International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Molecular Targets of Thymoquinone Protection Against Cisplatin-Induced Organ Toxicity: A Literature Review

Donny Hendriyanto[1,2], Sukri Rahman[3], Tofrizal[4], and Aisyah Elliyanti[5]*

[1]*Doctoral Program in Biomedical Sciences, Faculty of Medicine, Andalas University, Padang, Indonesia*
[2]*Department of Otorhinolaryngology-Head and Neck Surgery, Padang Pariaman General Hospital, Padang Pariaman, Indonesia*
[3]*Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Andalas University, Padang, Indonesia*
[4]*Department of Pathology Anatomy, Faculty of Medicine, Andalas University, Padang, Indonesia*
[5]*Nuclear Medicine Division of Radiology Department, Andalas University, Padang, Indonesia*

Abstract

Cisplatin provides successful results against cancer, but its clinical use is very limited due to serious side effects in the form of toxicity to various organs. Thymoquinone has been shown to function as a scavenger of free radicals generated after nerve damage and has antioxidant, anti-inflammatory, and anti-apoptotic effects. This article provides a review of molecular targets of thymoquinone protection against cisplatin-induced organ toxicity. The study used the literature review method with article searches on four databases, namely Pubmed, Google Scholar, ScienceDirect, and the Cochrane Library. The search process for articles using keywords, including related word synonyms and MESH. Cisplatin toxicity occurs through a cycle driven by increased oxidative stress, inflammation, and apoptosis. Cisplatin has serious side effects in the form of toxicity to several organs, including ototoxicity, gastrointestinal toxicity, nephrotoxicity, and hepatotoxicity. Thymoquinone was shown to have antioxidant, anti-inflammatory, and anti-apoptotic effects. There are several molecular targets that play an important role in the protection of thymoquinone against cisplatin toxicity, including antioxidant enzymes (SOD, CAT, GSH-Px, GST), anti-inflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, IL-10, NF-kB), anti-apoptotic and apoptotic protein (Bcl-2, Bax, caspase-3, caspase-8, caspase-9).

Keywords: *Nigella sativa*, antioxidant, inflammatory, chemotherapy, toxicity

Full-length article **Corresponding Author*, e-mail: donny.hendriyanto@yahoo.co.id

1. Introduction

Cisplatin is the most potent chemotherapy drug widely used for cancer treatment and the major choice of therapy for epithelial malignancies, especially head and neck cancer [1, 2]. Although cisplatin has shown successful results against cancer, its clinical use is very limited due to serious side effects in the form of toxicity to several organs, including ototoxicity, gastrointestinal toxicity, nephrotoxicity, and hepatotoxicity [3]. Cisplatin causes toxicity through two pathways, namely the intrinsic and the extrinsic pathways. In the intrinsic pathway, cisplatin will cause increased reactive oxygen species (ROS) and oxidative stress in mitochondria [4, 5]. In the extrinsic pathway, cisplatin will cause inflammation on the cell surface. This increased oxidative stress and inflammation will cause apoptosis in some organs [6, 7]. Thymoquinone is the most active compound found in black cumin (Nigella sativa). Thymoquinone has been shown to function as a scavenger of free radicals generated after nerve damage and has antioxidant, anti-inflammatory, and anti-apoptotic effects [8]. Thymoquinone compounds are still not widely known by people in Indonesia. In recent years, thymoquinone has become the focus of pharmacology studies because of its strong antioxidant properties [9]. The molecular target mechanism of thymoquinone protection against cisplatin ototoxicity is still not well understood. The aim of this review article is to explore the molecular targets of thymoquinone protection against cisplatin-induced organ toxicity underlying disease pathogenesis and its validity as a better treatment option.

2. Methods

2.1. Type of review

This type of study is a literature review that uses the literature study method. The literature search was carried out for three months, from May to July 2023.

2.2. Literature Search

The sources used in this review consist of relevant journals from search engines such as Pubmed, Google Scholar, ScienceDirect, and the Cochrane Library. Journal searches used Boolean terms (AND, OR, NOT). The author uses journals that only focus on keywords, namely "thymoquinone", "molecular", "cisplatin", and "organ toxicity", taking into account titles and abstracts that are appropriate to the topic of the review. The full text of the related articles was retrieved for further analysis.

2.3. Inclusion and exclusion criteria

The inclusion criteria in this review are all studies that discuss thymoquinone, molecular, cisplatin, and organ toxicity. The references used must not exceed the last five years. The exclusion criteria in this review are paid or not free and journals that do not contain information relevant to the topic of the study.

3. Results

3.1. Pathogenesis of cisplatin-induced organ toxicity

Cisplatin toxicity occurs through a cycle driven by increased oxidative stress, inflammation, and apoptosis. Cisplatin will go through two pathways, namely the intrinsic pathway and the extrinsic pathway [4]. In the intrinsic pathway, cisplatin will cause endoplasmic reticulum stress, deoxyribonucleic acid (DNA) damage, and increased oxidative nicotinamide adenine dinucleotide phosphate (NADPH) [8]. In the extrinsic pathway, cisplatin will bind to cell death and inflammation receptors on the cell surface [6], as shown in Figure 1.

3.2. Induction of oxidative stress

The molecules and pathologies responsible for cisplatin toxicity at the cellular level remain unclear, although oxidative stress is thought to be the most important factor. Oxidative stress is a state of imbalance between the generation of reactive oxygen species (ROS) in cells and tissues and the body's ability to detoxify them or counteract their adverse effects with antioxidants. ROS such as superoxide radicals (O-2), hydroxyl radicals (OH-), and hydrogen peroxide (H2O2) contribute to the formation of oxidative stress by altering enzyme activity, causing DNA lesions, increasing cell permeability, and ultimately leading to cell damage and cell death [6].

The antioxidant defense system includes enzymatic and non-enzymatic processes that control the generation of ROS, compensate for the effects of ROS by scavenging or reducing excess ROS levels, and maintain cellular redox homeostasis. Non-enzymatic antioxidants are dietary antioxidants, including vitamins (vitamin C and vitamin E) and phytochemicals (polyphenols, beta-carotene, and flavonoids), which exert their antioxidant activity by neutralizing ROS and protecting cell membranes from lipid peroxidation. Oxidative stress is also responsible for the post-translational modification of some protein antigens in autoimmune patients. These oxidative-induced post-translational modifications of protein antigens generate new epitopes that lead to the production of autoantibodies when the immune system recognizes them as non-self and stimulates B cells to fight them [10].

In rats treated with cisplatin, higher malondialdehyde (MDA) levels were found, while superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities were lower [1]. These results indicate the impact of oxidative stress on cisplatin-induced toxicity. Given this pathophysiological process, it has been suggested that reducing ROS levels while increasing antioxidant enzyme levels may protect against cisplatin-induced toxicity [8].

3.3. Mediation via the inflammatory pathway

Toll-like receptors (TLRs) are one of several widely studied immunological features associated with cisplatin-induced toxicity. TLRs bind to specific PAMP or DAMP arrays and, through several unique, and common downstream signaling systems, activate three key transcription factors, nuclear factor kappa B (NF-kB), activator protein-1 (AP-1), and interferon regulatory factor 3 (IRF3), which are responsible for enabling the expression and secretion of soluble pro-inflammatory signaling molecules such as cytokines and chemokines [10]. NF-kB can also mediate the up-regulation of pro-inflammatory cytokines and chemokines and can be considered a master regulator of inflammation as it can play an important role in the micro-management of both innate and adaptive immune responses [11]. NF-kB is also a 'master regulator' of numerous other homeostatic genes, allowing it to also alter cell cycle progression in conjunction with inflammasomes and other inflammatory factors, activate specialized immune cells to manipulate their maturation and differentiation processes, and influence the expression of tertiary features with additional roles in inflammation, such as adhesion molecules [12].

Pro-inflammatory cytokines and chemokines, such as IL-1, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) essentially serve as easily quantifiable indicators of cisplatin-induced toxicity as they are directly expressed in proportion to the severity of the disease [5]. Increased toxicity corresponds to an increase in IL-6, IL-1, and TNF-α of at least 20-50%, whereas protection from toxicity corresponds to a reduction in secretion of 50-80%. This is also directly related to the dose of cisplatin used and the exposure time [4]. Overall, the relationship between cytokine secretion and cisplatin toxicity does not appear to be linear; pro-inflammatory cytokines appear to actively contribute to the pathology of prolonged cisplatin exposure in a positive feedback loop [12].

3.4. Apoptosis pathway

Apoptosis is the programmed death of cells in response to pathological or physiological changes directed at eliminating dead, mutated, or aging cells. In other words, it can be said that it is a pathway of cleansing the biological system of dead cells that may cause potential health threats to the body if not eliminated. There are two main pathways of apoptosis: First, the intrinsic pathway and the mitochondrial pathways, which are regulated by the Bcl protein family. In this pathway, stimuli first cause an increase in mitochondrial membrane permeability and eventually release apoptogenic factors that cause membrane disruption and mitochondrial dysfunction. This dysfunction activates various apoptogenic proteases, such as caspases. Second, these caspases are also activated by the formation of death receptors on the cell surface. The activity of caspases such as caspase-3 or caspase-9 is being studied as a hallmark of apoptosis in cancer cells [4, 13].

3.5. Effect of cisplatin in organ toxicity

Cisplatin has shown successful results against cancer, its clinical use is very limited due to serious side effects in the form of toxicity to several organs, including ototoxicity, gastrointestinal toxicity, nephrotoxicity, and hepatotoxicity [3].

3.6. Ototoxicity

Cisplatin ototoxicity is still a serious problem in the field of medicine because it is the main cause of hearing loss in patients with malignancy. The incidence of cisplatin ototoxicity is still very high, namely 75-100% [4]. Research conducted in India found that 96.7% of patients who received cisplatin chemotherapy would experience ototoxic hearing loss. The impact of cisplatin ototoxicity is sensorineural hearing loss in both ears, starting at a frequency of 6,000–8,000 Hz, which will eventually affect lower frequencies if treatment is continued, accompanied by tinnitus. Although hearing loss is not a life-threatening condition, it is important because it interferes with quality of life, daily communication problems, and psychological disorders [1]. Distortion Product Otoacoustic Emission (DPOAE) examination is used to assess cisplatin ototoxicity, with a sensitivity of 100% and a specificity of 82–87%. Intraperitoneal injection of cisplatin at a dose of 15 mg/kg BW causes damage to outer hair cells (OHC) and a decrease in the signal-to-noise ratio (SNR) value in the DPOAE examination. The histopathological examination will strengthen the results taken at the DPOAE examination because the histopathological examination can assess the degree of organ corti damage in cochlear rats. Histopathology is the gold standard for establishing the diagnosis of ototoxicity [15]. Cisplatin will damage the cochlear OHC starting on the third day and reaching a maximum level on day 10. Cisplatin will cause ototoxicity through a pathway of increased ROS, oxidative stress, inflammation, and apoptosis in the inner ear [9]. The compound SOD can be used as a biomolecule involved in the processes of oxidative stress that cause cisplatin ototoxicity. The apoptotic process in the cochlea can be assessed by the degree of damage to the organ of Corti through histopathological examination [6, 16].

Gastrointestinal toxicity: The intestine's susceptibility to cisplatin's cytotoxic effects leads to the proliferation of gastrointestinal epithelial cells. Cisplatin chemotherapy-related intestinal toxicity includes various gastrointestinal changes, which significantly impact treatment adherence. The most frequent clinical symptoms related to cisplatin treatment are nausea, vomiting, loss of appetite, weight loss, digestive dysfunction, diarrhea, delayed gastric motility, mucositis, malabsorption, and barrier impairment. These symptoms may continue long after completion of the therapy regimen [16]. Cisplatin-induced gastrointestinal toxicity has been associated with events linked to oxidative stress mediated by reactive oxygen species. Intestinal antioxidants (SOD, CAT, GST, GR, TR, GSH) prevent oxidative damage by scavenging and clearing reactive oxygen species. Cell death linked to oxidative stress results in an inflammatory response and is crucial to the development of gastrointestinal toxicity caused by cisplatin. Activation of the nuclear factor kappa B (NFκB) and tumor necrosis factor-alpha (TNF) signaling pathways has been demonstrated to have a significant impact on cisplatin-induced intestinal damage [17].

3.7. Nephrotoxicity

The clinical use and efficacy of cisplatin are severely limited due to its severe adverse effects, particularly nephrotoxicity. It is estimated that nearly 30% of cancer patients treated with cisplatin can develop acute kidney injury (AKI) after receiving a single high dose of cisplatin. If left untreated, cisplatin-induced AKI can lead to chronic kidney disease (CKD), which can progress to end-stage renal disease (ESRD) and increase the risk of death [18].

When a patient is treated with a standard dose of cisplatin intravenously, the rate of elimination of cisplatin is approximately 25% within 24 hours and 50% within 5 days, with more than 90% of the total excretion occurring through renal excretion. Thus, renal excretion is the major route of elimination of cisplatin and the kidney can accumulate a greater amount of cisplatin than any other organ, which is responsible for nephrotoxicity. Renal toxicity occurs in 28-36% of patients treated with single doses of cisplatin at 50 mg/m2. Acute oliguric or non-oliguric renal insufficiency may be seen within 2 to 6 days after cisplatin overdose, while chronic renal failure may persist for more than 2 years when the patient is treated with 20 mg/m2/day of cisplatin intravenously for 5 days every 5 weeks. Nephrotoxicity is manifested by an increase in blood urea nitrogen (BUN), creatinine, and serum uric acid, and a decrease in creatinine clearance and electrolyte imbalance [19].

3.8. Hepatotoxicity

The liver is the primary location for most metabolic processes. Cisplatin rapidly diffuses into various tissues, with higher concentrations accumulating in the liver. Upon cellular entry, cisplatin undergoes hepatic metabolism, whereby the cytochrome P450 (CYP450) enzyme complex biotransforms it. One of the enzymes, CYP2E1, is often cited in the literature as the primary enzyme involved in hepatotoxicity. CYP2E1 is found in both the endoplasmic reticulum and mitochondria [20].

Overdosage of cisplatin may cause hepatotoxicity. This is mainly due to oxidative stress caused by increased transaminases and circulating bilirubin. Glutathione and glutathione reductase levels are significantly decreased, whereas glutathione peroxidase, catalase, and gamma-glutamyl transpeptidase are significantly increased after cisplatin therapy. It has also been reported that cisplatin treatment can increase cytochrome P450 levels, and the cytochrome P450-2E1 enzyme (a member of the cytochrome P450 family) is also responsible for liver damage [21].

3.9. Chemistry of thymoquinone

Thymoquinone (2-isopropyl-5-methyl-1, 4-benzo-quinone) is the most abundant component of Nigella sativa seeds (Figure 2), and most of the properties of Nigella sativa are attributed primarily to thymoquinone [9]. In addition to Nigella sativa, thymoquinone is an active ingredient in a number of plants including Juniperus, Monarda, Coridothymus, Agastache, and Satureja [22]. Thymoquinone is a non-toxic major bioactive compound obtained from the black seed oil of Nigella sativa L. It has a chemical structure as shown in Figure 3 and has the chemical formula C10H12O2 and a molecular weight of 164.204 g/mol [23]. Thymoquinone consists of the enol, keto, and mixture forms. The keto form is the major form that is involved in the pharmacological effects of thymoquinone. The concentration of thymoquinone in seed oil has been reported to be between 18 and 25 mg/ml [11]. The hydrophobic property of thymoquinone limits its bioavailability and drug formulation. There are different routes for the administration of thymoquinone including intravenous (iv), intraperitoneal (i.p), and oral subacute and subchronic administration.

Table 1. The effect of thymoquinone against cisplatin-induced organ toxicity

Organ Toxicity	Sampel	Cisplatin and TQ Dose	Effect of Thymoquinone	Reference
Ototoxicity	Wistar rats	Cisplatin dose: 15 mg/kg BW i.p Thymoquinone dose: 40 mg/kg/day i.p	- Increase DPOAE responses and ABR thresholds. - Decrease the degree of cochlear damage.	[3]
Gastrointestinal toxicity	Wistar rats (Swiss albino)	Cisplatin dose: 6 mg/kg BW i.p Thymoquinone dose: 1.5 mg/kg BW p.o	- Increase SOD, GSH-Px, CAT, GST, GR, TR activities, ALP, GGTase, LAP. - Decrease MDA, GSH, total SH levels, ACPase activity.	[16]
Nephrotoxicity	Wistar rats (Swiss albino)	Cisplatin dose: 6 mg/kg BW i.p Thymoquinone dose: 2 mL//kg BW p.o	- Increase creatinine clearance, and improved histopathological changes. - Decrease serum urea, serum creatinine, and urine volume.	[19]
Hepatotoxicity	Wistar rats (Male albino)	Cisplatin dose: 12 mg/kg BW i.p Thymoquinone dose: 500 mg/kg/day p.o for one month	- Increase SOD, GST, GSH-px, GSH, CAT activities, Serum albumin levels. - Decrease NF-kB, MDA, TNF-α, iNOs, IL-1β activities, NF-Kb-P65 activation, ALT, ALP, AST, γGGT, TB, LDH.	[24]

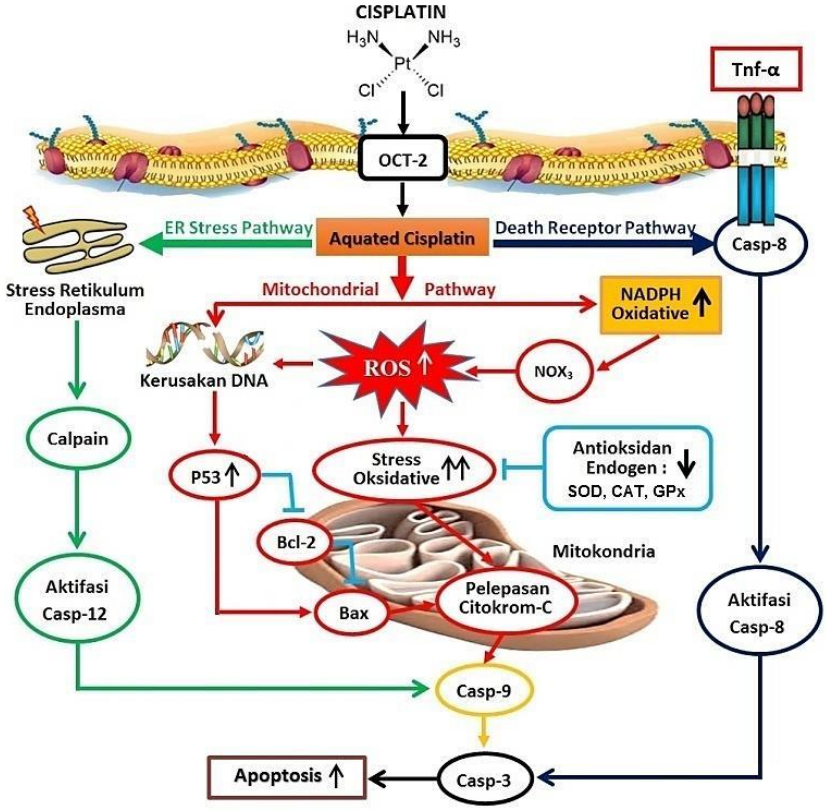

Figure 1. Pathogenesis of cisplatin-induced apoptosis

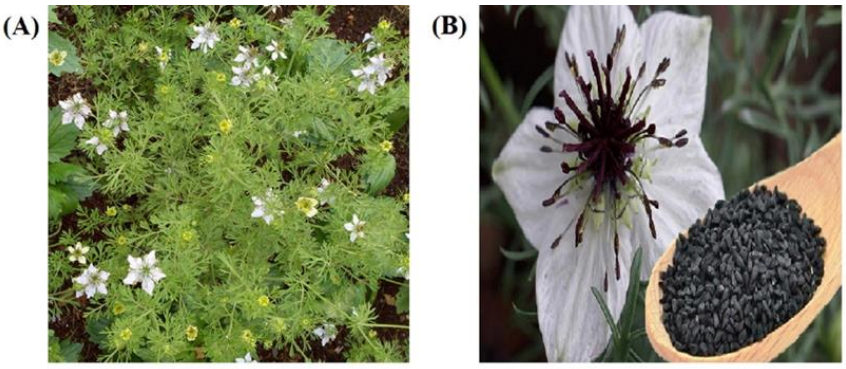

Figure 2. (A) Nigella Sativa Plant (B) Its Flower and Seeds

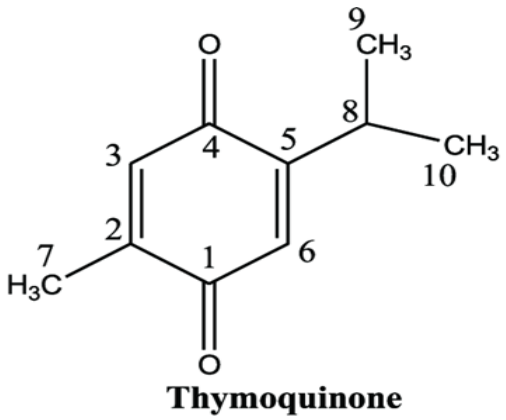

Figure 3. The chemical structure and atom numbering for Thymoquinone

After oral administration, thymoquinone is metabolized via the liver metabolizing enzymes such as DT-diaphorase (a quinine reductase) that modifies thymoquinone into a reduced form of thymohydroquinone. The clearance rate of thymoquinone after iv administration was 7.19 mL/kg/min, while oral administration was 12.30 mL/kg/min. The elimination half-life (T1/2) of thymoquinone was about 217 minutes. In addition, the percentages of thymoquinone protein binding in human and rabbit plasma were 98.99 and 99.19, respectively, which indicates the quick elimination and slow absorption of thymoquinone following oral exposure [23]. Toxicological studies indicate that oral administration of thymoquinone in the range of 10 to 100 mg/kg has no toxic or lethal effects in rats. The maximum tolerated dose of thymoquinone was 22.5 mg/kg in male and 15 mg/kg in female rats when injected i.p, whereas for oral administration in both male and female rats, the dose was 250 mg/[9].

4. Discussion

4.1. Protective effect of thymoquinone against cisplatin-induced organ toxicity

The effects of thymoquinone against cisplatin-induced organ toxicity, are shown in Table 1. Thymoquinone has been shown to function as a scavenger of free radicals generated after nerve damage and has antioxidant, anti-inflammatory, and anti-apoptotic effects [5].

4.2. Antioxidant effects

Thymoquinone can scavenge oxidative free radicals, including O-2, OH- and H2O2, and is responsible for controlling oxidative stress. Thymoquinone can scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) and prevent lipid peroxidation (LPO) by reducing MDA levels in cell membranes. Antioxidant enzymes such as catalase (CAT), GSH-Px, SOD, glutathione reductase, and glutathione S-transferase (GST) are the major enzymatic antioxidant systems of cells and tissues. CAT, SOD, and GSH-Px are the primary antioxidant enzymes directly involved in the elimination of ROS (O-2, OH-, H2O2) (Ali, 2021). On the other hand, glutathione reductase and GST are secondary antioxidant enzymes that accelerate the activity of primary antioxidant enzyme functions and lead to ROS detoxification by reducing peroxide levels. There is ample in vivo experimental evidence to support that thymoquinone increases endogenous antioxidant enzymes such as SOD, CAT, GSH-Px, GST, and glutathione reductase by protecting tissues from oxidative damage [8].

Thymoquinone exhibits otoprotective, neuroprotective, hepatoprotective, and nephroprotective effects by inhibiting these pathways. The transcription factor Nrf2 is also considered to be a very important culprit in the protection of organs against oxidative stress. Thymoquinone also exerts its antioxidant effects by regulating the Nrf2 pathway and strengthening antioxidant defenses [5].

4.3. Anti-inflammatory effects

Thymoquinone has a role in the inhibition of nitric oxide production by macrophages, demonstrating its anti-inflammatory activity. There are many cytokines such as TNF-α, IL-1, IL-2, IL-6, and IL-10 that play an important role in inflammation. In addition, NF-kB also plays an important role in toxicity by increasing the levels of pro-inflammatory cytokines. Thymoquinone also has an inhibitory effect on NF-kB during toxicity, thereby inhibiting the production of proinflammatory cytokines, which reduces inflammatory cell infiltration and has protective effects against tissue and organ damage. Thymoquinone administration is associated with reduced levels of TNF-α and IL-6 and thymoquinone also exhibits anti-inflammatory activity through suppression of NF-kB and inhibition of cytokine production [11].

Thymoquinone can regulate inflammatory molecules such as interferon, interleukins, TNF-α, oxidative stress, regulatory T cells, and various signaling pathways such as NF-kB, Janus kinase/signal transduction and activator of transcription (JAK-STAT), mitogen-activated protein kinase (MAPK) at the molecular level and epigenetic changes [10]. NF-kB is a family of inducible transcription factors considered to be key regulators of innate and adaptive immune responses. It regulates the expression of target genes that contribute to the inflammatory response, including pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, and TNF-α), chemokines (IL-18, MIP-1α, and MCP-1), cell adhesion molecules (VCAM-1 and ICAM-1), immune receptors and proteins involved in antigen presentation [23]. Thymoquinone exhibited anti-inflammatory properties by suppressing NF-kB activation, IkBα kinase activation, IKBα phosphorylation and degradation, nuclear translocation and phosphorylation of p65, and NF-kB-dependent reporter genes (TNFR1, TRAF2, TRADD, TAK1/TAB1, NIK, and IKK-β). Thymoquinone reduced the pro-inflammatory response produced by LPS-induced mast cells by increasing the number of repressive NF-kB homodimers and reducing NF-kB nuclear transactivation and TNF-α production. Due to the downregulation of NF-kB, thymoquinone strongly suppresses the expression of TNF-α, IL-6, IL-1β, COX-2, nitric oxide (NO), and NO synthase (iNOS) production [5].

The nephroprotective effect of thymoquinone was associated with decreased expression of NF-kB, TNF-α, IL-1β and IL-6, and NOD-containing pyrin domain-like receptor family 3 (NLRP3). Thymoquinone (50 mg/kg/day), a natural antioxidant, has been shown to ameliorate renal injury in rats by enhancing antioxidant capacity and inhibiting free radical production [5].

4.4. Anti-apoptotic effects

Thymoquinone induced apoptosis through increased levels of Bax protein and cytochrome C. They also showed that thymoquinone induced apoptosis through the p53-free pathway [11]. Thymoquinone showed a significant increase in the expression of the anti-apoptotic protein Bcl-2, and decreased apoptotic protein Bax, caspase-3, caspase-8, and caspase-9. It showed resistance to histopathological changes associated with cisplatin administration [15].

5. Conclusions

There are several molecular targets that play an important role in the protection of thymoquinone against cisplatin toxicity, including antioxidant enzymes (SOD, CAT, GSH-Px, GST), anti-inflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, IL-10, NF-kB), anti-apoptotic and apoptotic protein (Bcl-2, Bax, caspase-3, caspase-8, caspase-9).

Authors contributions statement

All authors contributed to this literature review. D. Hendriyanto, S. Rahman, and A. Elliyanti conceptualized,

designed, literature search, data acquisition, and analysis; D. Hendriyanto, A. Elliyanti, and Tofrizal prepared the article and critically revised the manuscript.

Conflict of Interest

The author reports no conflicts of interest in this work.

Acknowledgments

None

Fundings

No specific grant was given to this research by funding organizations in the public, private, or not-for-profit sectors.

Ethical statement

This article does not contain any studies regarding humans or Animals. Ethical clearance is not required as this is a synthesis of evidence from existing research; nonetheless, we have adhered to the guidelines of COPE and the requirements of ICMJE regarding publication ethics.

Availability of data and material

We declare that the submitted manuscript is our work, which has not been published before and is not currently being considered for publication elsewhere.

Code availability

Not applicable

Consent to participate

All authors participated in this research study.

Consent for publication

All authors submitted consent to publish this article research in IJCBS.

References

[1] F. Akdemir, M. Gozeler, S. Yildirim, S. Askin, M. Dortbudak, and A. Kiziltunc. (2018). The effect of ferulic acid against cisplatin-induced ototoxicity. Medicine Science. International Medical Journal. 7(3): 1–4. https://doi.org/10.5455/medscience.2018.07.8814

[2] H. Abdulbaki and M.A. Al-Deeb. (2023). Neuroprotective effects of ferulic acid and thymoquinone against deltamethrin-induced neurotoxicity in Drosophila melanogaster. Advancements in Life Sciences. 10(2): 289-297. https://www.als-journal.com/articles/vol 10issue2/10223.23/1799.pdf

[3] N. Kökten, O.K. Eğilmez, M. Erinç, A.I.D. Ekici, S. Serifler, E. Yesilada (2020). The Protective Effect of Nigella sativa Oil against Experimentally Induced Cisplatin Ototoxicity: An Animal Study. The Journal of International Advanced Otology. 16(3): 346–352. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7901441/

[4] D. Hendriyanto, M. Setiamika, and N. Primadewi. (2020). the Effect of Ginkgo Biloba Against Ototoxic Hearing Loss on Advanced Stage Undifferentiated Nasopharyngeal Carcinoma Receiving Cisplatin Chemotherapy. International Journal of Nasopharyngeal Carcinoma (Ijnpc). 2(02): 44–46. https://doi.org/10.32734/ijnpc.v2i02.3910.

[5] A. Anaeigoudari. (2022). Hepato- and reno-protective effects of thymoquinone, crocin, and carvacrol: A comprehensive review. Asian Pacific Journal of Tropical Biomedicine. 12(5): 185–196.

[6] E. Gentilin, E. Simoni, M. Candito, D. Cazzador, and L. Astolfi. (2019). Cisplatin-Induced Ototoxicity: Updates on Molecular Targets. Trends in Molecular Medicine. 25(12): 1123–1132.

[7] M. Khosravi, S.T.S. Asl, A.N. Anamag, M.S. Langaroudi, J. Moharami, S. Ahmadi, and R. Kasaeiyan. (2023). Parenting styles, maladaptive coping styles, and disturbed eating attitudes and behaviors: a multiple mediation analysis in patients with feeding and eating disorders. PeerJ. 11: e14880. https://doi.org/10.7717/peerj.14880

[8] M. Ardiana, B.S. Pikir, A. Santoso, H.O. Hermawan, and M.J. Al-Farabi. (2020). Effect of Nigella sativa Supplementation on Oxidative Stress and Antioxidant Parameters: A Meta-Analysis of Randomized Controlled Trials. Scientific World Journal. 1–7. https://doi.org/10.1155/2020/2390706

[9] J. Farooq, R. Sultana, T. Taj, S.M.B. Asdaq, A.J. Alsalman, M. Al Mohaini, M., et al. (2022). Insights into the protective effects of thymoquinone against toxicities induced by chemotherapeutic agents. Molecules. 27(1): 1–15. https://doi.org/10.3390/molecules27010226

[10] M.Y. Ali, Z. Akter, Z. Mei, M. Zheng, M. Tania, and M.A. Khan. (2021). Thymoquinone in autoimmune diseases: Therapeutic potential and molecular mechanisms. Biomedicine and Pharmaco-therapy. 134: 111157.

[11] A. Ahmad, R.K. Mishra, A. Vyawahare, A. Kumar, M.U. Rehman, and W. Qamar, et al., (2019). Thymoquinone (2-Isoprpyl-5-methyl-1, 4-benzoquinone) as a chemopreventive/ anticancer agent: Chemistry and biological effects. Saudi Pharmaceutical Journal. 27(8): 1113–1126.

[12] I.K. Domingo, A. Latif, and A.P. Bhavsar. (2022). Pro-Inflammatory Signalling PRRopels Cisplatin-Induced Toxicity. International Journal of Molecular Sciences. 23(13):7227. https://doi.org/10.3390/ijms23137227

[13] C. Fujimoto and T. Yamasoba. (2019). Mitochondria-targeted antioxidants for treatment of hearing loss: A systematic review. Antioxidants. 8(4): 1–19. https://doi.org/10.3390/antiox8040109

[14] M.G. Alrashedi. (2018). The protective role of thymoquinone against drugs toxicity: a review. Journal of Pharmaceutical Research International. http://www.journaljpri.com/index.php/JPRI/article/view/17897.

[15] F. Shahid, Z. Farooqui, and F. Khan. (2018). Cisplatin-induced gastrointestinal toxicity: An update on possible mechanisms and on available gastroprotective strategies. European Journal of Pharmacology. 827: 49–57.

https://doi.org/10.1016/j.ejphar.2018.03.009

[16] H.A. Sbeih, N. Mallepally, R. Goldstein, E. Chen, T. Tang, U.K. Dike et al. (2020). Gastrointestinal toxic effects in patients with cancer receiving platinum-based therapy. Journal of Cancer. 11(11): 3144-3150. https://doi.org/10.7150/jca.37777

[17] A. Iskander. and L.J. Yan. (2022). Cisplatin-Induced Kidney Toxicity: Potential Roles of Major NAD+-Dependent Enzymes and Plant-Derived Natural Products. Biomolecules. 12(8) :1078. https://doi.org/10.3390/biom12081078.

[18] M.A. Hannan, M.S. Zahan, P.P. Sarker, A. Moni, H. Ha, and M.J. Uddin. (2021). Protective effects of black cumin (Nigella sativa) and its bioactive constituent, thymoquinone against kidney injury: An aspect on pharmacological insights. International Journal of Molecular Sciences. 22(16): 1078.

[19] A.N. Rashid, S.A.S. Halim, S.L. Teoh, S.B. Budin, F. Hussan, N.R. Adib Ridzuan et al. (2021). The role of natural antioxidants in cisplatin-induced hepatotoxicity. Biomedicine and Pharmacotherapy. 144: 112328. https://doi.org/10.1016/j.biopha.2021.112328

[20] S. Ghosh. (2019). Cisplatin: The first metal based anticancer drug. Bioorganic Chemistry. 88: 102925. https://doi.org/10.1016/j.bioorg.2019.102925.

[21] S. Agarwal, R. Srivastava, and N. Mishra. (2019). An Overview of Therapeutic Potential of Thymoquinone. International Journal of Pharmaceutical Sciences and Research. 10(8): 3532–3539. https://doi.org/10.13040/IJPSR.09758232.10(8).3532-39
https://doi.org/10.1016/j.biopha.2020.111157
https://doi.org/10.4103/2221-1691.343386

[22] T. Farkhondeh, S. Samarghandian, A.M.P. Shahri, and F. Samini. (2018). The neuroprotective effects of thymoquinone: A review. Dose-Response. 16(2): 1–11. https://doi.org/10.1177/1559325818761455

[23] M.F. Noorbakhsh, F. Hayati, S. Samarghandian, S.H. Yazdi, and T. Farkhondeh. (2018). An Overview of Hepatoprotective Effects of Thymoquinone. Recent Patents on Food, Nutrition & Agriculture. 9(1): 14–22. https://doi.org/10.2174/2212798410666180221105503