Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 2, 2023; 168-178
https://doi.org/ 10.19106/JMedSci005502202309

Protective role of *Nigella sativa* oil against cisplatin-induced ototoxicity: a literature review

Donny Hendriyanto[1], Helmi[1,2]

[1]Faculty of Medicine, Universitas Andalas, Padang, Indonesia, [2]Faculty of Agriculture, Universitas Andalas, Padang, Indonesia

Submitted: 2021-11-21
Accepted : 2022-03-09

ABSTRACT

Cisplatin is widely used for the chemotherapy of head and neck cancer. However, it has a significant ototoxicity. *Nigella sativa* has been scientifically proven to have numerous benefits included to prevent adverse effect of a drug. This literature review aimed to evaluate the protective role of *N. sativa* oil against cisplatin-induced ototoxicity. Relevant publications were searched from PubMed and Google Scholar databases within the last 10 years. Ototoxicity due to cisplatin can occur through the intrinsic and extrinsic pathways. Cisplatin causes endoplasmic reticulum stress, DNA damage, increased reactive oxygen species (ROS) and inflammatory processes, resulting in increased apoptosis of cochlear outer hair cells. The active constituents of *N. sativa* including flavonoids, phenolics and thymoquinone can prevent the cisplatin-induced ototoxicity. Examination of endogenous antioxidants, antiapoptotic, and proinflammatory could be used as primary approach to evaluate the protective role of *N. sativa* against cisplatin-induced ototoxicity.

ABSTRAK

Cisplatin digunakan secara luas dalam kemoterapi kanker kepala dan leher. Namun demikian, cisplatin mempunyai efek samping ototoksiknya nyata. *Nigella sativa* terbukti secara ilmiah mempunyai berbagai manfaat termasuk mencegah terjadinya efek samping obat. Kajian pustaka ini bertujuan mengkaji peran efek pencegahan minyak *N. sativa* mencegah ototoksik akibat cisplatin. Publikasi yang relevan dicarik dari database PubMed dan Google Cendekia selama 10 tahun terakhir. Ototoksisitas akibat cisplatin dapat terjadi melalui jalur intrinsik dan ekstrinsik. Cisplatin menyebabkan stres retikulum endoplasma, kerusakan DNA, peningkatan *reactive oxygen species* (ROS) dan proses inflamasi, yang mengakibatkan peningkatan apoptosis sel rambut luar koklea. Senyawa aktif dalam *N. sativa* seperti flavonoid, senyawa fenol dan timoquinon dapat mencegah ototoksisitas akibat cisplatin. Pemeriksaan antioksidan endogen, antiapoptosis dan proinflamasi kemungkinan dapat digunakan menjadi pilihan utama untuk melihat peran protektif *N. sativa* terhadap ototoksisitas akibat cisplatin.

Keywords:
cisplatin;
Nigella sativa;
ototoxicity;
protective role;
side effect

INTRODUCTION

Cisplatin (cis-diamminedichloroplatinum) is a chemotherapy agent that is widely used and effective in the treatment of epithelial malignancies, especially head and neck cancer.[1,2] Despite promising result against cancer, clinical use is hampered by serious side effects such as gastrointestinal, peripheral neuropathic, nephropathic, bone marrow toxicity, and ototoxicity.[3,4] The effect of cisplatin ototoxicity is sensorineural hearing in the two ears, irreversible, starting at a frequency of 6000-8000 Hz, which will ultimately influence lower frequencies

*corresponding author: donny.hendriyanto@yahoo.co.id

if the treatment continues, joined by tinnitus.[5,6]

Ototoxicity due to cisplatin is still very high, particularly in children and the elderly. Where the level of ototoxicity due to cisplatin occurs in 75-100% of elderly and 22-70% of children.[7,8] The ototoxic effect of cisplatin are greatest in kids because of the potential for delays in education and psychosocial development.[9,10] To date, the mechanism of cisplatin-induced ototoxicity has not been completely clarified. This mechanism may involve many factors and many substances, so the management of cisplatin-induced ototoxicity remains unsolved.[11] The ototoxicity of cisplatin may occur through an apoptotic cycle driven by increased ROS in the inner ear.[12,13] The body produces endogenous antioxidants to inhibit the increase of oxidative stress induced by cisplatin. However, the production is not enough against very high oxidative stress due to cisplatin.[14,15] Therefore, exogenous antioxidants are needed to prevent cisplatin-induced ototoxicity.

Nigella sativa possesses several biological activities including anti-inflammatory, antibacterial, and antioxidant properties.[16] It contains active ingredients such as flavonoids, phenolics, and thymoquinone.[17] Thymoquinone is an active compound isolated from *N. sativa* which is an antioxidant. It is useful to prevent the drug-induced ototoxicity. Thymoquinones are polar polyphenol compounds that will inhibit the formation of ROS by suppressing xanthine oxidase compounds, then catalyzing the oxidation of hypoxanthine and xanthine into uric acid, while reducing O_2 and H_2O_2.[18] In this literature review, the protective role of *N. sativa* oil against cisplatin ototoxicity was reviewed.

MATERIALS AND METHODS

Literature was searched from PubMed and Google Scholar databases. The keywords used were “hearing loss” OR “ototoxicity” AND “cisplatin” AND “Nigella sativa”. A manual search was also conducted to identify additional key references. Literature searching was limited to publications in English or Bahasa Indonesia with a time limit of the last 10 years.

RESULTS

Cisplatin is an anticancer used to treat various malignancies, such as testicular cancer, ovarian cancer, head and neck cancer, and some pediatric malignancies.[19,20] Compared to other platinum compounds, cisplatin has the highest ototoxicity. Approximately 50% of head and neck cancer patients experience ototoxicity after treated with cisplatin.[21,22]

Ototoxicity is hearing loss because the side effects of certain medication. This condition can result in sensorineural hearing loss, irreversible, bilateral, and typically starts at high frequency, as well as tinnitus.[5] There are several criteria used to determine if ototoxicity has occurred, including the guidelines set by the American Speech-Language Hearing Association/ASHA (TABLE 1).

Since there is no cure for hearing loss caused by ototoxic medications, prevention becomes even more crucial. Preventive measured may include considering the utilization of neurotropic, antiapoptotic, and antioxidant drugs. Given the ototoxicity of cisplatin, antioxidants are the appropriate group of substances to help prevent ototoxicity due to cisplatin (TABLE 2).[21,27]

TABLE 1. ASHA criteria for ototoxicity

Criteria	Description
ASHA	Significant ototoxic change when one of three criteria is obtained: 1. Decrease ≥ 20 dB at least one frequency, 2. Decrease ≥ 10 dB at least two adjacent frequencies, 3. Loss of response on three successive frequencies that are on previous checks are still responding.

TABLE 2. Overview of relevant literature on ototoxicity of cisplatin

Author (year)	Country	Methods	n	Age (yo)	Cumulative cisplatin dose (mg/m^2)	Findings
Hodge *et al.*[23]	USA	Case report	1	29 yo	132 mg/m^2	Cisplatin causes ototoxicity and damage to the cochlea, it is necessary to continue monitoring for hearing damage when cisplatin is given.
Camet *et al.*[24]	United States	Retrospective review	153	3-13 yo	300-480 mg/m^2	Alternative dosing with lower amounts per dose may reduce CDDP accumulation in the cochlea and may potentially lead to less ototoxicity while retaining its anti-neoplastic properties.
Patatt *et al.*[25]	Brazil	Systematic review	634	0-19 yo	45-950 mg/m^2	Auditory changes after the use of platinum-based antineoplastic drugs were found, however, there was an important heterogeneity regarding the frequency of ototoxicity and the cumulative dose of the drugs used.
Clemens *et al.*[26]	Netherlands	Cross-sectional	168	0-17 yo	180–900 mg/m^2	Ototoxicity after platinum treatment may be irreversible and that longitudinal clinical audiological monitoring and care is required in long-term survivors of childhood cancer on a large scale.

DISCUSSION

Molecular mechanism of actions of cisplatin

Cisplatin acts as an anticancer during the S phase (DNA replication). It belongs to the genotoxic chemotherapy category, which causes irregularities in DNA, affecting DNA replication and cancer cell division.[28] Cisplatin is a DNA alkylating agent that works by modifying DNA bases, influencing DNA replication and transcription processes, and causing alterations in DNA.[29] Cisplatin attaches alkyl groups to DNA bases, this alteration of DNA construction can result in DNA fragmentation, caused by the activity of enzymes that cleave or remove the alkylated DNA bases. The activity of these DNA repair enzyme is a natural occurrence in response to DNA damage.[30]

Alkylating agents can increase the occurrence of mispairing of DNA bases, causing DNA alterations. Cisplatin binds to double-stranded DNA bases by forming cross-links between G (guanine) bases, resulting in nucleotides changes. Covalent bonds between guanine bases, mediated by cisplatin, can hinder the DNA replication process, ultimately leading to cell death.[15,31]

Immunological reaction to cisplatin chemotherapy

The activity of chemotherapy relies not just upon its cytotoxic impact on cancer cells, but also on its ability to influence immune cells. Some chemotherapeutic medications can induce damage, leading to protein expression on the cell surface, cytokine release, or plasma membrane disruption and release of the intracellular substance.[32]

The innate immune system

The effects of chemotherapy on macrophages have also been documented. Macrophages can differentiate blood monocytes into two distinct subtypes, namely classically activated (M1) and alternatively activated (M2) which possess effector or suppressive capacities, respectively. Solid tumor infiltrating macrophages (tumor-associated macrophages/ TAMs) share numerous characteristics with M2 macrophages and exert pro-tumorigenic functions based on their direct or indirect immune-suppressive effects (via cytokine production) on NK cells and T cells. In cancer patients, the presence of TAMs promotes cancer progression. Several studies have investigated the impact of chemotherapy in subverting the pro-tumorigenic activity of macrophages.[33]

Chemotherapy affects bone marrow hematopoiesis, unexpectedly influencing myeloid cell activation. Platinum-based compounds, such as cisplatin, have also been reported to modulate the percentage of myeloid cells by increasing dendritic cells and eliminating myeloid-derived suppressor cells (MDSC), thus promoting immune effector responses. A direct immunostimulatory effect of cytotoxic drugs on dendritic cell activity has also been reported. Cisplatin chemotherapy can influence dendritic cell movement likewise through indirect mechanisms.[34]

The adaptive immune system

Intensive chemotherapy treatment in cancer patients leads to profound depletion of all lymphocyte populations, particularly B cells. Cisplatin and low-dose paclitaxel synergize to produce specific CD8 T cells that exhibit strong responses through the release of IL-2 and IFN-γ, resulting in high therapeutic efficacy. Cancer often results in a Th1/ Th2 immune imbalance, which some antineoplastic drugs can help to address. Paclitaxel enhances Th1 cell immunity by increasing the levels of IFN-γ-releasing CD8 T cells and IL-2-releasing CD4 T cells (FIGURE 1).[34,35]

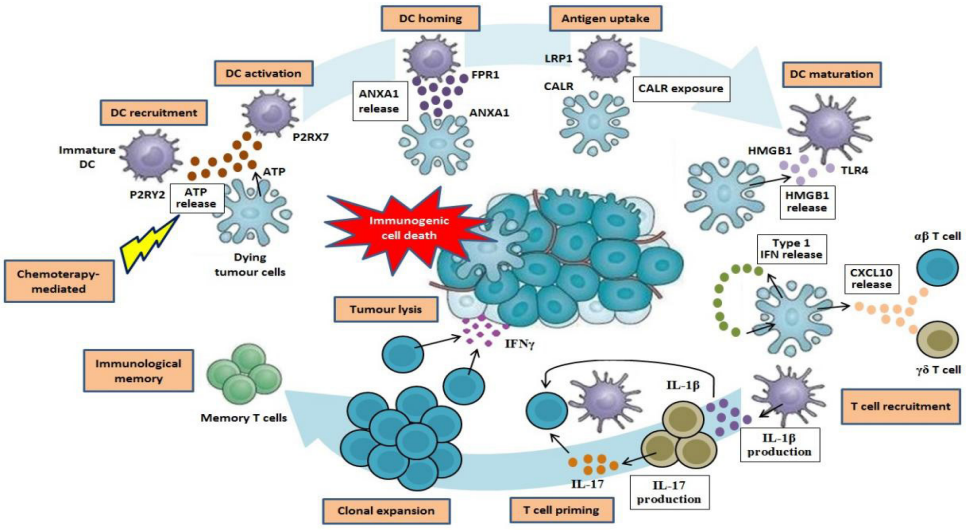

FIGURE 1. Mechanism of immunogenic cell death due to chemotherapy.[35]

Pathobiological mechanism of cisplatin ototoxicity

Cisplatin enters the outer hair cell (OHC) with the help of organic cation transporter-2 (OCT-2) as the vehicle medium. In OHC, cisplatin undergoes 2 pathways: the intrinsic pathway and the extrinsic pathway.[36,37] The intrinsic pathway consists of the mitochondrial pathway and the endoplasmic reticulum pathway. In the mitochondrial pathway, cisplatin causes an increase in oxidative NADPH and DNA damage, which leads to an increase in reactive oxygen species (ROS). DNA damage also results in an increase in p53, further raising ROS levels.[21] Increased ROS in mitochondria causes an increase in oxidative stress in the body, endogenous antioxidants (superoksida dismutase, glutation peroksidase, catalase, glutation reductase) that will protect/repress the increase in oxidative stress. However, due to the extremely high oxidative stress caused by cisplatin, the endogenous antioxidant activity is decreased. an increase in p53 also inhibits the anti-apoptotic Bcl-2 from blocking Bax, a pro-apoptotic protein.[38] Increased oxidative stress and Bax lead to the release of cytochrome-c which activates caspase-9 and caspase-3. In the endoplasmic reticulum pathway, cisplatin causes endoplasmic reticulum stress, resulting in calpain activation and an increase in caspase-12. Initiation of caspase-12 leads to the production of caspase-9 and caspase-3.[39] Caspase-3 induces apoptosis, ultimately causing ototoxicity.[31,40]

The extrinsic pathway, specifically through the death receptor pathway, is another process by which cisplatin induces ototoxicity. Cisplatin binds to death and inflammation receptors on the cell surface. Tumor necrosis factor-α (TNF-α) is an inflammatory mediator and cytokine that triggers apoptosis through death receptors. It associates with Fas protein (CD95). When Fas binds to its ligand, the membrane moves towards the ligand (FasL). At least three FasL molecules join to form the FADD (Fas-associated death domain), which binds to the inactive form of caspase-8, activating it and leading to the production of caspase-3. Caspase-3 induces apoptosis, which resulting in ototoxicity.[37,41] The pathological mechanism of ototoxicity of cisplatin is presented in FIGURE 2.[7,42]

Protective role of *N. sativa* against cisplatin ototoxicity

Nigella sativa is a natural plant that has been scientifically demonstrated to provide numerous benefits when consumed, either as oil or extract. *Nigella sativa* has several biological properties including an antioxidant, analgesic, antiinflammatory and antihistamine and its protective role against cisplatin ototoxicity may be associated with the antioxidant, anti-inflammatory, and immunomodulator activities (FIGURE 3).[43,44] The active compounds, minerals and nutrients contained in *N. sativa* include flavonoids, phenolics, thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, 4-terpienol, carvacrol, t-anethol, sesquiterpene longifolene, α-piene, thymol, alkaloids, proteins, fat, sugars, Cu, P, Zn and Fe.[17,45]

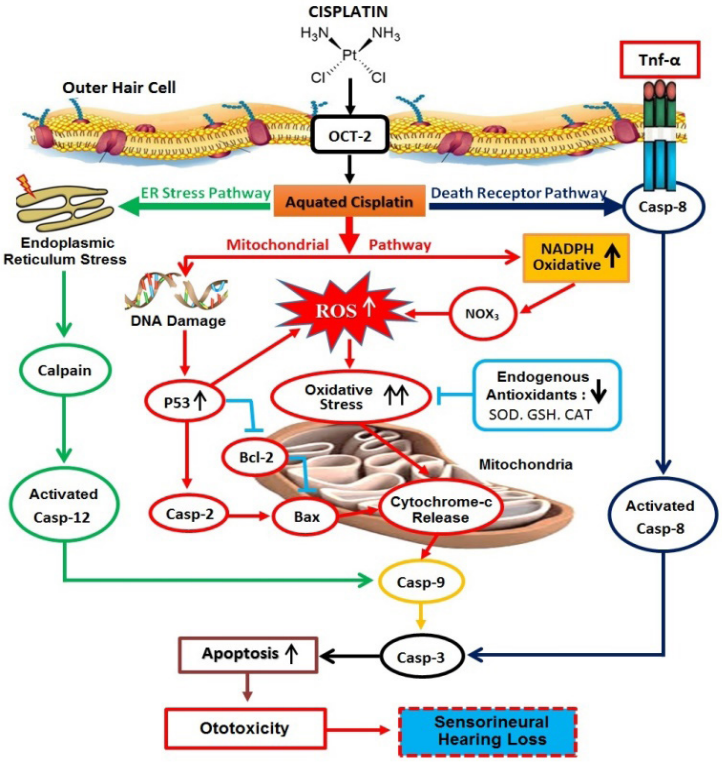

FIGURE 2. Pathobiological mechanism of ototoxicity cisplatin.[7,42]

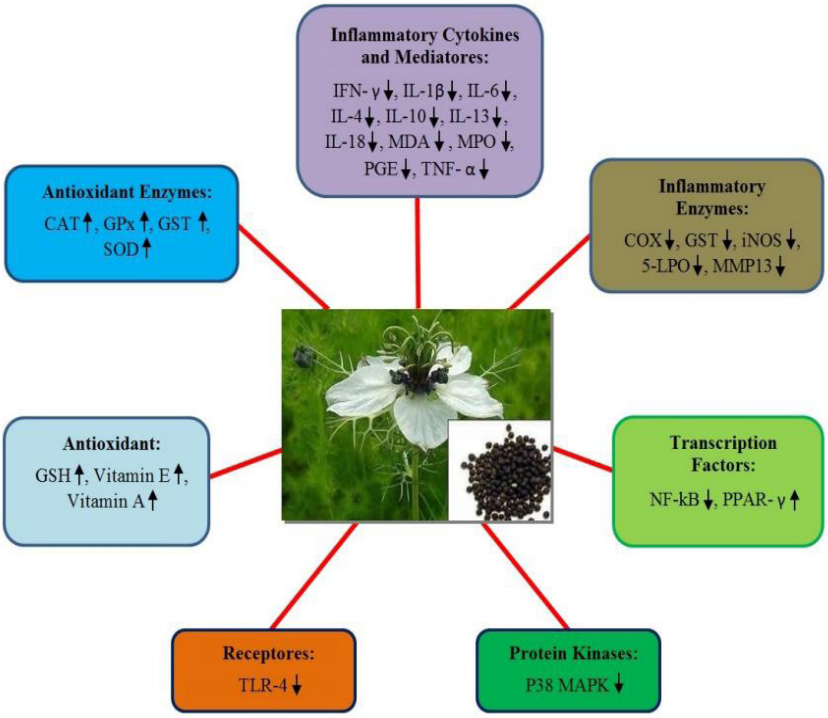

FIGURE 3. The role of *N. sativa* on molecular targets.[43]

Antioxidant

Nigella sativa extract belongs to the group of strong antioxidants, with IC_{50}= 80,433 μg/mL.[46] Flavonoids, phenolics, and thymoquinone are antioxidants that help forestall ototoxic effects. Thymoquinone compounds are polyphenolic compounds (hydroxyl gatherings) that are polar, allowing them to into polar solvents like ethanol, methanol, water, acetone, butanol, dimethyl formamide, and dimethyl sulfoxide. Polyphenols repress the formation of ROS by suppressing the enzyme xanthine oxidase, then catalyzes the oxidation of hypoxanthine and xanthine to uric corrosive while reducing O_2 and H_2O_2. Polyphenols act as antioxidants against oxidative stress, specifically as free radical scavengers, metal chelators in regulating cellular oxidation reactions, and by influencing enzymes involved in oxidative stress and increasing the production of of endogenous antioxidants. The antimicrobial activity of polyphenols works by damaging bacterial cell membranes, inhibiting fatty acid synthesis, and enzyme activity, thereby impeding bacterial growth and development.[18]

Superoxide dismutase (SOD) compounds are metalloenzymes containing copper, zinc or iron particles formed in the cytosol, and manganese-containing compounds formed in the mitochondrial matrix. It works by catalyzing the dismutation of superoxide into hydrogen peroxide and oxygen, with hydrogen peroxide being easy diffused across the plasma membrane. Superoxide dismutase is an endogenous antioxidant enzyme that has a very potent effect and functions as the body's first line of defense against free radicals. Superoxide dismutase activity can be utilized as a reference for measuring oxidative stress in the body.[47,48]

Antiinflammatory

Nigella sativa has anti-inflammatory potential. These effects include the reduction of NO, production of IL-1, cyclooxygenase-1 (COX-1) and COX-2, histone deacetylase (HDAC), as well as other pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, IFN-γ, and PGE_2.[49,50] Thymoquinone, one of the active compounds from *N. sativa*, can attenuate the inflammatory reaction caused by mast cells by blocking the transcription and production of TNF-α through the modulation of the proinflammatory transcription factor NF-Kβ.[51,52]

Tumor necrosis factor-α compound is a proinflammatory mediator that can not only play a role in the mechanism of apoptosis induction but also accelerate cancer progression. Some studies have concluded that TNF-α produces ROS and RNS, leading to DNA damage and promoting proliferation, invasion, and increased chemotherapy resistance by activating MCF-7 cells.[36]

Immunomodulator

The components of *N. sativa* have also been proven to strengthen and stabilize the body's immune system by increasing the ratio between T-helper and T-suppressor cells by 55%, with an average natural killer cell activity achievement of 30%.[49] Thymoquinone, as an active compound of *N. sativa*, also plays a role in diminishing cytokines produced by Th2, in particular, IL-4, IL-5, and IL-13, as well as decreasing serum IgE. A reduction in serum IL-4 and IgE can help prevent the inflammatory response and mucosal edema.[52]

CONCLUSION

Cisplatin-induced ototoxicity is still exceptionally high, particularly in children and the elderly. Cisplatin

causes ototoxicity through two pathways namely the intrinsic and extrinsic pathway. Cisplatin leads to endoplasmic reticulum stress, DNA damage, increased ROS, and inflammatory processes, resulting in an increase in apoptosis of the outer hair cells of the cochlea. *Nigella sativa* oil has a protective effect against cisplatin-induced ototoxicity through its biological activities as an antioxidant, immunomodulator, and antiinflammatory agent.

ACKNOWLEDGEMENT

The authors have no conflicts of interest to declare.

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