlled randomized clinical trial. *J Nephropathol*. 2013;**2**(2):129–34. doi: 10.12860/JNP.2013.21. [PubMed: 24475439]. [PubMed Central: PMC3891148].
20. Hemati S, Jolfaie NA, Gookizadeh A, Rafienia M, Ghavamnasiri MR. The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity in cancer patients treated with cisplatin-based chemotherapy: A randomized, placebo-controlled study. *J Res Med Sci*. 2012;**17**:S49–58.
21. Momeni A, Hajigholami A, Geshnizjani S, Kheiri S. Effect of silymarin in the prevention of Cisplatin nephrotoxicity, a clinical trial study. *J Clin Diagn Res*. 2015;**9**(4):OC11–3. doi: 10.7860/JCDR/2015/12776.5789. [PubMed: 26046020]. [PubMed Central: PMC4437094].
22. Smyth JF, Bowman A, Perren T, Wilkinson P, Prescott RJ, Quinn KJ, et al. Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: Results of a double-blind, randomised trial. *Ann Oncol*. 1997;**8**(6):569–73. doi: 10.1023/a:1008211226339. [PubMed: 9261526].
23. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: The PRISMA-IPD Statement. *JAMA*. 2015;**313**(16):1657–65. doi: 10.1001/jama.2015.3656. [PubMed: 25919529].
24. Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions 5.0.1*. Cochrane Collaboration; 2008.
25. Karademir LD, Dogruel F, Kocyigit I, Yazici C, Unal A, Sipahioglu MH, et al. The efficacy of theophylline in preventing cisplatin-related nephrotoxicity in patients with cancer. *Ren Fail*. 2016;**38**(5):806–14. doi: 10.3109/0886022X.2016.1163154. [PubMed: 27049176].
26. Mousavi SS, Zadeh MH, Shahbazian H, Khanzadeh A, Hayati F, Ghorbani A, et al. The protective effect of theophyline in cisplatin nephrotoxicity. *Saudi J Kidney Dis Transpl*. 2014;**25**(2):333–7. [PubMed: 24626000].
27. Shahbazi F, Sadighi S, Dashti-Khavidaki S, Shahi F, Mirzania M, Abdollahi A, et al. Effect of silymarin administration on cisplatin nephrotoxicity: Report from a pilot, randomized, double-blinded, placebo-controlled clinical trial. *Phytother Res*. 2015;**29**(7):1046–53. doi: 10.1002/ptr.5345. [PubMed: 25857366].
28. Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, et al. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: A randomised, double-blind, placebo-controlled study. *Eur J Cancer*. 2004;**40**(11):1713–23. doi: 10.1016/j.ejca.2004.02.029. [PubMed: 15251161].
29. Arany I, Safirstein RL. Cisplatin nephrotoxicity. *Semin Nephrol*. 2003;**23**(5):460–4. doi: 10.1016/s0270-9295(03)00089-5.
30. Ries F, Klastersky J. Nephrotoxicity induced by cancer chemotherapy with special emphasis on cisplatin toxicity. *Am J Kidney Dis*. 1986;**8**(5):368–79. [PubMed: 3538860].
31. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. *Toxins (Basel)*. 2010;**2**(11):2490–518. doi: 10.3390/toxins2112490. [PubMed: 22069563]. [PubMed Central: PMC3153174].
32. Arunkumar PA, Viswanatha GL, Radheshyam N, Mukund H, Belliyappa MS. Science behind cisplatin-induced nephrotoxicity in humans: A clinical study. *Asian Pac J Trop Biomed*. 2012;**2**(8):640–4. doi: 10.1016/S2221-1691(12)60112-9. [PubMed: 23569986]. [PubMed Central: PMC3609353].
33. Adil M, Kandhare AD, Dalvi G, Ghosh P, Venkata S, Raygude KS, et al. Ameliorative effect of berberine against gentamicin-induced nephrotoxicity in rats via attenuation of oxidative stress, inflammation, apoptosis and mitochondrial dysfunction. *Ren Fail*. 2016;**38**(6):996–1006. doi: 10.3109/0886022X.2016.1165120. [PubMed: 27056079].
34. Adil M, Kandhare AD, Ghosh P, Venkata S, Raygude KS, Bodhankar SL. Ameliorative effect of naringin in acetaminophen-induced hepatic and renal toxicity in laboratory rats: Role of FXR and KIM-1. *Ren Fail*. 2016;**38**(6):1007–20. doi: 10.3109/0886022X.2016.1163998. [PubMed: 27050864].
35. Darwish MA, Abo-Youssef AM, Khalaf MM, Abo-Saif AA, Saleh IG, Abdelghany TM. Vitamin E mitigates cisplatin-induced nephrotoxicity due to reversal of oxidative/nitrosative stress, suppression of inflammation and reduction of total renal platinum accumulation. *J Biochem Mol Toxicol*. 2017;**31**(1):1–9. doi: 10.1002/jbt.21833. [PubMed: 27550472].
36. Nematbakhsh M, Ashrafi F, Safari T, Talebi A, Nasri H, Mortazavi M, et al. Administration of vitamin E and losartan as prophylaxes in cisplatin-induced nephrotoxicity model in rats. *J Nephrol*. 2012;**25**(3):410–7. doi: 10.5301/jn.5000018. [PubMed: 21928232].
37. Hassan HA, Edrees GM, El-Gamel EM, El-Sayed EA. Amelioration of cisplatin-induced nephrotoxicity by grape seed extract and fish oil is mediated by lowering oxidative stress and DNA damage. *Cytotechnology*. 2014;**66**(3):419–29. doi: 10.1007/s10616-013-9589-8. [PubMed: 23761012]. [PubMed Central: PMC3973798].
38. Myung SK, Ju W, Cho B, Oh SW, Park SM, Koo BK, et al. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: Systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;**346**:f10. doi: 10.1136/bmj.f10. [PubMed: 23335472]. [PubMed Central: PMC3548618].
39. Kandhare AD, Patil MV, Bodhankar SL. L-Arginine attenuates the ethylene glycol induced urolithiasis in ininephrectomized hypertensive rats: role of KIM-1, NGAL, and NOs. *Ren Fail*. 2015;**37**(4):709–21. doi: 10.3109/0886022X.2015.1011967. [PubMed: 25682972].
40. Bolis G, Favalli G, Danese S, Zanaboni F, Mangili G, Scarabelli C, et al. Weekly cisplatin given for 2 months versus cisplatin plus cyclophosphamide given for 5 months after cytoreductive surgery for advanced ovarian cancer. *J Clin Oncol*. 1997;**15**(5):1938–44. doi: 10.1200/JCO.1997.15.5.1938. [PubMed: 9164205].
41. Bagri PK, Kapoor A, Kalwar A, Singhal MK, Singh D, Narayan S. Comparative analysis of cisplatin-induced nephrotoxicity in head and neck cancer and carcinoma cervix during concurrent chemoradiotherapy. *South Asian J Cancer*. 2014;**3**(4):217–20. doi: 10.4103/2278-330X.142979. [PubMed: 25422808]. [PubMed Central: PMC4236700].
42. Yonezawa A, Masuda S, Nishihara K, Yano I, Katsura T, Inui K. Association between tubular toxicity of cisplatin and expression of organic cation transporter rOCT2 (Slc22a2) in the rat. *Biochem Pharmacol*. 2005;**70**(12):1823–31. doi: 10.1016/j.bcp.2005.09.020. [PubMed: 16242669].
43. Sekine I, Kubota K, Tamura Y, Asahina H, Yamada K, Horinouchi H, et al. Innovator and generic cisplatin formulations: Comparison of renal toxicity. *Cancer Sci*. 2011;**102**(1):162–5. doi: 10.1111/j.1349-7006.2010.01764.x. [PubMed: 21054679].