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Review Article

Molecular Mechanism of chemical-induced cardio-toxicity: A Comprehensive review

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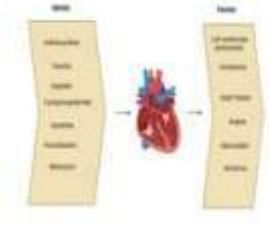
Name of Author:
Chanchal Gupta[1] , Dr Avijit Mazumder [2], Dr. Priyanka Bansal[3]

Affiliation:*[1]M.Pharma student Specialization in pharmacology ORCID Number:0009-0006-3740-5011 Department of Pharmacology, Noida Institute of Engineering and Technology (Pharmacy Institute)) Knowledge park-II, Greater Noida, Uttar Pradesh 201306, India*
[2]Professor and Director ORCID Number: 0000-0002-3053-8106 , , Noida Institute of Engineering and Technology (Pharmacy Institute) Knowledge park-II, Greater Noida, Uttar Pradesh 201306, India
[3]Assistant Professor, Noida Institute of Engineering and Technology (Pharmacy Institute) Knowledge park-II, Greater Noida, Uttar Pradesh 201306, India

Abstract: Chemical-induced cardiotoxicity has become a major problem in contemporary medicine, especially in the treatment of cancer, where medications like cisplatin, taxoids, and anthracyclines are essential for patient care but also carry the danger of permanent heart damage. These substances' complicated molecular processes of oxidative stress, mitochondrial malfunction, calcium dysregulation, and apoptotic pathway activation give rise to their cardiotoxicity.Procarbazine, quinidine, and cyclophosphamide are examples of chemotherapeutic medications linked to myocardial fibrosis, inflammation, and arrhythmias that further complicate their clinical use. Among the primary causes of molecular damage is the production of reactive oxygen species, which can cause DNA damage, lipid per-oxidation, and cell death. This paper offers a thorough explanation of how some drugs impact mitochondrial function, disrupt cellular homeostasis, and initiate signalling cascades that exacerbate cardiomyocyte damage. New evidence points to epigenetic alterations as additional causes of drug- induced cardiotoxicity, including aberrant DNA methylation and altered microRNA production. Even as our knowledge of these pathways has advanced notably, there is still a lot to discover about the interindividual variation in cardiotoxicity susceptibility. Heart risks can be increased by genetic predispositions, pre-existing cardiac problems, and the cumulative effects of many treatment regimens. Developments in human pluripotent stem cell-based models and biomarker identification have the potential to enhance the forecasting of cardiotoxic effects and provide focused preventative measures.
To increase patient safety during chemotherapy and other therapeutic settings and lessen poor cardiovascular outcomes, we hope to shed light on the molecular basis of chemical-induced heart injury.

Keywords: Cardiotoxicity, chemotherapeutic agents, oxidative stress, drug induce apoptosis, molecular mechanism)



Graphical abstract caption: Drug- Induced cardiotoxicity and associated pathologies

LIST OF ABBREVIATIONS

1. **hPSCs**- Human pluripotent stem cells
2. **MMC**- Mitomycin
3. **PA**- Procarbazine
4. **QND -** Quinidine
5. **CK-** Creatine kinase

6. **VDAC**-Voltage-dependent anion channel
7. **WGS -** Whole genome sequencing
8. **HSCT-** Hematopoietic stem cell transplantation
9. **ROS-** Reactive oxygen species
10. **ALDO-**Aldophosphamide
11. **CY-** Cyclophosphamide
12. **DOX-** Doxorubicin

INTRODUCTION

Cardiotoxicity can be a dose-limiting factor in the treatment of cancer, therefore, tumour response. It happens while using a number of cytotoxic medications. Additionally, cardiotoxicity may be the source of significant morbidity and long-term side effects in cancer patients who survive, which may be important in paediatrics. oncology in particular. It is well known that cytotoxic therapy frequently results in cardiotoxicity.1 The study of cardiotoxicity mechanisms and detecting biomarkers for cardiotoxicity by applying heart tissues from cancer patients are not feasible. Consequently, several research teams used rats and mice as in vivo experimental models. After treating the rats with different doses of DOX for varying durations, the chronic cardiotoxic effects of DOX were observed.2 One of the main reasons newly discovered medications have high attrition rates is cardiotoxicity. A major cause of mortality for cancer survivors is also cardiotoxicity brought on by anti-cancer therapies. Using cardiomyocytes generated from human pluripotent stem cells (hPSCs) for in vitro cardiotoxicity assessments might increase the predictability of cardiotoxicity for novel medications. Anthracyclines, including doxorubicin, are widely used and very successful chemotherapy drugs for a variety of cancers. However, these medications frequently cause cardiac issues, either early in the course of treatment or later. Anthracyclines exert potent anti-cancer effects primarily by inducing DNA damage in proliferating cells during DNA replication.3 Numerous widely used anticancer drugs may have cardiotoxic side effects and impair mitochondrial function. Imatinib (Gleevec), bevacizumab (Avastin), sunitinib (Sutent), mitoxantrone (Novantrone), trastuzumab (Herceptin), arsenic trioxide (Trisenox), cisplatin, and sorafenib (Nexavar) are a few of them. A few antiviral drugs, such as azidothymidine, and several oral diabetes drugs, such as rosiglitazone, can also have cardiotoxic side effects. Cocaine, alcohol, methamphetamine, ecstasy, and synthetic cannabinoids like spice and K2 are among the illegal drugs that might cause mitochondrial-related cardiotoxicity.4 Cardiotoxicity is the term used to describe the detrimental effects on the heart that can result in myocardial enlargement, arrhythmia, cardiomyopathy, and myocardial infarction. These side effects are frequently inevitable and frequently cause therapy to be stopped or drug development to fail, particularly when it comes to anticancer treatments.5 The absence of antioxidant enzymes such as catalase and superoxide dismutase makes cardiac tissue more susceptible to generating reactive oxygen species and accumulating oxidative stress.6 Since the 1940s, it has been well-recognized that pharmacological therapy can have cardiotoxic side effects, with digitalis and local anaesthetics impairing heart function.7 In pre-clinical trials that concentrate on acute time periods, such as seconds to a few hours after delivery, cardiac problems that arise later after therapy are overlooked.8 Up until now, cardiotoxicity has primarily been linked to negative outcomes in those who have used drugs. It can be identified in people after exposure when clinical symptoms have been established, and at this point, it may even be irreversible. 9

ANTHRACYCLINES

One of the most effective and often prescribed chemotherapeutics for treating malignancies is anthracyclines. Doxorubicin (DOX), sometimes referred to as adriamycin, is the most commonly used medication in this family. Daunorubicin, epirubicin, and valrubicin are also utilized.[10] Given that anthracyclines bind and inhibit topoisomerase IIβ, their mechanisms of cardiotoxicity have been studied. These cells communicate topoisomerase IIβ, which helps relax and separate DNA helices during transcription, thereby regulating gene expression and mitochondrial function. Doxorubicin causes DNA damage in vitro in topoisomerase IIβ+/+ but not Top IIβ−/− primary mouse embryonic fibroblasts and DNA damage in H9C2 cardio-myoblasts is inhibited by dexrazoxane is an inhibitor of topoisomerase II enzyme catalytic activity.11 Nitric oxide synthase, NADPH oxidase, and mitochondrial enzymes are among the enzymes activated by anthracyclines' induction of oxidative stress. Cardiotoxicity is a result of the buildup of reactive oxygen species, which are produced as a result of this activation. Apoptosis, pyroptosis, and autophagy are among the cell death mechanisms that anthracyclines also modify, resulting in cell death and exacerbating cardiotoxicity. Moreover, anthracyclines modify epigenetics, which includes modifications to microRNAs, histones, and DNA methylation. Cardiotoxicity is also exacerbated by these epigenetic modifications' deregulation of mitochondrial genes. DNA damage, suppression of protein synthesis and mitochondrial biogenesis, promotion of inflammatory response, ROS, and apoptosis formation are thought to be the causes of ANT

cardiotoxicity. Because of the myocardium's high mitochondrial density, ANT is more likely to remain in cardiomyocytes due to its tendency to collect in the mitochondria. Here, ANT metabolites increase intracellular free iron by blocking the translation of iron-sequestrating proteins. This results in the formation of very reactive iron-ANT complexes, which can initiate redox cycling and encourage excessive autophagy.[12] Regarding cardiotoxicity, the use of anthracyclines has been well investigated. Anthracyclines have been implicated with cardiomyopathy, congestive heart failure, and abnormalities of the electrocardiogram (ECG), including nonspecific ST-T shifts, elevated QT interval, and decreased QRS voltage. Within a year of beginning anthracycline medication, early onset effects might manifest as acute, subacute, or chronically progressive. It seems that youngsters are less likely to experience early-onset cardiotoxicity than late-onset clinical cardiotoxicity. [1] The loss of cardiomyocytes is primarily responsible for the progressive development of heart dysfunction. As a result, that has been acknowledged. The loss of cardiomyocytes is the primary cause of dysfunction. This has resulted in the realization of that. Anthracycline toxicity in the heart mostly affects these cells. However, recent research has discovered that other cell types may also be affected., including endothelial cells, cardiac fibroblasts, and cardiac progenitor cells.[13] Anthracycline-induced left ventricular dysfunction develops in a complex way.[14] However, this experience has spurred more investigation into the molecular pathways of anthracycline-induced cardiotoxicity, Mechanistically, these medications could prevent the action of Bio-Essays 27.1 to disrupt transactivating factors' ability to access DNA and/or processive enzyme complexes.[15] Since disruption of cardiac mitochondria and sarcoplasmic reticular membranes is a hallmark of ultrastructural heart damage following anthracycline therapy, we investigated the impact of anthracycline antibiotics on superoxide production by a rat heart mitochondrial fraction.[16] When localized to the cell's nucleus, the chromophore moiety of anthracyclines performs an intercalating activity, inserting between neighbouring base pairs of DNA to impede DNA and RNA synthesis, particularly within highly reproducing cells that prevent cell division.[17] Double-strand breaks and topoisomerase-2β activation result from this, causing cellular death and apoptosis.[18] Although there is no question that cardiomyocytes produce more ROS and have a lower antioxidant capacity, several studies have cast doubt on the idea that ROS play a major role in the, pathophysiology of AICs showing that doxorubicin-induced cardiac toxicity was not prevented by ROS scavenger treatment.[19] To create DNA cleavage complex from ternary Top2-doxorubicin, doxorubicin binds DNA and Top2. This results in DNA double-strand breaks, which, if unrepaired, cause cell death.[15] Numerous research have examined the possible antibacterial properties of anthracyclines as well as their other applications. 20the mechanisms of anthracycline-induced cardiotoxicity, show in (Figure :1)

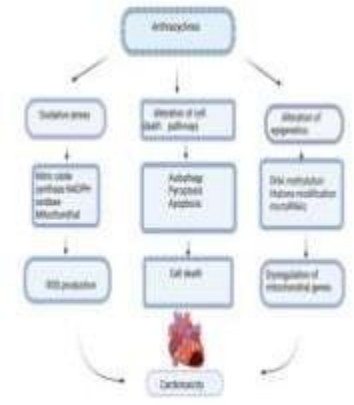


Fig .1 Mechanism of Anthracyclines induced Cardiotoxicity

TAXOIDS

Taxol is an excellent treatment for the three most common malignancies worldwide: lung, ovarian, and breast.[21] First-generation taxane used in chemotherapy medications toxoids, such as the semisynthetic compounds of taxol, docetaxel, cabazitaxel, and others has recently posed a serious threat to the use of taxol, Chronic cardiotoxicity is a side effect of chemotherapy medications. First, taxoids are administered, which disrupt cellular function and cause endothelial dysfunction by acting on microtubules. This interruption has several knock-on effects. On the one

hand, oxidative stress causes cell damage, endothelial dysfunction triggers the activation of inflammatory pathways, and myocardial injury damages the heart muscle cells. It causes oxidative stress-induced mitochondrial dysfunction, intracellular calcium overload due to calcium dysfunction, and cardiomyocyte apoptosis, which leads to cell death. These pathways all lead to chronic cardiotoxicity as the ultimate result. [22]

Taxus cuspidata callus culture, taxol was extracted. Gibson et al. (1993) reported that a culture of Taxus brevifolia only generated 7-xylosyl-10-deacetyl taxol.[23] Some cancers, including ovarian, breast, and squamous cancers, are often treated with the primary bioactive ingredient in Taxus species is taxol (generic name paclitaxel).[24] Heart risk factors were unstable angina, congestive heart failure, atrial fibrillation and significant coronary artery disease.[25] Although cardiotoxicity is a problem, the taxoids docetaxel and paclitaxel are nonetheless effective therapies for a variety of cancers.[26] Damage to the heart muscle caused by subcellular organelles might be another reason for paclitaxel-induced cardiotoxicity. [27] To improve drug solubility, paclitaxel is put in a cremophor EL vehicle; it is hypothesized that the cardiac abnormalities are caused by the vehicle rather than the cytotoxic medication. [28] However, the use of other drugs that include cremophor EL, like cyclosporin, has not been linked to cardiac rhythm abnormalities. Massive histamine release is one potential way cremophor EL might be cardiotoxic. [29] Animal research has shown that activating histamine receptors in heart tissue can cause arrhythmias and conduction abnormalities. Another theory for paclitaxel-induced cardiotoxicity is that it damages heart muscle by interfering with subcellular organelles. [30]

The mechanisms of toxoids -induced cardiotoxicity, show in (Figure :2)

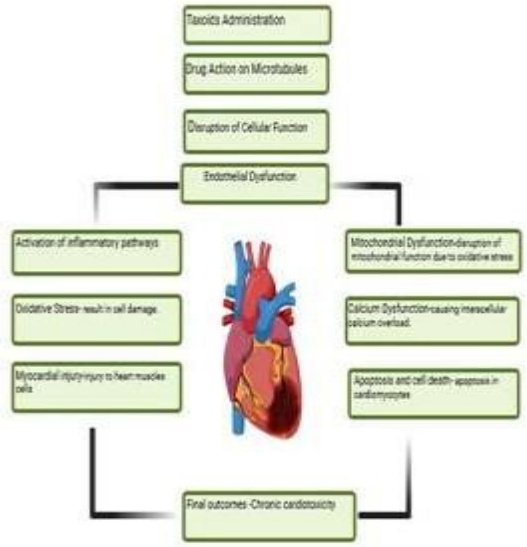
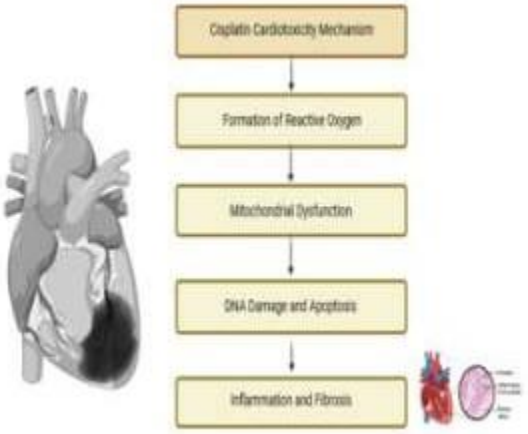


Fig .2 Mechanism of Taxoids induced Cardiotoxicity

CISPLATIN

Cisplatin is the platinum-based chemotherapeutic drug most frequently used for the treatment of osteosarcoma (OS) testicular, bladder, lung, ovarian, and other organ malignancies have been treated with cisplatin. Cisplatin mostly attaches to the purine ring's N7 position in DNA and is also referred to as cis-diamine dichloroplatinum.Its therapeutic use is limited by cisplatin's adverse effects that are cardiotoxic. The principal mechanisms associated with this cardiotoxicity include inflammation, oxidative stress, apoptosis, and mitochondrial dysfunction. [31] The cardiotoxicity of cisplatin, which also increases the risk of cardiovascular disease, significantly restricts its therapeutic usage as an anticancer drug.[32] Serum lactate dehydrogenase (LDH), acetylcholinesterase (Ach-E), tumour necrosis factor-alpha (TNF-α), oxidative stress markers, and Na+, K+-ATPase in cardiac tissue are measured to evaluate the cardiotoxic effects of cisplatin.[33] According to several research, oxidative stress, inflammation, and apoptosis are linked to the deadly consequences of CP.[34] In the end, cisplatin was employed in subsequent study stages. It was authorized as an anti-cancer drug in 1978 based on the results. [35] causing irreversible harm to DNA. Although it is a fundamental component of first-line cancer treatment, dose-dependent cardiotoxic side effects, including arrhythmias, chest discomfort, and heart failure,

significantly restrict its practical use.[36] Heart failure, arrhythmias, myocardial ischemia, and systolic dysfunction are among the cardiac symptoms associated with cisplatin-induced cardiotoxicity. [37] Its negative consequences include Cardiotoxicity, however, is a major issue that restricts the use of cisplatin and can be either acute or chronic. [38] Cardiotoxicity, which can be acute or chronic, is one of the main issues preventing cisplatin from being used widely.[39] We describe two patients who experienced bradycardia while taking cisplatin as part of a combined treatment.[40] Nonetheless, the treatment shows resistance indications, such as reduced drug accumulation in cells, improved repair of DNA damage, and cytosolic cisplatin inactivation,[41] Changes in mitochondrial structure and a depolarized mitochondrial membrane are associated with cardiac failure caused by cisplatin.[42] By upregulating cisplatin induces apoptosis and inhibits the growth of stem cells by upregulating the expression of pro-apoptotic genes and downregulating that of the crucial anti-apoptotic gene, Bcl-2. The end effects of this include mitochondrial dysfunction and cell death.[43] Cardiomyocytes undergo apoptosis, according to research on toxicity conducted both in vivo and in vitro. Complex and unidentified molecular processes underlie cisplatin's toxicity. Numerous research findings demonstrated that cisplatin-induced toxicity was caused by several routes. [44] Cisplatin's potential for cardiotoxicity restricts its use in medicine. Although it is unclear exactly how cisplatin causes these effects, it is believed to produce cardiotoxicity by directly harming cardiac myocytes and raising the production of reactive oxygen species. In cardiac tissue, cisplatin reduces the activity of antioxidant enzymes while raising lipid hydroperoxide levels and the total oxidative potential of tissues.[45] Cardiotoxicity is mostly caused by direct cardiac damage. After entering cells, cisplatin becomes active. Cancer cells' DNA is damaged by this process, which also stops them from proliferating and eventually kills them.[46] NADPH oxidase is essential for the cytotoxicity of reactive oxygen species, which are a primary contributor to tissue damage linked to cisplatin (CDDP) treatment. [47] Activating antioxidant genes and lowering ROS levels, nuclear factor erythroid 2-related factor 2 (Nrf2) translocate to the nucleus in response to oxidative stress. On the other hand, oxidative stress also raises nuclear factor kappa B (NF-κB) activity, which makes pro-inflammatory cytokines like tumour necrosis factor- alpha (TNF-α) more abundant.[48] Clinical studies is helpful in reducing cisplatin-induced cardiotoxicity. As a result, new treatment approaches are now required.[49] It primarily works by breaking DNA strands, which prevents cells from proliferating. They also change the formation of free radicals, intracellular calcium, and ion channel activity. [50] These other modes of action may aid their chemotherapeutic efficacy, but they also often result in negative side effects and the development of drug resistance. In this review, we concentrate on the characteristics of CPT's detrimental impact on the heart.[51] The mechanisms of cisplatin-induced cardiotoxicity, shown in(Figure :3)



CYCLOPHOSPHAMIDE

One of the most commonly used antitumor drugs is cyclophosphamide (CY), an old alkylating agent An alkylating anticancer drug called cyclophosphamide, Oxazaphosphorine, when substituted for this nitrogen mustard, exhibits strong cytotoxic and immunosuppressive effects.[52] One nitrogen mustard alkylating medication used to treat lymphoma, leukemia, and ovarian and breast cancers is cyclophosphamide (CYP). Its various dose-related cardiotoxicity, however, limits its clinical use. [53] Cyclophosphamide induces cardiotoxicity by

converting to acrolein, which in turn results in decreased endothelial nitric oxide synthase activity and production, inflammation of cardiomyocytes, and the creation of ROS. Furthermore, in cardiomyopathy, acrolein triggers caspase activation, which leads to apoptosis. Cardiotoxicity with chemotherapy 1139 Am J Cancer Res 2021;11(4):1132-1147 cites and calcium excess that causes heart failure. [54] Lethal cardiotoxicity from high CYP dosages is known to develop, leading to arrhythmias and heart failure in the long run. [55] Rarely fatal side effects might arise from cardiotoxicity caused by cyclophosphamide (CY). We have previously documented the cardiac events of 811 patients of allogeneic hematopoietic stem cell transplants (allo-HSCTs); 12 of these recipients (1.5%) had catastrophic heart failure.[56] Consequently, anticipating cardiotoxicity enables us to take prompt action and offer efficient therapies to lower morbidity and death rates. [57] Cyclophosphamide, the mainstay of adjuvant and metastatic BC, is used to treat most early and advanced illnesses.[58] Prodrugs like cyclophosphamide are metabolized in the liver to produce an active component and an inactive version called acrolein, which can directly harm the bladder and result in hemorrhagic cystitis. Non-clinical and big clinical investigations have thoroughly established adjuvant chemotherapy's acute toxicity.[59] However, it is still unknown what chemical mechanism underlies the mortality of cardiomyocytes caused by cardiac injury in CP.[60]Phosphoramide mustard gives CP its anti- neoplastic activity by interfering with DNA, one of its immunosuppressive and cytotoxic qualities. [61] According to the current research, CP-induced acute cardiomyopathy may be exacerbated by suppression of mTOR, AMPK signals, Klotho protein, and ALDH2 in cardiac tissues.[62] Through lymphoid and inflammatory cells' immunomodulatory functions, oral CPA therapy prevents the development and advancement of atherosclerosis.[63] Even though other conditioning agents are available for hematopoietic stem cell transplantation (HSCT) to treat hematological malignancies, bone marrow failure, or immunodeficiency.[64] Cyclophosphamide causes cardiotoxicity through a variety of mechanisms, such as oxidative and nitrative stress, the production of protein adducts that inflame the cardiomyocytes, altered calcium homeostasis, programmed cell death, myocardial swelling, nuclear splitting, vacuolization, and modifications to signalling pathways.[65] If treatment is not received, these incidents might lead to cardiac muscle illnesses, such as heart failure, which can be fatal.[66] It is crucial to comprehend the molecular process underlying these undesirable side effects since it has a direct bearing on the prognosis and survival rate of patients receiving chemotherapy.[67] To confirm that the ATP-sensitive potassium channel (KATP) was functioning, we co-administered glibenclamide (GP) (5 mg/kg/day) for five days, two hours prior to NIC (3 mg/kg/day). The coadministration of nitro-ω-l-arginine (l-NNA) at a dose of 25 mg/kg/day for five days further validated the function of endothelial nitric oxide synthase (eNOS") The findings demonstrated that CP was successful in inducing cardiotoxicity, as evidenced by a marked rise in heart weights, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), troponin I, cardiac tissue malondialdehyde (MDA), tumor necrosis factor alpha (TNF-α), interleukin 1β (IL1 β), and caspase-3 levels.[68] Patients who received high doses of chemotherapy have exhibited a reduction in plasma antioxidant content (Sabuncuoglu and Ozgunes, 2011) Several investigations have demonstrated that exposure to cyclophosphamide increases the generation of intracellular reactive oxygen species (ROS), indicating that its oxidative stress may cause physiological and biochemical adverse effects (Manda and Bhatia, 2003).[69] Troponin I and CK-MB concentrations rise when cyclophosphamide is administered, indicating cardiotoxic effects. Troponin I, creatine kinase (CK), and creatine kinase-MB (CK-MB) concentrations were assessed in the current investigation after CMF treatments. It is well known that these biomarkers are indications of cardiotoxicity [70]. Compared to the control group, albino rats given Cyclophosphamide had significantly higher blood levels of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol.[71] These two substances cause sudden heart failure, hemorrhagic myopericarditis, and arrhythmia, and they have comparable structures and patterns of cardiotoxic effects. Acute cardiotoxicity brought on by CP and IFO is mostly ascribed to an increase in free oxygen radicals and a diminished antioxidant defence system in the heart.[72]CP promotes the synthesis of Th2 cytokines, such as IL-4 and IL-10.17, while decreasing the release of interferon-gamma and IL-12. As a result, it helps with tumor vaccination, post-transplant alloreactivity management, and immune-mediated disease management. Its exact immunomodulatory mechanism is yet unknown, but research suggests that it primes host cells to accept donor T cells, activates T cell growth factors, and decreases regulatory T cells.[73] HPA promotes the cytotoxic apoptosis triggered by alkylation of DNA via PAM, aldophosphamide (ALDO) is an active metabolite of pharmacology, and the SC metabolites generated in sequence 4-hydroxycyclophosphamide (OHCP) are a significant and potent cause of toxicity. ALDO synthesis increased anticancer efficacy by avoiding OHCP but significantly decreased toxicity.[74]The mechanisms of Cyclophosphamide-induced cardiotoxicity, shown in(Figure 4

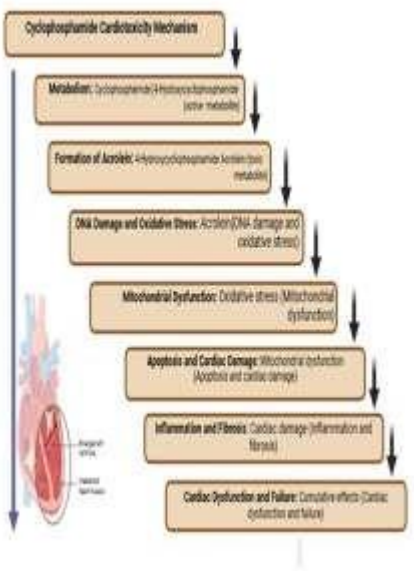


Fig 4. Mechanism of Cyclophosphamide induced Cardiotoxicity

QUINIDINE

Quinidine and quinine compounds (from Cinchona spp.) also affect myocyte sodium channels. Quinine toxidrome's cardiac component, or "cinchonism," is caused by its action as a Class I agent, some anticholinergic activity, and some inhibition of Na+/K+-ATPase, comparable to digoxin.[75] As standard clinical procedure, TDM for quinidine was administered to the three patients. Although our hospital's Ethical Review Board was notified of this TDM application, no official procedure was filed. At least four days after the initiation of QND treatment, plasma samples were taken to determine stable levels of the medication. Plasma is obtained by centrifuging whole blood from an artery line that is indwelling in EDTA tubes for five minutes at 3500× g. [76] According to Milligan et al. (2014), KCNT1 blockers, such as quinidine (QND), bepridil, and an antiarrhythmic medication, have been suggested as treatments for EIMFS because of their capacity to block KCNT1 mutant channels. For EIMFS patients, targeted treatment with QND has been introduced for compassionate purposes; nonetheless, the anticonvulsant impact varies, ranging from high pharmacological responses to ineffectiveness or extreme toxicity (Fukuoka et al., 2017).[77] We have looked into how quinidine interacts with the mitochondria's voltage-dependent anion channel (VDAC). Wistar rat neuronal tissue was used to purify VDAC, which was then used in in vitro bilayer electrophysiology tests. [78] Finding P-gp-overexpressing tumors noninvasively is essential before starting treatment. We report that free radicals may easily copolymerize Using acrylic acid and quinidine, a competitive inhibitor of P-gp, multiplexed polymeric P-gp-targeted imaging agents with turnable quinidine concentrations are produced. [79] Studies showed that in a concentration-dependent manner, quinidine reduced the amplitudes of pulse signals and the CI of hiPSC-CMs at doses of 12.5 μ mol/L and higher. A comprehensive trace analysis revealed that 0.5 hours after treatment, 3.13 μ mol/L quinidine considerably reduced the beating rate however, this rate recovered within 1 hour. However, 0.5 hours after injection, high quinidine concentrations (50 and 100 μ mol/L) stopped the automaticity of cells without self-healing during the observation period.[80] Previously used as antiarrhythmic medicines, quinidine, and quinine compounds (from Cinchona spp.) also affect myocyte sodium channels. [81] At larger dosages, quinidine causes ventricular fibrillation, tachycardia, and a longer QT interval by blocking myocyte sodium channels, which decreases depolarization.[82] The pharmacokinetics of quinidine are comparable. Only clinically insignificant variations in the tissue distribution of quinidine were noted following administration, indicating that sequestration throughout all tissues is a crucial feature. According to preclinical studies, following an intraperitoneal injection, the tissue/plasma Q-concentration ratio in the heart ranged from 6.8 after one hour to 20 after four hours, suggesting that cardiac tissue had greater Q- concentrations than plasma.[83] Adverse effects may result from short-term usage. According to data from COVID-19 therapy, QT/QTc prolongation is

concerning, especially when combined with azithromycin. Heart-harming: Valvulardiseases, cardiomyopathy, and conduction abnormalities have all been linked to long-term usage. Overdose symptoms appear quickly (within minutes to hours), with the most obvious being cardiotoxicity, which includes cardiovascular shock and collapse. [84]The mechanisms of Quinidine-induced cardiotoxicity, shown in (Figure :5)

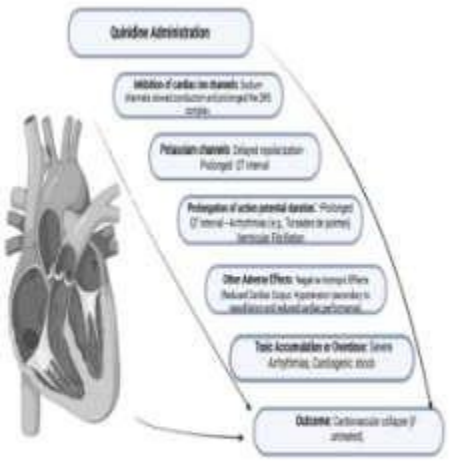
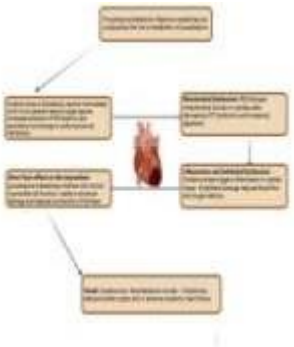


Fig 5. Mechanism of Quinidine induced Cardiotoxicity

PROCARBAZINE

Procarbazine (PA) is an anticancer medication that is most commonly used to treat cancer. Procarbazine is a cytotoxic chemotherapy drug used to treat Hodgkin's lymphoma and other brain malignancies. (2-dimethylhydrazine)-N-isopropyl-α-p-toluamide hydrochloride is another name for procarbazine (Pcb), an alkylating anticancer drug. For Hodgkin's disease, It has been used extensively as a helpful anticancer therapy. It is also used as part of a chemotherapy combination to treat central nervous system (CNS), melanoma, and bronchogenic carcinoma malignancies.[85] PCV's high toxicity significantly impacts the treatment plan due to significant side effects, 28.5% of patients had to stop receiving chemotherapy, according to research published in the Journal of Clinical Oncology9. According to different research, 31.3% of patients postponed therapy to allow the toxicity to go away.[86] Procarbazine is an oral active methylhydrazine compound with a molecular weight of 257.76, and the chemical formula C12H19N3 O-HCl. N-methyl-hydrazine, benzamide, PCB, PCZ, p-toluamide, natulan, and matulane are some of its other names. To treat brain cancer, it is used in combination regimens. Chemotherapy has the potential to harm granulosa cells and oocytes. Previous study suggests that procarbazine affects the ovaries through three main mechanisms oxidative stress, inflammation, and apoptosis.[87] It was anticipated that procarbazine would interact with DNA with a binding constant of 6.52 × 103 M−1. The binding mode was determined via molecular docking, which predicted that PCZ would interact with DNA through a groove binding mode with a binding affinity of -6.7 kcal/mole. To verify the type of groove binding, various tests were conducted. [88] Free radical species are produced when peroxidases and microsomal P450 systems oxidize PCZ. When PCZ is oxidized by one electron, a nitrogen-centered radical intermediate is created, leading to active methyl and benzyl radicals forming. It is believed that the nitrogen-centered radical has been altered to produce nitrogen and carbon-centered radicals. Even though oxidative stress and the production of free radicals have been suggested as components of the pharmacological processes of the majority of alkylating agents [89], they also seem to play a role in the organ toxicities that these medications show. [90] Mutations caused by procarbazine (PRC) in the germ cells Tissue samples were taken at least 28 days.[91] The World Health Organization (WHO) has classified this drug as an essential medicine since it was first licensed in 1969. Usually, oral prescriptions are given. Depressive symptoms, fatigue, nausea, and low blood cell counts are all linked to PA.[91] Procarbazine and dacarbazine-containing regimens were examined for their impact on stem cell genomic toxicity using whole genome sequencing (WGS) of hematopoietic stem and progenitor cell (HSPC) colonies from patients treated with eBPP, eBPDac, and ABVD.[92] When compared to age-matched normal HSPCs, we discovered that the minor excess somatic mutation loads in HSPCs from patients treated with ABVD and eBPDac were similar. On the other hand, the excess mutation load of 1153 was significantly higher in the HSPCs of patients

treated with eBPP. [93] Procarbazine is a prodrug that requires metabolic activation, which is mostly accomplished in aqueous solutions, however TMZ decomposes spontaneously into the reactive metabolite in the liver via cytochrome P450 (particularly CYP3A4). Nucleophilic diazonium ions are produced in both situations, and these ions methylate DNA and RNA at all nucleophilic locations. Pyrimidines and purines were among the twelve alkylation products used in the DNA. TMZ is used in both postoperative primary therapy and following maintenance therapy in conjunction with radiotherapy.[94] To approve the administration of each medication, all patients had full CBC and biochemistry tests performed before days 1, 8, and 29 of each cycle, including bilirubin, creatinine, phosphatase alkaline, alanine aminotransferase [alt], and aspartate aminotransferase.[95] Procarbazine triggers apoptosis in liver cells through the production of tumor necrosis factor (TNF), which Kupffer cells generate. Carmustine, lomustine, and streptozotocin are examples of nitrosoureas that alkylate and damage DNA and RNA, causing hepatic necrosis; trastuzumab, an antibody-drug combination, causes severe hepatotoxicity, including liver failure and death. Transaminase levels are frequently raised by methotrexate in 60–80% of individuals, it can also cause cirrhosis and fibrosis over time. Growth impairment and angiogenesis suppression are adverse effects of some chemotherapy medications that cause significant apoptosis and necrosis, which damages the heart and causes severe cardiotoxicity.[91] Just 3% of the mitochondrial genome is noncoding, mitochondrial DNA has more slowly efficient DNA repair processes and replicates more often than nuclear DNA. Furthermore, since it lacks protective histones and is close to the respiratory chain, mtDNA is more vulnerable to harm. Protein degradation, lipid peroxidation, and DNA damage are all possible outcomes of oxidative stress. Replacements, deletions, and missense mutations are examples of ROS-induced DNA damage that impairs mitochondrial function.[93] Since procarbazine and dacarbazine only have one DNA-binding reactive site per molecule, as opposed to two reactive sites for bifunctional alkylating agents, they are monofunctional as opposed to bifunctional. Crosslinking DNA strands is only possible with bifunctional alkylating chemicals. Monofunctional alkylating chemicals methylate DNA, primarily on guanine's O-6 and N-7 sites. These lesions have the potential to cause cytotoxic single-strand breaks that occur spontaneously or through the action of enzymes (Verly, 1974). It has also been determined that the cytotoxicity of monofunctional alkylating chemicals is mediated via mismatch DNA repair (Kat et al., 1993).[95] Gonadal injury is a major toxicity of the alkylating chemicals. They typically result in azoospermia or oligospermia in males by decreasing testicular germ cells. After a few years, spermatogenesis and fertility may resume (Whitehead et al., 1982). According to Lidtke and Kiesel (2012), alkylating drugs in women produce amenorrhea, which is linked to the reduction of mature and primordial ovarian follicles. As people age, amenorrhea becomes more common, and it is more likely to be permanent in older women. [96]The mechanisms of Procarbazine-induced cardiotoxicity, shown in (Figure :6)



Mechanism of Procarbazine induced Cardiotoxicity

MITOMYCIN

Mitomycin, an antibiotic first discovered in 1956, comes from Streptomyces species because of its alkylating activity, which stops DNA synthesis stop during cell mitosis, the chemical has been extensively employed as a chemotherapy treatment for non-small cell lung cancers as well as prostatic, bladder, and other organ neoplasias. MMC has been used in ocular operations because it functions as a wound-healing modulator and its effects are more pronounced in cells with a higher rate of mitosis. In 1963, MMC was initially used in ocular surgery as an adjunct to pterygium excision.[97] Streptomyces caespitosus was the source of the anticancer antibiotic mitomycin (MMC), which was used to treat many solid tumors, such as lung, breast, and uterine cancers, but specifically colorectal, stomach, and bladder cancers. By crosslinking and alkylating G–G interstrand links in DNA, the alkylating chemical MMC prevents transcription and DNA synthesis in vivo. Despite having a wide range of anticancer efficacy, myelosuppression, cardiotoxicity, pulmonary toxicity,

and nephrotoxicity were among the side effects that largely restricted MMC's clinical usage.[98] There are several ways that MMC seems harmful. Among the routes linked to mitomycin-induced toxicity was thought to be oxidative stress. Reduction of the mitomycin molecule in cycles by one electron, after the oxidation of oxygen molecules, results in the extremely reactive superoxide radical and the active MMC molecule, which harms biological components in several ways. This process is the source of MMC oxygen-dependent toxicity. DNA, lipids, protein thiols, and glutathione are among the macromolecules that reactive oxygen species (ROS) may harm. This can lead to genotoxic damage, enzyme deactivation, cell dysfunction, and even death. [103] MMC has been shown to cause cardiomyopathy1,2 which appears to be connected to the total dosage of the medication. Congestive heart failure (CHF), which manifests clinically similarly to CHF from other causes, is the most severe heart failure linked to mitomycin therapy. Two Furthermore, many reports demonstrated that MMC causes renal injury in the glomerulus and tubules when haemolytic uremic syndrome is present. 4-MMC- induced hepatotoxicity is less well understood and has hardly been described. Nonetheless, it is well recognized that MMC is extensively absorbed and processed in the human liver and that hepatotoxicity may result from an accumulation of the medication.5.

Numerous research has so far concentrated on strategies to avoid MMC adverse effects.[97] In contrast, females have often experienced mitomycin-C-induced PVOD in conjunction with a null connection with the EIF2AK4 gene mutation. PVOD may be indicated by tiredness and dypnea (according to the lung function test), low oxygen levels, decreased high-resolution lung tomography abnormalities, carbon monoxide diffusion capability, and the emergence of pulmonary edema after starting pulmonary vasodilator medication. A non- invasive method of diagnosis approach have been favoured to prevent potential difficulties in this area. An uncommon kind of treatment-resistant PH with a poor prognosis and a difficult diagnosis is a pulmonary veno- occlusive disease. [99] In addition to being widely in ophthalmology to avoid postoperative fibrosis by using topical medicine, particularly MMC and DNR have been shown in earlier research to suppress fibroblastic proliferation and reduce fibroblast collagen production. Free radical-induced chronic and dose-dependent cardiotoxicity is the most significant adverse consequence of DNR. MMC may cause transient bone marrow toxicity, which is one of its most dangerous adverse effects. [100]Chemical-induced cardiotoxicity has become a major problem in contemporary medicine, especially in the treatment of cancer, shown in Table :1.

Table 1: List of chemotherapy drugs that might be harmful to the heart

Serial No.	Compound	Cardiotoxic effect	Reference
1	Doxorubicin	LV dysfunction/HF/Arrhythmias	[101]
2	Daunorubicin	LV dysfunction/HF/Arrhythmias	[102]
3	Mitomycin C	Heart Failure	[100]
4	Cyclophosphamide	Cardiac Tamponade/Heart failure	[104]
5	Cisplatin	Angina/Heart failure	[105]
6	Epirubicin	LV dysfunction/HF/Arrhythmias	[106]
7	Mitoxantrone	LV dysfunction/HF/Arrhythmias	[107]
8	Melphalan	Acute Cardiomyopathy	[108]
9	Bleomycin	Myocardial Ischemia	[109]
10	Ifosfamide	Cardiac Tamponade/Heart failure	[110]

DISCUSSION

Numerous mechanisms that compromise the integrity and activity of cardiac cells can lead to chemical-induced cardiotoxicity. The production of ROS by anthracyclines, which are frequently used to treat cancer, results in mitochondrial malfunction, lipid peroxidation, and DNA damage. Doxorubicin, DNA, and topoisomerase 2 complexes increase cellular stress, which leads to cardiomyocyte mortality and chronic cardiac issues.

Paclitaxel and other taxoids stabilize microtubules and disrupt mitotic processes, which leads to aberrant calcium signaling and oxidative damage. Long-term heart failure risks are increased by these disturbances because they cause myocardial injury, endothelial dysfunction, and mitochondrial damage. Through inflammation and oxidative stress, cisplatin, another frequently used chemotherapy drug, causes cardiotoxicity. Apoptosis in cardiomyocytes is made worse by ROS and mitochondrial depolarization, whereas DNA adduct production upsets cellular homeostasis. Similarly, acrolein, a toxic byproduct of cyclophosphamide, causes inflammation and oxidative stress, which changes calcium homeostasis and damages the structure of the heart. Certain substances, such as procarbazine and quinidine, have distinct toxicities. Quinidine blocks ion channels, resulting in arrhythmias and prolonged QT intervals. Procarbazine increases oxidative stress and mitochondrial dysfunction, which disrupts ATP generation and results in cardiac fibrosis.

NEW PERSPECTIVES

The role of epigenetic alterations, such as histone modifications, DNA methylation, and microRNA

control, in mediating cardiotoxicity has been highlighted by recent studies. For instance, dysregulation of mitochondrial genes and apoptotic pathways exacerbates cellular damage. Personalized cardioprotective therapies are made possible by the identification of these molecular foundations using human pluripotent stem cell-derived cardiomyocytes and other sophisticated experimental models.

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There are still a lot of unanswered questions regarding the variation in cardiotoxicity across more difficult by variables such as genetic susceptibility, pre-existing illnesses, and co-administration of other medications. Therefore, for early diagnosis and prevention, finding trustworthy biomarkers and using systems biology techniques will be essential.

FUTURE DIRECTIONS

1. Personalized medicine: using biomarker profiling and genetic screening to identify high-risk individuals.

2. Innovative Interventions: Creating cardioprotective drugs, antioxidant treatments, and altered medication delivery methods to reduce side effects.

3. Regulatory Guidelines: Creating uniform procedures to keep an eye on heart health both during and after treatment.

The medical community can reduce the danger of cardiotoxicity and provide patients throughout the world with safer and more effective treatment regimens by utilizing developments in molecular biology and experimental models.

CONCLUSION

Cardiotoxicity is a major obstacle to the therapeutic use of many chemical substances, particularly in cancer. The study highlights the complexity of the molecular mechanisms behind drug-induced cardiac injury, such as oxidative stress, mitochondrial dysfunction, and apoptotic pathways.

Comprehensive preventative and mitigation methods are still difficult to implement, even if new options for early detection are presented by developments in experimental models and biomarker discovery.

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