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Review Article

EFFECTS OF PHYTOCHEMICALS AGAINST CISPLATIN-INDUCED TOXICITY

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ABSTRACT

Objective: Cisplatin, alkylating anti-cancer agent is most widely-used to treat cancers. Due to the various organ toxicities its use is limited. Current ongoing research has made us understand the detailed mechanisms of these toxicities. Some researchers studied the protective activity of phytoconstituents to mitigate these toxicities. Phytochemicals like Quercetin, Curcumin, Lycopene, Chrysin, Sinapic acid, etc have been studied for their protective activity against all these toxicities. In this review, importance of phytoconstituents and detailed mechanism of their protective activity against Cisplatin-induced toxicities are discussed.**Conclusion-** The main focus of this article is to provide broader knowledge regarding prevention of Cisplation induced toxicities and reduce the mortality rate. This can be achieved by adding combination of Phytochemicals and Cisplatin which can give synergistic and combination effects.

Keywords: Cisplatin-induced toxicity, Quercetin, Curcumin, Chrysin, etc..

INTRODUCTION

Cisplatin [cis-diamminechloroplatinum (II)] is a DNA alkylating anticancer drug used for treating various types of cancers. It is used in non-small cell lung cancer, bladder cancer, cervical cancer, ovarian cancer, head and neck cancer, and testicular cancer [1] .The exact mechanism of toxic action of a platinum-based drug is not known. Inter and intrastrand crosslink in DNA, peculiarly including two adjacent guanine or guanine-adenine bases has been observed after cisplatin administration. The most severe side effects associated with Cisplatin are the peripheral motor and sensory neuropathy, ototoxicity, nephrotoxicity, myelotoxicity and electrolyte disturbance. Due to its high toxicity, Carboplatin has extensively replaced in combination chemotherapy for the treatment of ovarian and lung cancer. For specific tumors like metastatic germ cell tumors, high dose of Cisplatin is administered [2]. 20% of patients getting high-dose cisplatin treatment develop severe renal dysfunction [3]. The detailed mechanism for all these toxicities is unknown. Many authors by review and research have illustrated different molecular pathways for an occurrence of these toxicities. Table 1 enlists detailed information regarding toxicities occurring due to Cisplatin administration.

Table 1: Cisplatin-Induced Toxicity Details.

Toxicities	Epidemiology	Symptoms and Pathophysiology	Proposed Mechanisms	Current Management
Nephrotoxicity	Experienced in more than 70 % pediatric patients. [3]	- Necrosis and apoptosis in tubules. - Elevated levels of BUN and Creatinine in blood	- Dysfunctioning of renal transporters. [4] - Initiation of an inflammatory response by TNF α. [5] - Involvement of CDK protein and E2F1. [6] - Activation of MAPKs, ERK, p38 and JNK. [10, 11]	- Saline hydration and mannitol administration is the standard method adopted. [7] - A Chronomodulated schedule is implemented. [8,9] - Amifostine is been approved for treatment. [12] - Thiols like sodium thiosulfate and mesna are used for rapid excretion of Cisplatin. [13]
Hypomagnesaemia	About 75 % population suffers from Hypomagnesaemia.	Tetany, muscular weakness, tremulousness, dizziness, paresthesia and personality changes.	- Dysfunctioning of renal transporters. - Competition in Cations. - Accumulation of Cisplatin. [2]	- i.v. magnesium sulfate (2–4 g). - Oral magnesium oxide and Oral preparations include magnesium gluconate and magnesium sulfate. [14]
Ototoxicity	60 % pediatric patients suffered from irreversible hearing loss. [15]	Sensory hair cells within the cochlea and inner ear are affected.	- Involvement of OCT2 and CFTR1. - Tumor suppressor p53 involved.	Use of Otoprotectants- - Amifostine - Gingko biloba extract - Sodium thiosulphate

Phytochemicals are (non-nutritional) bioactive substances that can be found in certain vegetables, fruits, and grains. Some positive effects on health are attributed to phytochemicals. A large number of phytochemicals have been identified, but for many of them the potential beneficial effects are still unknown and require elucidation [16].

A wide variety of phytochemicals and they differ in their potential activity, but, functionally, they can be grouped as follows:

1. Antioxidants
2. Anti-carcinogens
3. Anti-oestrogens
4. Anti-inflammatory agents
5. Immunomodulatory agents

These phytochemicals have shown potent anti-cancer activity as well as protective activity against anti-cancer drug toxicity when investigated. The epidemiological evidence regarding the consumption or use of natural phytochemicals as chemopreventive agents showed positive results. The exact mechanism for protective activity has been widely studied. These phytochemicals interact with signaling and metabolic pathways involved in growth, proliferation, differentiation, and cell survival or death. Recently, new pathways involved in cancer are been discovered. These involve mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR), and nuclear factor kappa-beta (NF-κB) pathways. Phytochemicals are investigated to alter these pathways and in most cases, positive results are obtained. Antioxidant, anti-inflammatory, immunomodulatory and anti-carcinogenic activities of these phytochemicals also play important role in preventing Cisplatin-induced toxicity. Some international organizations like the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), have recommended an increase in such phytochemicals obtained from certain vegetables, fruits, and grains. Table 2 enlists the investigated phytochemicals which proved beneficial in reducing Cisplatin-induced toxicity [16, 17].

Table 2: Phytochemicals Beneficial In Reducing Cisplatin-Induced Toxicity.

Phytochemicals showing protective activity against Cisplatin - induced toxicity	
Quercetin	Chrysin
Curcumin	Resveratrol
Lycopene	Sulforaphane
Capsaicin	Genistein
Vetiver oil	Sinapic acid

Let's see in brief the research done on some of the phytoconstituents in order to ameliorate Cisplatin induced toxicities-

QUERCETIN [18]

Penélope D. Sánchez-González et al carried out study to investigate potential of Quercetin to prevent Cisplatin induced nephrotoxicity. The results indicated that quercetin was able to prevent the cisplatin-induced deterioration of diverse mechanisms associated with renal function. The renal effects of quercetin include maintenance of renal blood flow and reduction of inflammation and oxidative stress, all of which are known to be primary pathophysiological events involved in inducing cisplatin nephrotoxicity, or in amplifying the damage. In the kidneys, quercetin inhibits or reduces all damaging events and signals induced or activated by cisplatin. This might indicated that there is a hierarchical organization of all these pathophysiological events, with quercetin acting at the very root (likely tubular cytotoxicity). This study sheds some light into the mechanisms supporting the differential action of quercetin on the kidneys and tumour, and reinforces the promising potential of quercetin to prevent cisplatin nephrotoxicity.

CURCUMIN [19]

Ramin Rezaee et al studied Curcumin in order to reverse Cisplatin induced toxicity. In this researchers stated that Curcumin is able to modulate multiple molecular targets which play vital role in inducing toxicity. Curcumin was found to balance Cisplatin induced neurotoxicity, ototoxicity and nephrotoxicity through antioxidant and anti-inflammatory mechanisms. In this perspective, Curcumin modulated Nrf2 and NF-κB transcription factors. The study concluded that curcumin reduces chemoresistance via different mechanisms and decreases the adverse effects of CP without impairing its anti-tumor efficacy.

LYCOPENE [20]

This study was carried out by Kazim Sahin et al in order to investigate role of Nrf2/HO-1 signaling pathway in Cisplatin induced nephrotoxicity when Lycopene was administered. This study reported that Nrf2-deficient mice displayed increased NF-κB activation in response to lipopolysaccharide. Lycopene supplementation inhibited NF-κB, and increased Nrf2, accompanied by an increase in HO-1, and selected antioxidant enzymes and glutathione. The researchers concluded that lycopene might inhibit NF-κB by scavenging the reactive oxygen species, and by activating the antioxidant machinery through Nrf2 activation. The study reported that lycopene supplementation could increase the level of Nrf2/HO-1, catalase, GPx and SOD, when compared to the cisplatin- treated group of animals.

- **CHRYSIN** [21]:

Sarwat Sultana et al studied the effect of Chrysin on Cisplatin induced toxicity. The rats administered with chrysin showed lowered BUN and serum creatinine levels as compared with the control rats. In this study, it was clearly evident from the histopathological examination of kidney tissues that chrysin significantly prevented disruption of the normal renal architecture, which was distorted by cisplatin administration

SINAPIC ACID [22]

Mushtaq Ahmad Ansari carried out the study on Sinapic acid to investigate the protective activity of Sinapic acid in mitigating Cisplatin-induced toxicity. Sinapic acid ameliorated kidney function, upregulated antioxidant levels. It also downregulated lipid peroxidation and nitric oxide levels in cisplatin-injected rats, resulting in significant reductions in oxidative stress and replenishment of endogenous antioxidant enzymes. Sinapic acid reduced levels of the pro-apoptotic caspase-3 and Bax proteins and upregulated the anti-apoptotic Bcl-2 protein. It also alleviated the extent of histological impairment and reduced neutrophil infiltration in renal tubules.

CONCLUSION

In 21st century, the number of cases of Cancer patients is increasing at higher rate. Due to various toxic effects of anti-cancer agents, their use has become limited. Currently available strategies for management of Cisplatin induced toxicities focuses on decreasing the specific toxicity and its symptoms. They do not reduce actual pathological issues at cellular levels and also has some of their complications. Phytochemicals in combination with Cisplatin can be used for increase efficacy and synergistic effects.

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