Archives of Pharmaceutical Sciences Ain Shams University 2025; Vol. 9(2): 336-350

OPEN ACCESS

Pharmacology and Toxicology

Review Article

Paclitaxel-Induced Cardiotoxicity: Mechanisms, Molecular Insights, and Clinical Implications

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ABSTRACT

Paclitaxel is a well-known chemotherapeutic agent used to treat various cancers, including breast, lung, and pancreatic cancers. However, its effectiveness is limited by significant adverse effects, including neurotoxicity, nephrotoxicity, hepatotoxicity, testicular toxicity, and cardiotoxicity. In this review, we focused on its potential cardiotoxicity. The mechanisms underlying Paclitaxel-induced cardiotoxicity have not been thoroughly elucidated. In the current review, we highlighted the possible mechanisms involved in Paclitaxel-induced cardiotoxicity. This may include activation of oxidative stress as evident by elevation in cellular lipid peroxidation, and decrease in Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), and Catalase (CAT) activity. Moreover, oxidative stress induces cell death, as well as activation of the inflammatory response. Paclitaxel-induced inflammation was evident by the release of inflammatory cytokines and chemokines. In addition, ferroptosis, which is a form of cell death characterized by accumulation of iron, is thought to be a possible underlying mechanism of Paclitaxel-induced cardiotoxicity. Furthermore, Paclitaxel causes cardiotoxicity through stimulation of apoptotic pathways. Taking all together, Paclitaxel-induced cardiotoxicity affects the quality of life of cancer patients and is considered a challenge facing pharmaceutical research nowadays.

Keywords: *Paclitaxel; Cardiotoxicity; Oxidative Stress; Ferroptosis; Apoptosis; Inflammation*.

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Citation | El-Naggar YM, George MY, El Wakeel S, . Elsherbiny DA, 2025. Paclitaxel-induced Cardiotoxicity: Mechanisms, Molecular Insights, and Clinical Implications. Arch Pharm Sci ASU 9(2): 336-350

DOI: 10.21608/aps.2025.371857.1220

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 17 April 2024. **Accepted** 17 May 2025.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

Increasing numbers of cancer survivors have been noted worldwide, as shown in 2020 when around 19.3 million new invasive cancer cases were diagnosed, with the expectation that the number will rise by 2040 to 28.4 million new cases each year **[1]**. Although this rising number of cancer survivors seems to be a predominantly favorable outcome of improved cancer therapies, it results in a growing population of patients requiring specialized care post-treatment, who endure severe and long-standing side effects from their cancer therapies **[1, 2, 3]**. One of the most concerning side effects is cardiovascular toxicity. Chemotherapy-induced cardiotoxicity refers to heart damage resulting from cancer treatments, particularly chemotherapy. It can vary in severity, affecting patients temporarily or permanently, and is a significant complication

despite the effectiveness of chemotherapy in treating cancer **[4]**.

As mentioned, chemotherapy and targeted medicines have significantly enhanced the prognosis of oncology patients. Nonetheless, these antineoplastic therapies may induce deleterious cardiovascular consequences, which may result in acute or delayed cardiac dysfunction. These prevalent cardiovascular complications, known as cardiotoxicity, may necessitate the alteration or discontinuation of life-saving antineoplastic treatments, potentially decreasing their efficacy **[5]**. The emergence of cardiotoxicity may be influenced by the class, dosage, delivery method, and duration of anticancer medication therapy, in addition to individual risk factors. The cardiotoxic adverse effects may be reversible if cardiac function is restored after drug cessation, or irreversible, marked by injury and loss of cardiac myocytes **[6]**. Chemotherapy-induced cardiotoxicity can be visible as irregularities in the cardiac rhythm, elevated blood pressure, inadequate cardiac blood supply, thromboembolism, heart failure, systolic dysfunction, as well as other dysfunctions **[7]**.

Chemotherapeutic agents associated with significant cardiac complications include anthracyclines such as doxorubicin, alkylating agents including cyclophosphamide, and taxanes such as paclitaxel. Among other agents that induce cardiotoxicity are platinum agents, fluorouracil, and immunotherapy **[8, 9, 10]**.

Taxanes are natural diterpenoid compounds derived from yew plants, named after the Latin term for yew (*Taxus* species). Paclitaxel is one of the most recognized members and, to date, the most clinically utilized **[11]**. Taxol, the generic designation for paclitaxel, is a secondary metabolite synthesized by *Taxus* species and, to a lesser degree, by coniferales such as cephalotaxus, Podocarpus *gracilior*, or Corylus *avellana*. It was identified in the 1960s by the National Cancer Institute as part of a screening study for the plant kingdom. Later, paclitaxel received FDA approval as anticancer drug in 1998 **[12]**. Other taxanes synthesized from paclitaxel have been introduced onto the market. The most renowned semisynthetic taxane, docetaxel, received FDA approval for clinical usage in 1996. Another semisynthetic taxane, Cabazitaxel, was approved by the FDA in 2010 for the treatment of prostate cancer **[11]**. Paclitaxel is regarded as one of the most effective natural-source anticancer agents due to its potency, broad spectrum of activity, and relatively low incidence of side effects **[13]**. Numerous studies have validated the efficacy of paclitaxel in the treatment of ovarian cancer, breast cancer, and nasopharyngeal carcinoma, and it is also utilized in the management of pancreatic and lung cancers **[14, 15]**.

In light of the fact that the mechanisms that may be responsible for the cardiotoxicity caused by paclitaxel have not been thoroughly elucidated, the purpose of this review is to elaborate the possible underlying mechanisms of paclitaxel-induced cardiotoxicity.

2. Main body

2.1. Pharmacokinetics of paclitaxel

The pharmacokinetics of paclitaxel significantly influence treatment efficacy and the side effect profile, making it essential to comprehend paclitaxel pharmacokinetics **[16]**. Paclitaxel is administered via intraperitoneal or intravenous route; it cannot be given orally due to its limited bioavailability, as ATP-binding cassette family (ABC) transporters facilitate the outflow of paclitaxel back into the intestinal lumen **[16]**. ABC transporters are expressed in diverse tissues including the liver, colon, kidney, and brain, where they play a critical role in the absorption, distribution, and excretion of drugs **[17]**. A recent study demonstrated improved oral

bioavailability of paclitaxel by combining it with the P-glycoprotein inhibitor KR30031. Similarly, the co-administration of paclitaxel with ketoconazole enhanced the drug's bioavailability by approximately 1.6–1.7 times compared to the controls **[18]**. Paclitaxel is a hydrophobic compound sometimes provided as a paclitaxel-camphor complex to improve its solubility. This method enhances solubility but may potentially result in significant hypersensitivity reactions, The advent of nab-paclitaxel, a nanoparticle version of paclitaxel, has led to enhanced solubility and decreased hypersensitivity, Paclitaxel exhibits a high affinity for plasma proteins (90%) and is predominantly metabolized to its primary metabolite 6-alpha-hydroxy paclitaxel, which is formed through CYP2C8, while its minor metabolites, 3'-p-hydroxypaclitaxel and 6a, 3'-p-dihydroxypaclitaxel, are produced by the action of CYP3A4 **[16, 19]**. Ninety percent of the medicine undergoes hydroxylation by the CYP3A4, CYP3A5, CYP1A2, and CYP2C8 enzymes in the liver and is subsequently eliminated in stool. Fewer than 10% of the medication is excreted by the kidneys **[20]**.

2.2. Pharmacodynamics of paclitaxel

Paclitaxel, in contrast to other chemotherapeutic agents that target DNA and RNA synthesis or induce DNA damage, facilitates microtubule construction during cell division while simultaneously inhibiting depolarization, resulting in cell cycle arrest in the G2/M phase and ultimately cell death **[21]**. Paclitaxel enhances the production of reactive oxygen species (ROS), resulting in an imbalance between antioxidants and ROS, which induces oxidative stress, ultimately leading to cellular death and Paclitaxel-related toxicities **[22-24]**. Moreover, Paclitaxel has been demonstrated to cause endoplasmic reticulum stress **[25]**.

2.3. Multi-organ toxicities of paclitaxel

Paclitaxel treatment induces many toxicities, including hepatotoxicity, renal toxicity, cardiotoxicity, testicular toxicity, and neuropathy **[22-24]** (**Fig 1)**.

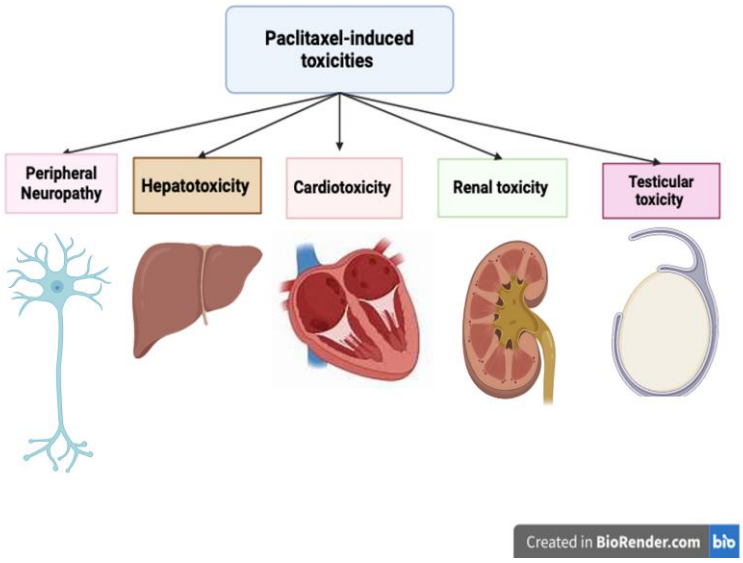

Fig. 1. Paclitaxel-induced multi-organ toxicities.

2.3.1. Paclitaxel-induced neurotoxicity

Peripheral neuropathy is one of the most consequential and dose-limiting adverse effects of paclitaxel, impacting around 50% of patients. Symptoms encompass pain, tingling, cold sensitivity, and numbness, frequently manifesting in a "stocking-glove" distribution, with numerous patients additionally having allodynia (pain elicited by normal stimuli) **[26]**. This neuropathy significantly affects quality of life, necessitating investigation into its underlying causes and potential remedies **[27]**.

Paclitaxel-related peripheral neuropathy, or paclitaxel-induced peripheral neuropathy, entails damage to motor, sensory, and autonomic nerves. Research in mice has demonstrated elevated levels of activating transcription factor-3 in dorsal root ganglion neurons, signifying neuronal injury. Axonal degeneration and a decrease in intra-epidermal nerve fibers have been noted, emphasizing the dorsal root ganglion as a principal locus of injury. In addition, oxidative stress, inflammation, mitochondrial impairment, and microtubule disruption are among the processes underlying taxane-induced neuropathy **[28]**.

2.3.2. Paclitaxel-induced hepatotoxicity

Paclitaxel administration can potentially lead to hepatotoxic events in cancer patients **[29]**.

Moreover, Paclitaxel induced oxidative stress, diminishes antioxidant levels, elevates liver enzymes, intensifies hepatic injury during therapy, and induces significant, potentially fatal, hepatic necrosis in mice **[23]**. In addition, Paclitaxel has been reported in rats to increase serum liver enzymes (AST and ALT), induce hepatic oxidative stress, inflammatory responses, and apoptosis as well as hepatic tissue congestion, dilatation, epithelial vacuolization, and mononuclear cell infiltration **[29, 30]**.

2.3.3. Paclitaxel-induced nephrotoxicity

Paclitaxel elevates oxidative stress in renal tissue, resulting in increased creatinine and blood urea nitrogen concentrations **[22]**. Histopathological analyses indicated pathology alterations after PXT administration including renal corpuscle atrophy, brush boundary injury, vacuolar degeneration, and desquamation in the kidneys **[31]**, moreover, Paclitaxel-induced nephrotoxicity is evident by an increase in creatinine, and uric acid while the decrease in antioxidant markers like superoxide dismutase (SOD), reduced glutathione (GSH), and glutathione peroxidase (GPx) leads to renal lipid peroxidation **[24]**.

Paclitaxel administration to rats increased the serum levels of urea, uric acid, and creatinine. In addition, Paclitaxel induced renal oxidative stress, inflammation, apoptosis, as well as severe deleterious pathological lesions **[30]**.

2.3.4. Paclitaxel-induced testicular toxicity

Paclitaxel is recognized for inducing testicular toxicity, as evidenced by various studies. It induces oxidative stress, indicated by elevated levels of malondialdehyde (MDA) and a reduction in the antioxidant defense mechanisms, specifically superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Additionally, it increases apoptotic markers, as shown by heightened levels of the pro-apoptotic marker Bax and diminished levels of the anti-apoptotic marker Bcl-2, alongside an increase in inflammatory markers NF-κB, IL-1β, and TNF-α **[24]**. Another pathway that is thought to be included in testicular toxicity is the activation of JNK/MAPK signaling pathways **[32]**.

2.3.5. Paclitaxel-induced cardiotoxicity

The daily discovery of new anticancer medications is suspected to extend survival time;

yet, these drugs have led to a rising incidence of cardiovascular disorders among cancer survivors, giving rise to the phrase "cardio-oncology." **[33]**. Paclitaxel induces abnormal cardiac manifestations, particularly conduction blockages, sinus bradycardia, bradycardia, ventricular tachycardia, CHF, and ischemic symptoms **[34, 35]**. Furthermore, one of the recognized manifestations of paclitaxel-induced cardiotoxicity is a reduction in ejection fraction (EF), indicating impaired cardiac function. Despite this concerning side effect, instances of mortality directly attributed to paclitaxel-induced cardiotoxicity are infrequently documented in the literature **[36, 37]**. Paclitaxel is a microtubule-stabilizing agent utilized in the treatment of various solid tumors, including ovarian and breast cancer. Following its clinical introduction, its cardiotoxic effects were promptly observed, indicating that microtubules play a role in calcium regulation within the heart. The experimental model utilizing isolated adult rat ventricular myocytes demonstrated a decrease in the interval from peak contraction to relaxation, hence heightening the heart's vulnerability to multiple arrhythmias, arrhythmias, their reported negative inotropic effect of paclitaxel may be partially due to decreases release of calcium from the sarcoplasmic reticulum **[38, 39]**. The impact of paclitaxel on cardiac function is explored in numerous studies. One mechanism involves paclitaxel's ability to elevate oxidative stress in various tissues, including the heart. It has been established that chemotherapy-induced cardiotoxicity is primarily mediated by ferroptosis, a form of cell death characterized by intracellular iron accumulation. Ferroptosis is predominantly triggered by an imbalance between oxidative stress and antioxidant defenses. Furthermore, paclitaxel modifies the histopathology of cardiac tissue, resulting in diffuse edema, hemorrhage, congestion, degeneration, apoptosis, and necrosis **[33, 40, 41]**.

2.4. Mechanisms of paclitaxel-induced cardiotoxicity

Several mechanisms are probably involved in paclitaxel-induced cardiotoxicity, including oxidative stress, ferroptosis, apoptosis, and inflammation **(Fig. 2)**.

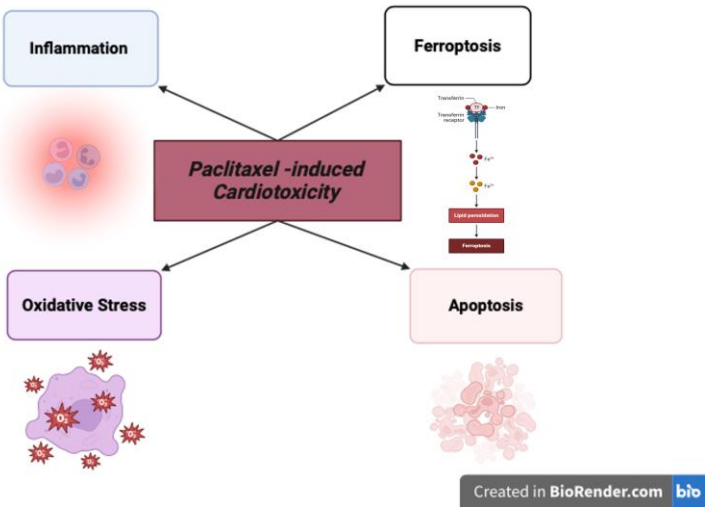

Fig. 2. Potential mechanism underlying paclitaxel-induced cardiotoxicity.

2.4.1 Oxidative stress

Oxidative stress has been identified as a cardinal pathway associated with Chemotherapy-induced cardiotoxicity **[33, 41-43]**. Oxidative stress is defined by the disproportion between the generation and degradation of ROS or reactive nitrogen species (RNS). ROS are highly reactive molecules derived from the metabolism of oxygen or nitrogen. ROS and RNS may include free radicals such as the superoxide radical ($O_2 \cdot^-$), hydroxyl radical (OH·), and nitric oxide (NO·). Nonetheless, additional non-free radicals, including hydrogen peroxide (H_2O_2) and peroxynitrite (ONOO−), may also be present. ROS generate enzymatic processes in the mitochondria, marked by the reduction of oxygen via the electron transport chain. Moreover, the endoplasmic reticulum and peroxisomes serve as additional sources of ROS. Various physiological functions, including protein phosphorylation, transcription factor activation, immunity, and death, are contingent upon the cellular concentration of ROS **[44]**. ROS oxidizes cellular components such as mitochondrial membranes, proteins, and DNA, ultimately leading to their degradation. Numerous cellular organelles possess an inherent ability to eliminate and neutralize ROS and RNS. The antioxidant system, encompassing both enzymatic and non-enzymatic components, can stabilize or neutralize the effects of free radicals on cellular constituents. An antioxidant defense system primarily consists of CAT, SOD, GPx, and glutathione reductase (GSR) protecting the body and its tissues from cellular damage generated by ROS and RNS **[45]**. Nonetheless, when reactive species reach critical quantities within cells, their harmful consequences swiftly eclipse their advantages, as antioxidant defenses become overwhelmed. The failure to keep redox equilibrium, whether from excessive synthesis or diminished clearance of reactive species, results in oxidative stress. Oxidative stress disrupts numerous physiological functions by the interaction of reactive species with cellular components, including DNA, RNA, lipids, and proteins **[46]**. Damage to cells has been demonstrated to significantly compromise their survival. Oxidative stress has been demonstrated to play a role in the etiology of numerous metabolic illnesses, malignant situations, and neurological diseases **[43, 47, 48]**.

Several studies have demonstrated the oxidative stress implication in paclitaxel-induced cardiotoxicity. Rats receiving paclitaxel showed elevation in cardiac lipid peroxidation and nitric oxide content along with decreases in cardiac GSH content, as well as CAT, SOD and GPx activity **[22, 40, 49]**.

2.4.2. Ferroptosis

Recent studies have emphasized the significance of ferroptosis in cardiovascular illnesses. The equilibrium between intracellular oxidative stress and antioxidant defense is essential for the regulation of ferroptosis. Tumor cells can prevent ferroptosis by enhancing various antioxidant defense mechanisms, whereas numerous anticancer medicines depend on diminishing antioxidant defenses and facilitating ferroptosis in cancer cells. However, such ferroptosis-induced anticancer medicines frequently exhibit insufficient tissue selectivity and may also damage the heart, leading to ferroptosis-induced cardiotoxicity **[33]**.

The concept of ferroptosis emerged from investigations into therapeutic alternatives for RAS mutations in cancer treatment. Two distinct molecules, the ferroptosis inducers RSL3 and Erastin, were identified, demonstrating a unique form of cell death that diverges from apoptosis (a caspase-dependent cell death), necrosis (a

cytolytic cell death with inflammatory characteristics), and autophagy (a lysosome-mediated degradation process governing cell homeostasis and fate). This form of cell death is marked by iron accumulation and lipid peroxidation, as evidenced by the inhibition of cell death following the administration of deferoxamine, a recognized iron chelator. Intracellular iron is primarily influenced by iron absorption, utilization, efflux, and the autophagy of ferritin stores, which elevate the levels of labile iron within the cell. An increase in intracellular iron results in heightened ROS production via the Fenton reaction. The iron-dependent Fenton chain reaction is probably important for ferroptosis. ROS oxidizes cellular components leading to their degradation, while the antioxidant system neutralizes their effects hence preventing many forms of cell death, including ferroptosis **[50, 51]**.

Ferroptosis is marked by lipid peroxidation. Monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) serve many physiological functions, such as components of the cell membrane, energy sources, and signaling molecules. PUFAs are more prone to oxidation, hence they play a greater role in ferroptosis. The synthesis of PUFA derivatives implicated in ferroptosis relies on the two critical enzymes for PUFA biosynthesis, Acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). Moreover, glutamine metabolism or glutaminolysis is a metabolic process essential for ferroptosis, which encompasses the absorption of glutamine, its transformation into α-ketoglutarate, and its subsequent catabolism in the mitochondria to generate acetyl-CoA, which is utilized for fatty acid synthesis in the cytosol. Glutamine absorption by mitochondria relies on membrane amino acid transporters, such as Solute Carrier Family 1 Member 5 (SLC1A5) **[50, 52]**.

Remarkably, transporters of amino acids across cellular membranes are important to cellular metabolism, nutrient supply, and energy homeostasis **[53]**. The system xc- is an amino acid transporter system consisting of two subunits, SLC7A11 and SLC3A2 **[50]**. Both transmembrane protein SLC7A11 and SLC3A2 are regarded as negative regulators in ferroptosis **[54, 55]**. This system imports cystine and exports glutamate. Intracellularly, cystine is readily reduced to cysteine, a limiting precursor for GSH synthesis, which is commonly regarded as the principal antioxidant in humans. GSH is crucial for the activity of GPX-4. The selenoenzyme serves as a crucial inhibitor of ferroptosis by transforming deleterious phospholipid hydroperoxides into benign phospholipid alcohols. Genetic depletion of GPX-4 can lead to several forms of cellular death, including ferroptosis, apoptosis, pyroptosis, and necroptosis **[50]**.

The involvement of paclitaxel in ferroptosis has been investigated. Interestingly, the tumor suppressor p53 plays an important role in paclitaxel-induced ferroptosis through downregulation of SLC7A11 (cystine/glutamate antiporter) and SLC1A5 (glutamine transporter). Prior research has shown that paclitaxel can upregulate the expression of the p53 and p21 apoptotic genes while downregulating the expression of SLC7A11 and SLC1A5 in colorectal carcinoma and lung cancer cells, which are protective pathways against ferroptosis **[56]**. Combination of paclitaxel and ferroptosis inducer RSL3 synergistically prompted ferroptosis, through the suppression of SLC7A11 in hypopharyngeal squamous carcinoma cells with mutant *p53* (*mtp53*), where low-concentration paclitaxel was able to augment the ferroptosis induced by RSL3 through upregulating the expression of mtp53 **[57]**.

2.4.3. Apoptosis

It has been approved that apoptosis is a cardinal pathway in chemotherapy-induced cardiotoxicity **[58, 59]** and paclitaxel in particular can induce apoptosis in cardiac cells, causing cell death **[60]**.

The term apoptosis was initially introduced in a 1972 publication by Kerr, Wyllie, and Currie to characterize a physically unique kind of cell death **[61]**. Apoptosis refers to the cessation of cellular growth, during which the cell undergoes morphological alterations culminating in its death, without the release of cellular components into the surrounding environment or the activation of an inflammatory response. The concept of apoptosis relies on the activation of a sequence of cysteine-aspartic proteases referred to as caspases. Caspases are classified into two categories: initiator caspases (2, 8, 9, and 10) and executioner caspases (3, 6, and 7) **[62, 63]**. Upon detection of damage, initiator caspases become activated, resulting in the activation of effector caspases. The activation of executioner caspases initiates a cascade of events resulting in DNA fragmentation via endonuclease activation, degradation of nuclear proteins and the cytoskeleton, crosslinking, expression of ligands that recruit phagocytic cells, and the formation of apoptotic bodies **[64]**.

Apoptosis is initiated by two mechanisms: intrinsic (mitochondrial pathway) and extrinsic (death receptor pathway) **[63, 65]**. The intrinsic pathway is initiated by various factors, including hormones, growth factors, radiation, toxins, hypoxia, viral infections, and hyperthermia, which enhance mitochondrial membrane permeability and facilitate the release of pro-apoptotic proteins, such as cytochrome c. This protein binds to Apaf-1 and caspase-9, thereby commencing the apoptosis cascade. These processes are meticulously regulated by a cohort of proteins referred to as the BCL-2 family. These proteins can be categorized into pro-apoptotic proteins (e.g., Bak, Bcl-10, Bax, Bad, Bid, Bim, Bik, Blk) that modulate the release of cytochrome C by influencing mitochondrial membrane permeability, and anti-apoptotic proteins (such as Bcl-2, Bcl-x, Bcl-w, Bf-1, Bcl-XL, B-XS, Bcl-w, BAG) that inhibit this release. The equilibrium between pro-apoptotic and anti-apoptotic proteins is essential for ascertaining the occurrence of apoptosis, hence facilitating appropriate cell growth and development. The extrinsic pathway is primarily initiated by the interaction of death receptors (DR) with their respective ligands. DRs are a subset of receptors within the TNF superfamily, which encompasses TNF, Fas ligands (Fas-l), and TNF-related apoptosis-inducing ligand (TRAIL), along with various members exhibiting distinct ligands. The pathway commences with the surveillance by natural killer cells and macrophages, resulting in the secretion of various death ligands **[66, 67]**. Upon the binding of DR to its corresponding ligand, procaspase 8 is recruited to a death-inducing signaling complex (DISC) situated on the cytoplasmic domain of the ligand-bound DR, facilitated by the binding of death domain/adaptor proteins, specifically the FAS-associated death domain (FADD) or TNF receptor (TNFR)-associated death domain (TRADD), which promote the interaction between procaspase 8 and DISC. Interaction results in the activation of procaspase 8 and the subsequent synthesis of caspase 8, which triggers apoptosis through the activation of effector procaspases **[68, 69]**. Moreover, Caspase-8 cleaves Bid into tBid, which induces the intrinsic pathway, hence releasing cytochrome c **[70]**.

The mRNA levels of caspase-3, as well as BCL-2-associated X protein (BAX), and the tumour necrosis factor receptor superfamily member 6 (FAS) were elevated in the paclitaxel-treated vessels in a murine model for restenosis **[71]**. The expression of tBid, DR5, and

cleaved caspase-8 was enhanced by paclitaxel treatment in PC9 cells, which were derived from a formerly untreated adenocarcinoma patient, thus paclitaxel triggered the activation of the extrinsic pathway of apoptosis **[72]**.

2.4.4. Inflammation

The role of inflammation in chemotherapy-induced cardiotoxicity has been investigated **[73]**. Inflammation begins with the recognition of harmful stimuli by immune cells, which release inflammatory mediators that activate the inflammatory process **[74]**. Monocyte Chemoattractant Protein-1 (MCP-1), which belongs to the CC chemokine family, plays a crucial function in the inflammatory process by attracting or augmenting the production of other inflammatory factors or cells. This primary method of migration and infiltration of inflammatory cells, such as monocytes/macrophages and other cytokines, contributes to the progression of numerous illnesses at the site of inflammation. MCP-1 has been implicated in the etiology of various illness states, either directly or indirectly, including new coronavirus, malignancies, neuroinflammatory diseases, rheumatoid arthritis, and cardiovascular diseases **[75]**.

Paclitaxel can induce cardiotoxicity through modulation in the inflammatory response, it is evidenced that systemic administration of Paclitaxel can upregulate proinflammatory proteins and atherothrombotic mediators such as MCP-1 (Monocyte Chemoattractant Protein-1) which is a principal chemokine of the CC family that governs the movement and recruitment of monocytes, enhances cytokine production, promotes adhesion molecule expression, and induces the release of ROS in monocytes **[76]**. Paclitaxel can also suppress the nuclear factor erythroid 2-related factor 2 pathway, which regulates the expression of different genes whose products have roles in antioxidant and inflammatory responses, as well as the detoxification of toxic entities **[77]**. Remarkably, Nrf2 mitigates inflammation by inhibiting the transcriptional enhancement of pro-inflammatory cytokines. Consequently, Nrf2 loss in myocardial infarction results in elevated inflammatory cytokines and chemokines, indicating its vital function in modulating the inflammatory response **[78, 79]**.

3. Treatment modalities in Paclitaxel-induced cardiotoxicity

Clinical cardiac monitoring of patients receiving paclitaxel treatment is essential, especially for patients receiving cardiotoxic chemotherapy combinations such as anthracycline, to find early signs of heart toxicity. Moreover, paclitaxel discontinuation can be a lifesaver in patients with significant cardiac diseases such as heart failure symptoms or a noticeable deterioration in left ventricular function. Stopping the medication can help prevent further heart damage, and managing each toxicity with its appropriate supportive care **[35, 80]**.

Experimental research was conducted to examine the efficacy of alternative therapies in mitigating the cardiotoxicity caused by paclitaxel. Rutin and hesperidin were among the medications tested; the study was conducted on rats, and the findings demonstrated a notable improvement in heart function enzymes, heart histopathology, antioxidant defence, and cardiac lipid peroxidation **[22]**.

Misoprostol is another pharmacological agent that has been investigated for its potential protective effects. In a preclinical study conducted on rats, the findings were promising. The administration of misoprostol appeared to mitigate the pro-apoptotic effects induced by PXT. Additionally, it contributed to strengthening the cellular antioxidant defense

mechanisms and led to significant improvements in key cardiac enzyme markers, suggesting a protective role in maintaining cardiac function **[40]**. Moreover, treatment with royal jelly exhibited a cardioprotective effect on rats. It significantly alleviated histopathological damage and reduced oxidative stress, both of which had been worsened by PXT administration **[81]**. Further Clinical trials are required to ensure both the safety and efficacy of these drugs in alleviating PXT-induced cardiotoxicity.

Conclusions and future directions

Future studies require much information about the underlying mechanism of paclitaxel-induced cardiotoxicity, as more attention has been paid to other classes that cause cardiotoxicity, such as the anthracycline class.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Availability of the data and Material

Data will be made available on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was not funded or supported by any person or group.

Author contribution

Y.M.E.: Literature review, Supervision, Data collection, Writing – First draft. S.E.: Data collection, Literature review, Investigation, Writing - Review & Editing, Supervision. M.Y.G.: Conceptualization, Literature review, Writing - Review & Editing, Supervision. D.A.E.: Conceptualization, Literature review, Writing - Review & Editing, Supervision. All authors approved the final version of the manuscript.

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