

A review on cisplatin-induced ototoxicity: Focusing on recent advances in natural remedies

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Abstract

Background: Despite the efficiency, many side effects have been reported for cisplatin, which is a well-known anti-cancer agent. Among them we can point to ototoxicity, which seriously reduces the quality of life in cisplatin-receiving patients. Since the approach of using natural ingredients in clinic has been growing in recent years, herein, we intend to gather delegated documentations of the presented scientific reports regarding various aspects of cisplatin-induced ototoxicity (CIO) focusing on some effective natural remedies.

Methods: Well-known scientific databases such as Google Scholar, Scopus, and PubMed were employed to search the target keywords. Then, to prepare the literature, the selected contents were reviewed, analyzed, and modified at several stages.

Results: Recent studies have shown that the prevalence of CIO is very high and most cisplatin-receiving patients suffer from this complication to a certain degree. Along with other underlying factors, the roles for reactive oxygen species (ROS) and apoptotic factors have been found very significant in forming the process of CIO. In order to alleviate the complication, various pharmacological and non-pharmacological treatments have been introduced and suggested. Particularly, special attention has been paid to natural products in recent decades. In this regard, many of these compounds were found efficacious and safe.

Conclusion: This review showed that, many natural products are able to attenuate CIO through various mechanisms, among which anti-oxidative and anti-apoptotic pathways would be the most important ones. Therefore, as a novel pharmacological approach, they have the potential to be focused in future mechanistic studies.

Keywords: Cancer, Chemotherapy, Cisplatin, Ototoxicity, Natural products

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INTRODUCTION

As a debilitating disorder, ototoxicity, which can be caused by being exposed to some drugs and toxins, seriously complicates the quality of life of patients. Ototoxic agents affect vestibular and cochlear organs, leading to reversible and irreversible damages. Among the ototoxic drugs, anti-malarial agents, loop diuretics, macrolide, and aminoglycoside antibiotics and some anti-cancer drugs can be mentioned. Platinum based chemotherapeutic agents are essential component of many cancer chemotherapy protocols and have been found effective in the treatment of various types of cancer including head and neck, ovarian, testicular, cervical, bladder, head and neck, and non-small cell lung cancers (1-4). Cisplatin is one of the renowned platinum based chemotherapeutic drugs that usually causes bilateral ototoxicity. At the beginning of the treatment, not only the hearing loss usually occurs corresponding to high frequencies but also hearing the lower frequencies might be affected

(5-8). Although the severity of the damage would depend on the administered dose, it is a very common side effect and about 93% of the patients treated with this drug report some degree of irreversible hearing loss (3, 9-11). Many research studies have been carried out to justify the high prevalence of this complication, as a result, various mechanisms have been proposed in this domain (12-15). It is believed that the severity of ototoxicity in cisplatin-treated patients varies from case to case and these patients customarily may suffer from otalgia and tinnitus (which are defined as ear pain and the perception of noise in ears, respectively) or some degrees of hearing loss. It is important to note that, genetic polymorphisms can underlie the severity and prevalence of these variations (16). In recent years, numerous studies have been conducted in order to attenuate cisplatin-induced ototoxicity (CIO) (17-20). Among them, the use of herbal products have always received a substantial attention from the scholars (21, 22). Regarding natural products as a valued reservoir of novel medicines and complementary products,

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they keep on representing a challenge to science in consequence of phytochemical diversities bringing about varied biological effects. Subsequently, the aim of this study was to review the various aspects of CIO focusing on the important natural remedies.

METHODS

Referenced articles (published over the last three decades) were selected by searching through well-known scientific databases such as Google Scholar, Scopus, and PubMed. The terms, "Cancer", "Chemotherapy", "Cisplatin", "Ototoxicity" and "Natural products" were used as the keywords. Selected contents were reviewed at several stages before writing the literature and the final manuscript was approved by all the authors.

RESULTS

Prevalence of CIO

Several risk factors can exacerbate the severity of CIO including anemia, renal failure, head and neck irradiation or hypoalbuminemia. As can be deduced from the studies, underage and elderly patients are more exposed to the risk (1). In this regard, the prevalence of severe hearing loss among cisplatin-treated patients has been reported 40%–80% for adults and 90% for pediatrics (23). Besides, the gender of the patients is the other variable, which is debatable in this scope as males are more susceptible than females to develop the condition (24). On the other hand, several genetic factors influence the severity of CIO. Seeing that some genotypes are not able to metabolize and detoxify cisplatin, therefore, the patients would be more exposed to the risk (25). Furthermore, the duration of the therapy and the administered dose together with the nutritional status of the patients would directly affect the severity of the mentioned complication (6). More to the point, considering the increasing rate of cancer in developing countries, the use of chemotherapy drugs and prevalence of their side effects would be higher in these countries (26). Taken as a whole, the high incidence of cancer and the growing use of chemotherapy drugs, on one hand, and the high prevalence of ototoxicity in patients receiving cisplatin, on the other hand, would justify the burgeoning bulk of studies in this area.

Molecular Mechanisms

In recent years, researchers have established valuable findings regarding the mechanisms involved in the development of CIO. Many of these outcomes support the undeniable role of reactive oxygen species (ROS) in this process. In view of the fact that the body's antioxidant capacity is limited, cisplatin induced over-production of free radicals brings about oxidative stress leading to harmful effects. The involvement of signal transducers and activators of transcription (STATs), NF- κ B protein complex, NADPH oxidases such as NOX3 and high mobility group (HMG) proteins have also been reported (5, 25, 27). These mechanisms may finally result in damages in neurons of the spiral ganglion, the hair cells in the organ of Corti, and the epithelial cells of the stria vascularis (25). Likewise, alkylation- like reactions would play an important role in the

mentioned processes. It would be a mechanism by which cisplatin damages the nuclear DNA. High mobility group proteins are a type of protein that are able to inhibit transcription factors following binding to DNA. The result could also be starting the apoptosis process (6). The involvement of BCL2-associated X (BAX) proteins has also been demonstrated in these processes. Research evidence indicate increased levels of BAX and decreased levels of BCL2 (an anti-apoptotic protein) proteins following cisplatin administration (28). The mentioned mechanisms would lead to dysfunctions in cochlear outer cells and then gradually may affect other regions (29). So, it can be concluded that ROS production, the involvement of signal transducers and activators of transcription (STATs), NF- κ B protein complex, NADPH oxidases such as NOX3 and high mobility group (HMG) proteins, alkylation- like reactions, and imbalances between apoptotic and anti-apoptotic factors may be the leading underlying causes for CIO. However, the exact molecular pathways are still unclear.

Natural Pharmaceutical Approaches

Not surprisingly, the widespread usage of natural products available among the populace for treating different sorts of disorders regardless of their effectiveness and safety especially between people with low literacy, makes it ever more essential to acquire the necessary evidence-based information around the natural remedies for developing more efficient, safe, and reliable natural treatments. In the past couple of decades, the approach to the use of natural resources for producing pharmaceutical compounds has received considerable attention. Natural remedies are mainly originated and produced from different kinds of medicinal plants, certain types of animals or of microorganisms (30-36). In this manuscript, we aimed to list some important natural compounds in the literature that have been found effective in preventing or improving CIO.

Peanut Sprout

Peanut sprout, which is known to be rich in various valuable nutrients, had been the subject of numerous studies reporting about its useful pharmacological effects. Its anti-cancer, anti-inflammatory, and anti-aging effects, on one hand, and its antioxidant capacity, on the other hand, have caught researchers' attention to this natural product (37-41). Among its valuable pharmacological abilities, its attenuating effect on CIO can be mentioned. In a study conducted by Youn *et al.* it was revealed that peanut sprout would be able to stimulate the Akt/Nrf-2 pathway in the auditory cells. They declared that the observed stimulation would justify its antioxidant and consequently otoprotective effects (41).

Paeoniflorin

Paeonia lactiflora, which is a well-known medicinal plant, grows in different regions of the world. In many countries, its various applications in traditional medicine have been reported before (42). Biological activities of this plant would be due to its different bioactive compounds (9, 42). Paeoniflorin, a monoterpene glycoside, is one of the key bioactive compounds whose neuroprotective potential as well

as its anti-apoptotic, anti-oxidative, and anti-inflammatory effects have been investigated and reported in previous studies (43, 44). In a recent study in 2019, the attenuating effect of paeoniflorin on CIO was evaluated. The results of the study indicated that paeoniflorin would be able to improve CIO via decreasing the production of ROS, increasing PINK1 expression, reducing the accumulation of BAD proteins on mitochondria, and consequently diminishing the cisplatin-induced mitochondrial apoptosis in spiral ganglion neurons (9).

Chrysin

It has already been substantiated that honey and propolis are two rich sources of chrysin (45). This natural flavone has attracted the attention of many researchers in recent years due to its various pharmacological properties. Anti-allergic, antioxidant, and anti-inflammatory effects are the only small part of this compound's medicinal properties. Besides, otoprotective effect of chrysin have also been evaluated and it has been shown that it would be effective in preventing CIO (45, 46).

Astragalosides

For centuries, *Astragalus membranaceus* has been holding a special place in traditional medicine of different countries. After China, its medicinal usage has also become popular in other countries such as the US and Japan (47). Many of its pharmacological effects, such as the antioxidant properties, are due to the activity of a class of phytochemicals namely astragalosides (48). It has been reported that the attenuating effect of this plant on CIO was due to the antioxidant capacity of its astragalosides (49).

Resveratrol

Grapes and peanuts are two sources of the natural polyphenol, resveratrol (50). Cardioprotective, cancer preventive and estrogen receptor modulatory effects of resveratrol as well as its other pharmacological effects have been reported in the pertinent literature in this domain (51). Over the past decade, there have been several studies available online about the protective effect of resveratrol against CIO. These studies have suggested the antioxidant capacity of resveratrol as the mechanism underlying its otoprotective property (21, 52-54).

Korean Red Ginseng

People in East Asia have found Korean ginseng (*Panax ginseng*), an effective medicinal plant for centuries. Japan, Korea, and China are some of the countries where the herb has been widely used regarding different medical purposes such as the treatment of cardiovascular diseases, cancers, and diabetes (55, 56). The effect of Korean red ginseng (the steamed root of the plant) on CIO has also been assessed in several studies. It was stated that the anti-apoptotic, anti-oxidative, and anti-inflammatory effects of the plant would play a significant role in its protective effects against the ototoxicity (57-59).

Melatonin

In physiological conditions, the pineal gland is responsible

for the secretion of melatonin. In addition to regulating the circadian cycle, melatonin seems to be involved in maintaining immune function (60). The efficacy of melatonin in attenuating CIO has also been evaluated. All the studies confirm the protective role of melatonin against CIO. Although other mechanisms such as dopaminergic modulation have been reported for actions of melatonin, the main mechanism for its otoprotective effects, seems to be through antioxidative pathways (61-64).

Vitamin E

As a well-known antioxidant, vitamin E has always been a focal point for researchers to find its various beneficial therapeutic effects. It is a lipid soluble compound and the RRR- α -tocopherol is the most common form of this vitamin in natural resources. Numerous therapeutic effects have been attributed to vitamin E to date. Abilities in attenuating the oxidative stress in hemodialysis patients, improving the condition of myocardial infarction patients, and enhancing the bone histomorphometry parameters have been reported for vitamin E as well as the other significant beneficial effects (65-70). Apart from these therapeutic effects, vitamin E treatment has been shown to improve CIO. In recent studies, the antioxidant activity, neuroprotecting and inhibiting lipid peroxidation and DNA fragmentation within the cochlea have been noted as the underlying protective mechanisms against CIO (71-75).

Curcumin

The medicinal use of curcumin, a famous phytochemical which is extracted from *Curcuma longa*, has been of particular interest to researchers for years. It seems to be beneficial in various diseases such as arthritis, diabetes, and Alzheimer's disease (76). In addition to these applications, the mitigating effect of curcumin on CIO has also been proven. It is reported that curcumin would attenuate the mentioned toxicity via increasing Heme Oxygenase-1 gene expression and Nrf-2 translocation, as well as antioxidant and anti-inflammatory activity (74, 76-79).

Lycopene

Tomatoes are natural sources of a carotenoid, which is called lycopene. In addition to its antioxidant property, lycopene has been known for its cognitive enhancing, neuroprotective, and anti-inflammatory properties (80, 81). Moreover, some useful therapeutic effects on CIO have been reported in which the inhibitory effects on oxidative process, inflammatory, and apoptotic pathways have been declared to be among the involved protective mechanisms (82-84).

Caffeic Acid

Caffeic acid phenethyl ester (CAPE) is another useful natural compound, which is found in some natural resources. CAPE is famous for its antioxidant, anti-inflammatory, and immunomodulatory capacity, which are the underlying mechanisms for various therapeutic effects (85). Among them the beneficial effects on vascular and reperfusion injuries have already been reported. On the other hand, its effectiveness on reducing CIO have been shown in previous

Table 1. Some important natural compounds attenuating cisplatin-induced ototoxicity

Natural Compound	Mechanism	Ref
Peanut sprout	Stimulating the Akt/Nrf-2 pathway in the auditory cells, Antioxidant capacity	(41)
Paeoniflorin	Decreasing the production of reactive oxygen species, Increasing PINK1 expression, Reducing the accumulation of BAD proteins on mitochondria and consequently diminishing the cisplatin induced mitochondrial apoptosis in spiral ganglion neurons	(9)
Chrysin	Strong antioxidant and anti-inflammatory properties	(46)
Astragalosides	Antioxidant capacity	(49)
Resveratrol	Antioxidant capacity	(21, 52-54)
Korean red ginseng	Anti-apoptotic, anti-oxidative and anti-inflammatory effects	(57-59)
Melatonin	Dopaminergic modulation, antioxidative pathways	(61-64)
Vitamin E	Antioxidant activity, neuroprotection and inhibiting lipid peroxidation and DNA fragmentation within the cochlea	(71-75)
Curcumin	Increasing Heme Oxygenase-1 gene expression and Nrf-2 translocation, as well as antioxidant and anti-inflammatory activity	(74, 76-79)
Lycopene	Inhibitory effects on oxidative, inflammatory and apoptotic pathways	(82-84)
Caffeic acid	Antioxidant effects	(88, 89)

studies. Although studies have suggested that all the mentioned mechanisms may underlie the protective effects of caffeic acid against CIO, more emphasis has been placed on its antioxidant activity as the responsible protective pathway (85-89).

CONCLUSION

The main goal of this article was to review a collection of natural compounds that would help cisplatin receiving patients cope better with ototoxicity, the well-known side effect of the drug. Some of the compounds such as melatonin, curcumin, and vitamin E have attracted more attention in recent studies. As discussed, among the mechanisms through which these compounds act, antioxidant, anti-inflammatory and anti-apoptotic pathways may be the most important ones (Table). Each of these pathways can be a target for future studies and therefore a key to find better treatments for cisplatin-induced ototoxicity.

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