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Role of Flavonoids in Cisplatin-Induced Nephrotoxicity: an Integrative Review

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ABSTRACT

Introduction: cisplatin is one of the most effective anticancer drugs, but one of the main limiting factors for its use is nephrotoxicity. Recently, the use of flavonoids has become a promising approach inprotection against cisplatin-induced kidney injury. Therefore, the objective here was to investigate, through an integrative review, the protective effects of flavonoids in the prevention and treatment of cisplatin-induced nephrotoxicity.

Review: The search was decided by the PICO strategy, carried out in the main health databases: Medline / PubMed, Web of Science and Science Direct, from 2011 to 2020, using the following combination of descriptors: ("KidneyDiseases" OR Nephrotoxicity OR "Renal Toxicity") AND (flavonoids OR 2-Phenyl-Benzopyrans) AND (Cisplatin). The results were composed of 17 articles. Multiple mechanisms have been involved in the pathophysiology of cisplatin-induced kidney injuries, such as oxidative stress, apoptosis, and inflammation. Cisplatin administration led to significant changes in the biological biomarkers, oxidative stress, inflammation, morphological changes, apoptosis and phosphorylation. The administration of some flavonoids induced protective effects against cisplatin-induced kidney injury;this renoprotection can be attributed, for example, to the ability to boostantioxidants andattenuate inflammation and apoptosis in the kidney, thus reversing the nephrotoxicity state.

Conclusion: Thus, although studies have shown positive results in the use of flavonoids, it is still necessary to deepen research and clinical analyses to elucidate the best way to use these substances, in addition to clarifying the administration frequency and to which patients to administer them.

Keywords: Chemotherapy; Side effects; Morphological changes; Kidney disease.

Introduction

Cisplatin (cis-diaminodichloroplatin), inorganic antineoplastic platinum, is one of the most effective anticancer drugs. It is extensively used and has often been considered as thechemotherapy agent of choice for the treatment of a wide variety of solid tumors, such as in the testicles, ovaries, esophagus, head and neck, cervix, non-small cell lung, breast, and bladder[1–3].

Chemotherapy is one of the most promising alternatives for the treatment of a variety of cancers, and numerous efforts are directed to the development of anticancer drugs with good therapeutic effects and few side effects[1].

Systemic toxicity and adverse effects associated with anticancer drugs are the main limitations of their use for the treatment of malignancy[4] cisplatinum, or cis-diamminedichloroplatinum (II. In this context, one of the main limiting factors of cisplatin use is these side effects on normal tissues, which include neurotoxicity, ototoxicity, nausea and vomiting, and nephrotoxicity[5].

Despite enormous advances in understanding the mechanisms underlying cisplatin-induced renal toxicity, there is a lack of effective treatments to improve this nephrotoxicity[6].

For years, several approaches have been tried to reduce these effects, such as synthesizing and tracking cisplatin analogs that have lower toxicity in normal tissues, performing saline hydration and diuresis[5,7]. In various clinical situations, cisplatin discontinuation remains the only option to prevent additional kidney damage in affected patients, as no definitive treatment regimen is currently available to completely address renal damage due to cisplatin[7].

In fact, cisplatin-induced nephrotoxicity is one of the main causes of significant morbidity and mortality among patients, making it urgent to develop potential pharmacological agents to avoid the deleterious effects of this substance, without, however, reducing its anti-cancer effect[6,8].

Recently, the use of flavonoids has become a promising approach in protection against cisplatin-induced kidney injury[9] we investigated the potential renoprotective effect and underlying mechanism of fisetin using rat model of cisplatin-induced nephrotoxicity. The elevation in serum biomarkers of renal damage (blood urea nitrogen and creatinine. Despite this, side effects remain an important factor that limits the use and efficacy of cisplatin in cancer therapy[5].

In this context, this study aimed to investigate, through an integrative review, the protective effects of flavonoids in the prevention and treatment of cisplatin-induced nephrotoxicity.

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Materials and Methods

An integrative review is a unique approach to combining data from various research projects, including experimental and non-experimental research. For its elaboration, an integrative review requires the implementation of phases that present a methodological rigor in search of evidence on a given subject. This method goes through the stages of problem identification, literature research, data evaluation, data analysis and presentation[10,11].

Strategy for identifying studies

In the first phase, the search question was decided by the PICO (Population, Intervention, Comparation and Outcomes) strategy: What is the effect of flavonoid intervention on cisplatin-induced nephrotoxicity in patients, animals or cells? The search strategy was carried out through research in the main health databases: Medline / PubMed, Web of Science and Science Direct, from 2011 to 2020, through the descriptors: Kidney Diseases, Nephrotoxicity, Renal Toxicity, Flavonoids and 2-Phenyl-Benzopyransl, and Cisplatin.All descriptors except "nephrotoxicity" were identified in the Health Sciences Descriptors (DeCS) of the Virtual Health Library and in Medical Subject Headings (MeSH) of the PubMed database. The descriptors were combined as follows: ("Kidney Diseases" OR Nephrotoxicity OR "Renal Toxicity") AND (flavonoids OR 2-Phenyl-Benzopyrans) AND (Cisplatin).

The articles were researched between August and September 2020. Access to federated academic communities, available in CAPES Journals, was used to obtain complete and free articles.

Inclusion and exclusion criteria

For the discussion of the data and interpretation of the research, the approach to the subject was considered; the year of publication; the availability of the article available in full for CAPES journals, the appropriateness of the article in relation to the subject. Dissertations, review studies, letters, opinions or perspectives and comments were excluded, as well as articles that did not evaluate the effect of flavonoids or the combination of flavonoids alone.

Data extraction and evaluation

The data were organized and categorized in a spreadsheet of the Microsoft Excel 2010 program, where the publication's identification, research objectives, method and type of study were recorded.

After data categorization, the articles were read in full and evaluated for quality and risk of bias. For the evaluation of experimental research articles, the criteria established by Arrive essential 10[12] were used, so that articles that did not clearly describe the approval by the ethics committee, the randomization of animals, the number of animals per group, as well as a clear description of the statistical evaluation were excluded.

The presentation of the articles found, along with their inclusion and exclusion categories, as well as the applied distribution, is presented in the PRISMA stream (Figure 1)[13].

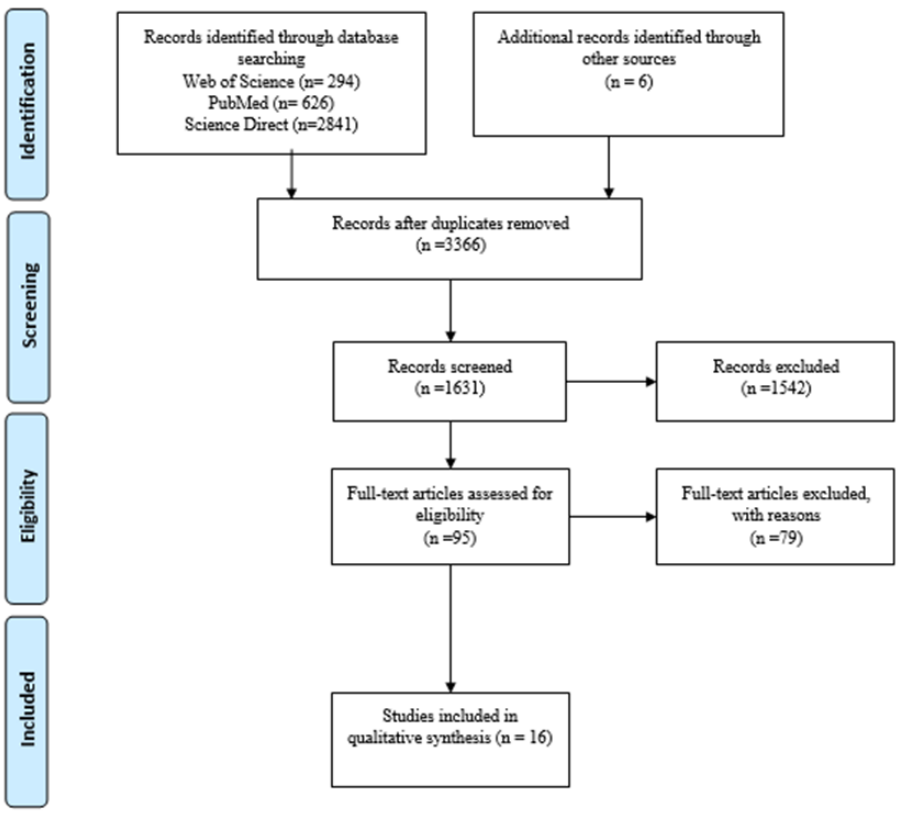

Figure 1. Prisma Flow diagram for include/exclude criteria and data process

Results

The research with keywords in the Science-Direct platform yielded 3787 results, and these were restricted to 2841 results when the restriction factor for the last ten years was considered. After screening, which involved reading the title and abstract, 53 articles were selected. These were analyzed by the proposed selection criteria, resulting in articles read in full that then, after qualitative analysis and based on the purposes of the study, were reduced to 6 articles.

By searching with keywords in Pub-Med, 626 results came up, and these were restricted to 450 results when the restriction factor for the last ten years was considered. After screening, which involved reading the title and abstract, 23 articles were selected, which were analyzed by the proposed selection criteria, resulting in articles read in full that then, after qualitative analysis and based on the purposes of the study, were reduced to 5 articles.

In Web of Science, the search yielded 294 papers, and those which, despite appearing in the search result, did not approach the subject adequately with the variables of interest in this study, were excluded. After screening, 18 articles were selected for reading in full. Then, 6 articles were selected and included in this review.

Therefore, the results include 16 articles from the three research platforms that respect the pre-established parameters as inclusion criteria in this review. Table 1 summarizes the main results of the intervention with flavonoids in nephrotoxicity induced by cisplatin.

Table 1. Main aspects of studies on nephrotoxicity induced by cisplatin, in chronological order, in articles published from 2011 to 2019.

Authors, year	Typeofstudy	Protocol of induction of Nephrotoxicity with CP	Flavonoids/dose/duration	Mainaspects	Periodical
Sanchez-Gonzalez *et al.*, 2011[15]	Experimental research (in vivo)	Single dose of CP in 11th day (4 mg/kg, i.p.)	Quercetin (50 mg/kg/day, i.p.) 7 days later the breast adenocarcinoma cells were inoculated	In a model of tumor-bearing rats, quercetin prevents the nephrotoxic effect of cisplatin without affecting its anti-tumor activity.	Nephrol Dial Transplant
Sahu *et al.*, 20149	Experimental research (in vivo)	Single dose i.p of CP (5 mg/kg dissolved in normal saline) in 3th day	Fisetin (40 µl of 0.625 mg or 40 µl of 1.25 mg / kg i.p) [dissolved in PEG200 / DMSO (7**µ**3)] once a day for 7 consecutive days	Fisetin reduced oxidative stress, restored the activity of mitochondrial respiratory enzymes and suppressed apoptosis in kidney tissues. In addition, it inhibited the activation of NF-κB and attenuated the release of subsequent pro-inflammatory mediators in renal tissues.	PLoSOne
Ju *et al.*, 2015[22]	Experimental research (in vivo)	CP 40µM for the times indicated in serum-free condition	Apigenin (5, 10, 20 µM) for 1 h	Apigenin reduces p53 activation and promotes the PI3K / Akt pathway, but inhibits cell growth due to its ability to induce cell cycle arrest in S and G2/M phases.	Evidence-Based Complementary and Alternative Medicine
Malik *et al.*, 201[51]	Experimental research (in vivo)	Single injection of CP (8 mg/kg, i.p) on the 7th day.	Nobiletin 5 mg/kg; i.p. for 10 days	Nobiletin mediated increasedurea nitrogen in the blood (BUN)and serum creatinine and, furthermore, it reduced oxidative stress, inflammatory cytokine, tumor necrosis factor alpha (TNF-α) and pro-apoptoticBax in renal tubules.	Experimental and Toxicologic Pathology
Chao *et al.*, 2016[23]	Experimental research (in vivo)	Single dose CP (20 mg/kg, i.p)	Hyperin (20, 40, 80 mg/kg) i.p for three consecutive days.	Hyperin attenuated histological changes. The levels of BUN, creatinine, reactive oxygen species (ROS), malondialdehyde (MDA), TNF-α, interleukins(IL-1β and IL-6), nuclear factor-κB(NF-κB) induced by cisplatin were also inhibited by hyperin.	International Immuno pharmacology
Arab *et al*, 2016[19]	Experimental research (in vivo)	single injection of CPi.p. (7.5 mg / kg) on the second day 1 h after tangeretin administration.	50 mg / kg or 100 mg / kg of tangeretin. for one week.	Treatment with tangeretin, in a dose-dependent manner, decreased serum creatinine and urea levels. Pretreatment with tangeretin (100 mg/kg) reduced the levels of MDA, caspase-3, TNF-α, NF-κB, p65, nitric oxide synthase (iNOS), nitric oxide (NO) and nuclear factor erythroid 2-related factor 2(Nrf2). Furthermore, it restored the reduced glutathione (GSH) and glutathione peroxidase (GPx) activity and increased IL-10.	Chemico-Biological Interactions
Li *et al.*, 2016[16]	Experimental research (in vivo)	CP (20mg/kg.ip) in 4th day or in 1th day of the protocol.	Pre-treatment with Eriodictyol (40 mg/kg) for three consecutive days or Treatment with Eriodictyol for three days after the CP	Eriodictyol protected against CP-induced kidney injury by inhibiting oxidative stress and inflammation through activating Nrf2 and inhibiting NF-κB activation	European Journal of Pharmacology
Alhoshani *et al.*, 2017[17]	Experimental research (in vivo)	Single dose of 5 mg/kg of CP on the tenth day	Rutin orally 30 mg / kg, dissolved in water for 14 days	Rutin attenuated CP nephrotoxicity through its antioxidant properties and also the p38-MAPK inhibitor.	BMC Nephrology

Hassan *et al.*, 2017[18]	Experimental research (in vivo)	CP (7.5 mg/kg, i.p.) for three days starting at day five.	Apigenin (3 mg/kg, i.p.), Myricetin (3mg/kg, i.p.) or their combination respectively, for seven days.	Apigenin, myricetin and their combination significantly reduced blood BUN, serum creatinine, caspase-3 TNF-a, IL-6, COX-I and COX-II, MDA levels and significantly increased GSH level and catalase (CAT) activity parallel to, histopathological improvement in kidney tissues.	Pharmaceutical Biology
Sanchez-Gonzalez *et al.*, 2017[24]	Experimental research (in vivo)	CP (4 mg/ kg i.p.), starting from day 10 after tumor implant.	Quercetin (50 mg/kg-1) once a day for 9 days i.p.), beginning from day 7 after inoculation of tumor cells.	Quercetin exerted protection in a cancer model in vivo related to itsantioxidant, vascular, anti-inflammatory and antiapoptotic effects, but these properties do not affect themechanisms responsible for the antitumor effect of cisplatin.	Food and Chemical Toxicology
Tomar *et al.*, 2017[7]	Experimental research (in vivo)	Single dose CP (8 mg/ kg, i.p) on 7th day	Galangin (100 mg/kg).	Galangin reduced oxidative stress apoptosis and inflammation through suppression of mitogen-activated protein kinases (MAPKs) pathway.	Phytomedicine
Li *et al.*, 2018[8]	Experimental research (in vivo)	Single dose CP (20 mg / kg, i.p).	Xanthohumol (12,5, 25, 50 mg / kg) i.pfor three consecutive days	Xanthohumolreduced the serum levels of BUN, creatinine, ROS, MDA, TNF-α, IL-1β, IL-6, NF-κB and IκBα phosphorylated, and(Toll-like 4) TLR4 in kidney tissues and increased the levels of GSH, superoxide dismutases(SOD), and the expression of Nrf2 and Heme oxygenase-1(HO-1).	International Immunopharmacology
Vasaikar *et al.*, 2018[14]	Experimental research (in vivo)	Single dose of CP (20 mg/kg)	D-Pinitol (20 and 40 mg/ kg/day) orally for a period of 7 days.	D-Pinitol significantly ameliorated biochemical levels of serum and urinary creatinine and BUN. Tissue homogenate levels of TNF-α, IL-6, IL-1β and the renal expression of tissue nitrites and histopathological changes were also significantly decreased	Chemico-BiologicalInteractions
Wang *et al.*, 2018[25]	Experimental research (in vivo e in vitro)	Single injection of CP with 8 mg/kg	Astilbin 50 mg/kg for 10 days.	Astilbin improved renal dysfunction, decreasing tubular epithelial cell apoptosis and enhancing antioxidant capacity. Further analysis indicated the chemopreventive role of astilbinmay occur through the activation of Nrf2and inhibition of inflammation.	Food and Chemical Toxicology
Sun *et al.*, 2019[6]	Experimental research (in vivo)	Single injection of CP i.p (20 mg / kg) in 5th day.	Pre-treatment with scutellarin (30 or 60 mg / kg/v.o)for 5 consecutive days.	Scutellarin preventedthe expression induced for CP of p-Stat-3, p-p38, p62, TNF-α, IL-6, Bax and Bcl-2. The levels of cleaved caspase-3, cleaved PARP and p53 were also inhibited. Scutellarin suppressed apoptosis, inflammation and activation of autophagy.	Biomedicine & Pharmacotherapy
Zhou *et al.*, 2019[21]	Experimental research (in vivo)	CP (20 μM) for 24 hours on the second day	Pretreated with various concentrations of icariin for 24 h on the first day	Icariin has antioxidant, anti-inflammatory and anti-apoptotic effects on stress. The main mechanism of action is mediated by the ROS-mediated PI3K/Akt pathway.	Biomedicine & Pharmacotherapy

Discussion

The present study investigated the protective effect of flavonoids in the prevention and treatment of cisplatin-induced nephrotoxicity. With this review, it was demonstrated that several flavonoids have a protective role in nephrotoxicity because they act in the preservation of renal biomarkers (Urea, cretin, BUN), in the reduction of oxidative stress (GSH, MDA, MPO), reduction of inflammation biomarkers (TNF-α, IL-6, IL-1β, iNOS) and in contributing to the maintenance and restoration of histopathological parameters.

Flavonoids are a class of phytochemicals with ubiquitous distribution and lower toxicity compared to other phytochemicals. These properties of flavonoids qualify them as suitable candidates to be used in the treatment of various human diseases, even offering protection against nephrotoxicity induced by cisplatin, and they can be considered a clinically potent, non-harmful and well-tolerated supplement to chemotherapy, indicated by their promising data[14].

In this sense, it should be noted that cisplatin is associated, in particular, with nephrotoxicity, which in turn alters the normal structural and functional profile of the kidney. This renal toxicity is dose and time-dependent and is manifested, for example, by increased serum creatinine and urea BUN, thus limiting cisplatin's clinical use in about 30% of patients undergoing therapy with an initial dose of 50-100 mg/ m2 of cisplatin[1,9,14].

The administration of cisplatin led to a significant decrease in glomerular filtration rate with a high level of serum creatinine and urea nitrogen, indicating renal function disorder. It can be affirmed, through the analysis of serum creatinine and BUN levels, together with urinary creatinine, that renal function and renal toxicity worsen, because about 72 h after chemotherapy administration, there is a significant increase in these markers[6–8,14].

Treatment with flavonoids D-Pinitol or xanthohumol,

rutin, scutellarin, galangin, tangeretin, eriodictiol, quecertine, apigenin and myricetin significantly reduced serum creatinine and BUN levels[1,6,8,14–18].

In addition to renal biomarkers, multiple mechanisms have been implicated in the pathophysiology of cisplatin-induced renal injury, such as oxidative stress, apoptosis and inflammation[1,19]. Currently, it is believed that oxidative stress and ROS formed in the presence of cisplatin are some of the main predisposing factors of this toxicity[1].

Oxidative stress can be evaluated by the measurement of the level of MDA, a marker of lipid peroxidation, together with the antioxidants GSH, SOD and the estimation of CATas markers of the enzymatic and non-enzymatic antioxidant defense system. It can also be affirmed that because cisplatin promotes a significant increase in levels of MDA, TBARS and ROS and a significant decrease in GSH, SOD and CAT in renal tissue homogenates, it favors a state of marked oxidative stress[7,8,14,20].

One of the possible mechanisms of ROS generation is based on the entry of cisplatin into the tubular cells by the carrier of organic cations 2 (OCT2), which undergoes hydrolysis to form positively charged electrolytes that accumulate in negatively charged mitochondria. This leads to reduced activity of mitochondrial respiratory complexes, resulting in the generation of reactive oxygen species. Reactive oxygen species produced by cisplatin also activate other proteins that support pathological processes, such as apoptosis andnecrosis, in particular the proteins of the MAPK family, and inflammation[1].

Stimulation of the inflammatory response further exacerbates damage to renal tissue, and can also induce renal vasculature injury, resulting in decreased blood flow and ischemic injury, thus contributing to a decline in glomerular filtration rate. These events together culminate in the loss of renal function during cisplatin nephrotoxicity, triggering acute renal failure[5].

According to Vasaikar *et al.* (2018) and Sun *et al.* (2019), the inflammatory action of cisplatin can be observed mainly by the increase in the concentration of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1β, as well as by the expression of iNOSin renewable tissues, which show a sharp increase about 72 hours after the administration of the substance alone. This increase in the level of inflammatory cytokines in the research groups that have been treated with cisplatin is indicative of the role of inflammation in cisplatin-induced nephrotoxicity[7,8,20]. Cisplatin also favors the decline of the anti-inflammatory IL-10 cytokine[19].

In the present study, we observed that pre-treatment/treatment with flavonoids tangeretin[19], galangin[7], scutellarin[6], D-Pinitol[14], xanthohumol[8], eriodictiol[20], apigenin, myricetin[18], rutin[17], fisetine[9], and icariin[21] had a significant effect on the reduction of inflammatory parameters induced by cisplatin.

It is worth noting that morphological changes also play a crucial role in nephrotoxicity, since renal tissues exposed to cisplatin may present significant damage to the renal cortex and external medulla[16].

Vasaikar *et al.* (2018) demonstrated that cisplatin administration led to severe and generalized necrosis with dilation, rupture of glomeruli structure, enlargement of the urinary space and edema. In addition, other researchers have shown that cisplatin also causes significant tubular vacuolar changes, including tubular epithelial cell changes, tubular cystic degeneration and dilation, extensive epithelial vacuolization, hyaline cylinder formation, brush edge loss and epithelial cell nuclei, inflammatory cell infiltration, and also glomerular tuft atrophy along with proteins and cell cylinders in the lumen of the tubules. Congestion of intertubular blood capillaries and diffuse inflammatory cellular infiltrate were also observed[6,8,19].

Regarding flavonoids administered in the analyzed studies, it was observed that pre-treatment/ treatment with scutellarin[6] galangin[7], xanthohumol[8], tangeretin[19], eriodictiol[16], D-Pinitol[14], apigenin, myricetin[18], rutin[17], and fisetine[9] significantly mitigated several morphological changes in animals treated with cisplatin.

The graphical abstract (Figure 2) summarizes the main results of this study.

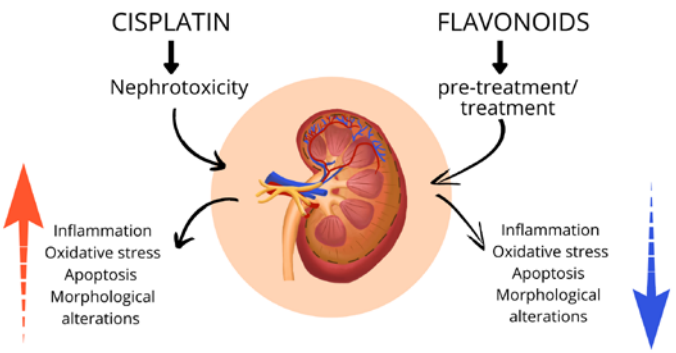

Figure 2. Graphical abstract

Conclusion

In a variety of cases, we demonstrated that flavonoids, many of them found in foods such as fruits and vegetables, improve the damage associated with nephrotoxicity. Our results demonstrated that the flavonoids analyzed, for the most part, had protective effects against cisplatin-induced kidney injury. This renoprotection can be attributed, for example, to the ability to boost antioxidants and attenuate inflammation and apoptosis in the kidney, thus reversing the state of nephrotoxicity provoked by the administration of cisplatin. This nephrotoxicity more specifically included a pro-oxidative state, a pro-inflammatory state, with declining renal function, and a pro-apoptotic state, marked by morphological changes promoted by cisplatin chemotherapy.

Although studies have shown positive results in the use of flavonoids as possible complementary treatments for patients undergoing anticancer therapy using cisplatin chemotherapy, suggesting that they constitute a promising adjuvant therapy in combating the side effects it provokes, it is still necessary to deepen research and clinical analyses. These will contribute to elucidating the best way to use flavonoids, in addition to the frequency of administration and the profile of patients who should receive them.

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References

1. Malik S, Suchal K, Gamad N, Dinda AK, Arya DS, Bhatia J. Telmisartan ameliorates cisplatin-induced nephrotoxicity by inhibiting MAPK mediated inflammation and apoptosis. Eur J Pharmacol. 2015;748:54–60.
2. Van Angelen AA, Glaudemans B, Van Der Kemp AWCM, Hoenderop JGJ, Bindels RJM. Cisplatin-induced injury of the renal distal convoluted tubule is associated with hypomagnesaemia in mice. Nephrol Dial Transplant [serial online]. 2013; 28:879–89. Available from: https://pubmed.ncbi.nlm.nih.gov/23136218/ . Acessed Jun 21,2021.
3. Sarkar FH, Li Y. Using chemopreventive agents to enhance the efficacy of cancer therapy. Cancer Research. Cancer Res; [serial online].2006 ; 66: 3347–50. Available from: https://pubmed.ncbi.nlm.nih.gov/16585150/. Acessed Jun 21,2021.
4. Dasari S, Bernard Tchounwou P. Cisplatin in cancer therapy: Molecular mechanisms of action . European Journal of Pharmacology. Elsevier; [serial online]. 2014;740:364–78. Available from: https://pubmed.ncbi.nlm.nih.gov/25058905/ . Acessed Jun 21,2021
5. Pabla N, Dong Z. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. Kidney International. Nature Publishing Group [serial online]. 2008; 73: 994–1007. Available from: https://pubmed.ncbi.nlm.nih.gov/18272962/. Acessed Jun 21,2021
6. Sun CY, *et al*. Renoprotective effect of scutellarin on cisplati-induced renal injury in mice: Impact on inflammation, apoptosis, and autophagy. Biomed Pharmacother [serial online]. 2019; 1:112. Available from: https://pubmed.ncbi.nlm.nih.gov/30797149/. Acessed Jun 21,2021
7. Tomar A, *et al*. Galangin ameliorates cisplatin induced nephrotoxicity in vivo by modulation of oxidative stress, apoptosis and inflammation through interplay of MAPK signaling cascade. Phytomedicine [serial online]. 2017;34:154–61. Available from: https://pubmed.ncbi.nlm.nih.gov/28899498/. Acessed Jun 21,2021
8. Li F, Yao Y, Huang H, Hao H, Ying M. Xanthohumol attenuates cisplatin-induced nephrotoxicity through inhibiting NF-κB and activating Nrf2 signaling pathways. Int Immunopharmacol. 2018; 61:277–82.
9. Sahu BD, Kalvala AK, Koneru M, Kumar JM, Kuncha M, Rachamalla SS, *et al*. Ameliorative effect of fisetin on cisplatin-induced nephrotoxicity in rats via modulation of NF-κB activation and antioxidant defence. PLoS One [serial online]. 2014 ;9:9. Available from: https://pubmed.ncbi.nlm.nih.gov/25184746/. Acessed Jun 21,2021.
10. Whittemore R, Knafl K. The integrative review: Updated methodology. Journal of Advanced Nursing. J Adv Nurs [serial online]. 2005; 52:546–53. Available from: https://pubmed.ncbi.nlm.nih.gov/16268861/. Acessed Jun 21,2021.
11. Whittemore R, Chao A, Jang M, Minges KE, Park C. Methods for knowledge synthesis: An overviel. Heart and Lung: Journal of Acute and Critical Care. Heart Lung; [serial online]. 2014; 43: 453–61. Available from: https://pubmed.ncbi.nlm.nih.gov/25012634/. Acessed Jun 21,2021.
12. Kilkenny C, Browne W, Cuthill I, Emerson M, Altman D. Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research. J Pharmacol Pharmacother [serial online]. 2010;1:94. Available from: https://pubmed.ncbi.nlm.nih.gov/21350617/. Acessed Jun 21,2021.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med [serial online]; 2009; 6. Available from: https://pubmed.ncbi.nlm.nih.gov/19621070/. Acessed Jun 21,2021.
14. Vasaikar N, Mahajan U, Patil KR, Suchal K, Patil CR, Ojha S, *et al*. D-pinitol attenuates cisplatin-induced nephrotoxicity in rats: Impact on pro-inflammatory cytokines. Chem Biol Interact [serial online]. 2018; 290:6–11. Available from: https://pubmed.ncbi.nlm.nih.gov/29752894/. Acessed Jun 21,2021.
15. Sanchez-Gonzalez PD, Lopez-Hernandez FJ, Perez-Barriocanal F, Morales AI, Lopez-Novoa JM. Quercetin reduces cisplatin nephrotoxicity in rats without compromising its anti-tumour activity. Nephrol Dial Transplant [serial online]. 2011 ;26:3484–95. Available from: https://academic.oup.com/ndt/article/26/11/3484/1832109. Acessed Jun 21,2021.
16. Li CZ, *et al*. Eriodictyol attenuates cisplatin-induced kidney injury by inhibiting oxidative stress and inflammation. Eur J Pharmacol [serial online]. 2016;772:124–30. Available from: https://pubmed.ncbi.nlm.nih.gov/26723515/. Acessed Jun 21,2021.
17. Alhoshani AR, Hafez MM, Husain S, Al-Sheikh AM, Alotaibi MR, Al Rejaie SS, *et al*. Protective effect of rutin supplementation against cisplatin-induced Nephrotoxicity in rats. BMC Nephrol [serial online]. 2017 ;18(1). Available from: https://pubmed.ncbi.nlm.nih.gov/28619064/. Acessed Jun 21,2021.
18. Hassan SM, Khalaf MM, Sadek SA, Abo-Youssef AM. Protective effects of apigenin and myricetin against cisplatin-induced nephrotoxicity in mice. Pharm Biol [Internet]. 2017 [cited 2021 Jun 21];55(1):766–74. Available from: https://pubmed.ncbi.nlm.nih.gov/28064632/
19. Arab HH, Mohamed WR, Barakat BM, Arafa ESA. Tangeretin attenuates cisplatin-induced renal injury in rats: Impact on the inflammatory cascade and oxidative perturbations. Chem Biol Interact [serial online].2016;258:205–13. Available from: https://pubmed.ncbi.nlm.nih.gov/27616468/. Acessed Jun 21,2021.
20. Li CZ, Jin HH, Sun HX, Zhang ZZ, Zheng JX, Li SH, *et al*. Eriodictyol attenuates cisplatin-induced kidney injury by inhibiting oxidative stress and inflammation. Eur J Pharmacol [serial online].2016; 772:124–30. Available from: https://pubmed.ncbi.nlm.nih.gov/26723515/. Acessed Jun 21,2021.
21. Zhou Y dan, Hou J gang, Yang G, Jiang S, Chen C, Wang Z, *et al*. Icariin ameliorates cisplatin-induced cytotoxicity in human embryonic kidney 293 cells by suppressing ROS-mediated PI3K/Akt pathway. Biomed Pharmacother [serial online]. 2019;109:2309–17. Available from: https://pubmed.ncbi.nlm.nih.gov/30551489/. Acessed Jun 21,2021.
22. Ju SM, Kang JG, Bae JS, Pae HO, Lyu YS, Jeon BH. The flavonoid apigenin ameliorates cisplatin-induced nephrotoxicity through reduction of p53 activation and promotion of PI3K/Akt pathway in human renal proximal tubular epithelial cells. Evidence-based Complement Altern Med [serial online]. 2015. Available from: https://pubmed.ncbi.nlm.nih.gov/26089934/. Acessed Jun 21,2021.
23. Chao CS, Tsai CS, Chang YP, Chen JM, Chin HK, Yang SC. Hyperin

inhibits nuclear factor kappa B and activates nuclear factor E2-related factor-2 signaling pathways in cisplatin-induced acute kidney injury in mice. Int Immunopharmacol [serial online]. 2016;40:517–23. Available from: https://pubmed.ncbi.nlm.nih.gov/27764742/. Acessed Jun 21,2021.
24. Sánchez-González PD, *et al*. Differential effect of quercetin on cisplatin-induced toxicity in kidney and tumor tissues. Food Chem Toxicol [serial online]. 2017 ;107:226–36. Available from: https://pubmed.ncbi.nlm.nih.gov/28669851/. Acessed Jun 21,2021.
25. Wang S wei, Xu Y, Weng Y yuan, Fan X yu, Bai Y feng, Zheng X yan, *et al*. Astilbin ameliorates cisplatin-induced nephrotoxicity through reducing oxidative stress and inflammation. Food Chem Toxicol [serial online]. 2018;114:227–36. Available from: https://pubmed.ncbi.nlm.nih.gov/29471006/. Acessed Jun 21,2021.

Mini Curriculum and Author's Contribution

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