

Original Article



The Renal Protective Function of Chrysin in Cisplatin-induced Kidney Toxicity: Insights From Bee-derived Natural Compounds

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ABSTRACT

Background: One common medication used in chemotherapy is cisplatin. Despite its effectiveness, it has side effects such as cytotoxicity and genotoxicity. Chrysin, a type of flavonoid, protects cells from free radicals and neutralizes them.

Objectives: Our research focuses on the defensive effect of chrysin in counteracting the cytotoxic effects of cisplatin on Vero cells, which are a standard model.

Methods: Cisplatin was placed in contact with the Vero cells at IC₅₀ concentration of cisplatin and a single dose of chrysin at 200 µg/mL. The cells were pretreated with varying concentrations of chrysin (40, 80, 120, 160, and 200 µg/mL). The study assessed cell viability, reactive oxygen species production, and glutathione levels.

Results: The results of this research were an increase in cell viability, a decrease in the amount of reactive oxygen species, and an increase in the level of cellular glutathione in the groups treated with a higher concentration of chrysin.

Conclusion: We found that chrysin can indeed protect cells from the damage caused by cisplatin, thanks to its antioxidant properties. We can use chrysin in our daily diet and also in combination with chemotherapy.

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Introduction

Maintaining the health of the kidney, as a vital organ, has essential effects on the quality of an individual's life [1]. Many components and materials could protect nephrons from injury and cure renal failure. At the same time, plenty of things damage it, such as drugs and free radicals that are produced due to metabolism, lack of activity, and diseases [2]. Cis-diaminedichloroplatinum, cisplatin (CDDP), is one of the chemotherapeutic medications most frequently used to treat various human cancers [3]. Still, renal toxicity is the dominant dose-limiting side effect and is noticed in almost 30% of sufferers [4]. The most severe form of acute kidney injury happens in 20%–30% of sufferers and results in CDDP-cutoff chemotherapy [5]. However, over an extended period of clinical medications, therapeutic failure is brought on by side effects like nephrotoxicity, neurotoxicity, and myelosuppression that impact the entire hematopoietic population and lead to the development of chemoresistance.

Preclinical research has shed light on the cellular and molecular mechanisms underlying cisplatin nephrotoxicity. These mechanisms impact intracellular stressors, such as endoplasmic reticulum stress, oxidative stress, mitochondrial pathology, and DNA damage [6]. For many years, one important factor that has been investigated in cisplatin-induced nephrotoxicity is oxidative stress. Research indicates that the primary mechanism by which cisplatin damages renal tubular and glomerular cells is by inducing oxidative stress, which results in cell necrosis and apoptosis, vascular defects, and robust immune response [7].

Accordingly, variant mixtures have been assessed in combination with cisplatin [8].

The organic and physiologically active flavone chrysin (5,7-dihydroxyflavone) is extracted from chamomile, *Pleurotus ostreatus*, and honeycomb [9]. Anticancer, neuroprotective, antiviral, antibacterial, anti-asthmatic, anti-inflammatory, hepatoprotective, nephroprotective, cardioprotective, antidepressant, and antiarthritic activities are the most candid pharmacological characteristics of chrysin [10]. It is thought to possess the ability to destroy free radicals because of the hydroxyl groups in CH at positions five and seven. Research has indicated that the CH group encompasses all effects, including those that are anti-inflammatory, anti-diabetic, anti-allergic, anti-apoptotic, and antioxidant [11]. The constant absorption of chrysin in humans is estimated to range from

0.5 to 3 grams per dose [12]. In this work, we investigated chrysin's effects against cisplatin-induced nephrotoxicity using Vero cells as a renal model. Chrysin is known for its role in reducing oxidative stress.

Materials and Methods

Preparation of medicine and materials

Cisplatin was prepared in a vial under the brand Sigma-Aldrich (CAS:15663-27-1), and chrysin in powder under the brand Herbst (CAS: 480-40-0MF). The cell line was purchased from Pasteur Institute cell bank.

Cell lines

The Vero cell lines from the Pasteur Institute in Tehran, Iran, were cultivated in RPMI-1640 (Gibco, Berlin, Germany) supplemented with 10% fetal bovine serum, 100 µg/mL streptomycin, and 100 IU/mL penicillin (all from Gibco-BRL, Germany). In an atmosphere consisting of 5% CO₂ and 95% air mixture, cell cultures were incubated at 37 °C after being adjusted for exponential growth [13].

MTT assay

Chrysin was applied in varying concentrations to renal cells (derived from the kidney cell line) based on the assessment of cell toxicity. This metabolic test is competitive and measures mitochondrial function. In the mitochondria of living cells, the yellow-colored MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), a tetrazole, is reduced to the unresolved purple-colored formazan.

Only in the presence of active mitochondrial reductase enzymes does the reduction occur.

As a result, the number of living cells can be used to determine this response precisely. Chrysin was prepared in 40, 80, 120, 160, and 200 µg/mL concentrations. While the positive control group was exposed to a half-maximal inhibitory concentration (IC₅₀) dose of cisplatin, and the negative control group was left untreated [14].

Calculating reduced glutathione (GSH) levels

The reaction mixture, which included 0.4 mL of phosphate buffer, 0.1 mL of sodium azide, 0.1 mL of H₂O₂, 0.2 mL of glutathione (GSH), 0.2 mL of ethylenediaminetetraacetic acid (EDTA), and 0.2 mL of homogenate was incubated for 10 minutes at 37 °C. After adding 0.5 mL of trichloroacetic acid to stop the reaction, the tubes

were centrifuged at 2000 rpm. Three milliliters of disodium hydrogen phosphate and 1 mL of DTNB, Ellman's reagent (5,5'-dithiobis-(2-nitrobenzoic acid), were added to the supernatant, and the color developed was read at 420 nm right away. The GSH oxidized activity of glutathione peroxidase (GPx) was expressed as μ mole/minute/mg of protein [15].

Measurement of oxidative stress

Approximately 4×10^4 cells per well were cultured in 96-well plates (black wall/clear bottom) for 24 hours. The medium was then aspirated, and the cells were washed twice with Hanks' balanced salt solution (HBSS). Cells were then treated with the studied chrysin concentrations (40, 80, 120, 160, and 200 μ g/mL) for 1 hour at 37 °C 24 h before cisplatin treatment (120 μ g/mL). After treatment, the cells were washed twice with HBSS and incubated in 2 mL of fresh culture medium without FBS. 2', 7'Dichlorodihydrofluorescein diacetate was added at a final concentration of 10 μ M and incubated for 20 minutes. The cells were washed twice with phosphate-buffered saline and maintained in 1 mL of culture medium. We assessed reactive oxygen species (ROS) by immediately analyzing the cells with a fluorescent plate reader using 488 nm for excitation and detection at 535 nm. We selected untreated cells as a negative control and cells treated with 0.1 mM H_2O_2 as a positive control [16].

Statistical analysis

One-way analysis of variance and Tukey honestly significance differences (HSD) test were used for multiple data comparisons. $P < 0.05$ was considered significant. IC_{50} values were calculated by PRISM software, version

8 using nonlinear regression. Standard deviations represent the average results of duplicate experiments.

IC_{50} values were compared using the student t-test, which measures the effectiveness of a substance in causing cell death or inhibiting cell growth. Therefore, the lower amount of IC_{50} represents higher toxicity of a compound leading to death or inhibition of cell growth. Data are presented as Mean \pm SD. Statistical differences between groups were analyzed using one-way ANOVA followed by Tukey's post hoc test.

Results

To study the effect of chrysin on cell viability upon exposure to cisplatin, after the MTT assay, Vero cells pretreated with chrysin exhibited different behavior than the control group. The results show that the maximum concentration has a significant effect in contrast to the control (Figure 1).

Influence of chrysin on glutathione content

According to the results of the glutathione measurement method, treating the cells with chrysin changes the amount of glutathione compared to the negative control group (Figure 2).

Protective effect of chrysin on cisplatin-induced ROS generation

According to the results, 120 μ g/mL cisplatin resulted in an increase in ROS levels compared to the control group ($P < 0.05$) (Figure 3).

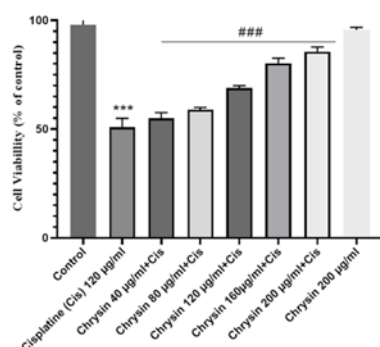
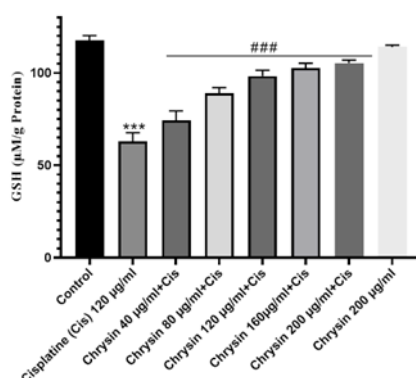


Figure 1. Comparing the effects of different concentrations of chrysin with cisplatin (120 μ g/mL) on the toxicity levels of the Vero cell line using the MTT method

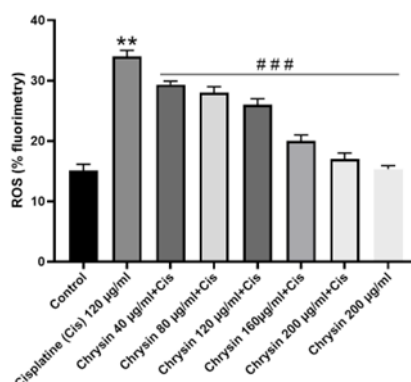
***Comparing cisplatin in IC_{50} with control ($P < 0.001$), ###Comparing chrysin (40, 80, 120, 160, 200 μ g/mL) + cisplatin (in IC_{50}) with cisplatin (IC_{50}) ($P < 0.001$).



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Figure 2. Comparing the effects of different concentrations of chrysin with cisplatin (120 µg/mL) on the GSH levels of the Vero cell line

***Comparing cisplatin in IC_{50} with control ($P < 0.001$), ###Comparing chrysin (40, 80, 120, 160, 200 µg/mL) + cisplatin (in IC_{50}) with cisplatin (IC_{50}) ($P < 0.001$).



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Figure 3. Comparing the effects of different concentrations of chrysin with cisplatin (120 µg/mL) on the ROS generation in the Vero cell line

***Comparing cisplatin in IC_{50} with control ($P < 0.05$), ###Comparing chrysin (40, 80, 120, 160, 200 µg/mL) + cisplatin (in IC_{50}) with cisplatin (IC_{50}) ($P < 0.001$).

Discussion

Flavonoids are the main group of plant alternative metabolites with tremendous vital activities that are useful for human health. There is growing interest in studying flavonoids because they act through physiological mechanisms and many signaling pathways involved in many medical diseases [17].

Chrysin is a flavonoid found in fruits, vegetables, plants, and mainly in honey. Chrysin has antioxidant effects by enhancing the antioxidant system, defeating pro-oxidant enzymes, scavenging free radicals, and chelating redox-active transition metal ions [18].

Oxidative damage occurs when the production of ROS impairs the antioxidant system's ability to destroy ROS, ultimately leading to cell damage [19]. One of the sources of ROS generation is chemical agents such as chemotherapy drugs [20].

Cisplatin is frequently utilized in the treatment of leukemia, lymphomas, breast cancer, testicular cancer, ovarian cancer, head and neck cancer, cervical cancer, and sarcomas [21]. Due to the high effectiveness of this drug in cancer, despite its side effects, its use is very common. Side effects such as DNA damage, cytotoxicity, ROS generation, mutagenicity, tumorigenesis, and genotoxicity have been mentioned in the research [22]. To protect patients from the side effects of cisplatin, physicians prescribe some diets and protective compounds

along with the drug [23]. Chrysin can scavenge free radicals, and it belongs to its hydroxyl groups. Because of that, we designed this study based on the protective effect of chrysin against cisplatin-induced cytotoxicity on Vero cell lines.

Many studies have proved that chrysin could raise cell viability and protect cells. Talebi et al., in their studies about cardiometabolic diseases, found that chrysin could protect the cardiovascular system by enhancing the inherent antioxidative defense system, which helps cells to live [24].

In our investigation using the MTT method, we observed that chrysin elevated cell viability compared to the positive control (cisplatin at IC_{50}). This correlation was evident as higher concentrations of chrysin led to increased cell viability. Our findings indicate that chrysin mitigates cisplatin-induced lipid peroxidation, xanthine oxidase activity, and reduction in glutathione levels, as well as a decline in the activities of antioxidant enzymes (catalase, glutathione reductase, superoxide dismutase (SOD), glutathione peroxidase, and glucose-6 phosphate dehydrogenase) and phase-II detoxifying enzymes (glutathione-S-transferase and quinone reductase) [25]. In another study on the effects of chrysin on cell protection in cadmium toxicity by Simsek et al., it was found that chrysin has cell protection properties and can prevent kidney toxicity and heal damaged cells [26]. The investigation into mechanisms showed that chrysin could decrease Dox-induced apoptosis by lowering the expression of p53, Bax, cytochrome c, and caspase-3. Also, suppressing pathways activated by doxorubicin, such as Akt and VEGF pathways, causes the survival of kidney cells [27].

GSH depletion is another problem caused by cisplatin toxicity and cell harm [28]. Based on our results in the group treated with cisplatin (in IC_{50}), GSH depletion is obvious but decreased in groups pretreated with chrysin. Chrysin could increase the GSH level of cells by its potential antioxidant power [11]. Chrysin could decrease the genotoxicity damage of mitomycin c via inducing activation of the antioxidant system in the level of SOD, GPx, and GSH [29]. However, chrysin can initiate cellular apoptosis by GSH depletion in cancer cells and sensitize neoplasm to chemotherapy drugs [30]. Chrysin could act as a double-edged sword, depending on the situation; because of that, it could be used for prophylaxis or therapy [31]. Chrysin stimulates the transcription factor known as nuclear factor erythroid-derived 2-related factor (Nrf2), leading to upregulation of genes encoding

antioxidant and phase II detoxification enzymes, including GSH reductase and GSH S-transferase (GST) [32].

As we mentioned, cisplatin could raise the generation of ROS, and chrysin, as a free radical scavenger, could reduce it [33, 34]. According to our results, groups treated with chrysin and cisplatin show ROS at high levels. The highest level belongs to a positive control (cisplatin in IC_{50} concentration) in contrast with the negative control. Still, based on the chrysin concentration, we could see decreasing in ROS level, and in the group with a single dose of chrysin (200 μ g/mL), we saw the minimum level of ROS in treated groups. This means that cisplatin increases ROS, but in the groups exposed to chrysin at the same time, ROS production decreased and as the concentration of chrysin increased, the reduction in ROS production was more significant.

Conclusion

In the end, according to the data obtained from the test, chrysin can protect cells, and this feature is visible in the two parameters of glutathione and ROS production. Also, this substance helps cell survival, which was visible in the MTT test results.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Vice-Chancellor of Mazandaran University of Medical Sciences, Sari, Iran (Code: IR.MAZUMS.RIB.REC.1402.124).

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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