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Review Article

A REVIEW ON THE CHEMICAL-INDUCED EXPERIMENTAL MODEL OF CARDIOTOXICITY

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ABSTRACT

Drug-induced cardiotoxicity is a major concern during drug development, prompting the need for reliable experimental models to thoroughly assess potential cardioprotective drugs. The review delves into the intricacies of various models for drug-induced cardiotoxicity in experimental animals, with a specific focus on streptozotocin, isoprenaline, and antineoplastic drugs like cisplatin, doxorubicin, and 5-fluorouracil in rats and mice. Streptozotocin-induced cardiotoxicity is characterized by oxidative stress, inflammation, and mitochondrial dysfunction, resulting in myocardial damage and impaired cardiac function. Preclinical studies employing streptozotocin-induced cardiotoxicity models have revealed crucial pathways related to diabetic cardiomyopathy, aiding the evaluation of potential cardioprotective interventions. Isoprenaline, a beta-adrenergic agonist, is known for inducing acute myocardial injury resembling cardiac ischemia and heart failure in animals. Its mechanism involves overstimulation of beta-adrenergic receptors, calcium overload, oxidative stress, and apoptosis. Isoprenaline-induced models have offered insights into acute myocardial injury pathophysiology and facilitated the screening of cardioprotective agents against Myocardial Infarction (MI) and injury. Antineoplastic drugs, such as cisplatin, doxorubicin, and 5-fluorouracil, are linked to significant cardiotoxic effects, including cardiomyopathy and heart failure. Animal models have revealed dose-dependent cardiomyopathy, shedding light on underlying mechanisms like oxidative stress, Deoxyribonucleic Acid (DNA) damage, and mitochondrial dysfunction. The article aims to consolidate the current understanding of the pathophysiology and mechanisms behind drug-induced cardiac damage. Additionally, it underscores the importance of using animal models in preclinical evaluations to assess drug safety and efficacy and to develop potential cardioprotective therapies.

Keywords: Cardiomyopathy, Chemotherapeutics, Doxorubicin, Cytotoxic agents, Cisplatin

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INTRODUCTION

This review includes information obtained from various research and review articles from the year 2000 to 2023 using multiple electronic databases such as ScienceDirect, PubMed, Scopus, repurposed drug database, Google Scholar, Web of Science, and Scirus. Search keywords used were cardiotoxicity, chemotherapeutics, streptozotocin, drugs-induced cardiotoxicity, experimental models for cardiotoxicity, doxorubicin, and mechanisms involved in the induction of cardiotoxicity.

Cardiotoxicity refers to the harmful effects on the heart caused by certain medications. This can lead to various issues like irregular heart rhythms, low blood pressure, rapid breathing, swelling, heart muscle damage, and changes in how the heart functions [1]. The main processes causing these problems include the formation of harmful molecules and an overload of calcium in heart cells, along with a lack of protective antioxidant systems and a potential immune response triggered by the drug. Cardiovascular diseases remain a leading cause of morbidity and mortality globally, emphasizing the urgency to develop novel therapies to improve patient outcomes. The potential side effects associated with current treatments are another concern that prompts the search for molecules that can protect without adverse impacts [2-4]. There is a growing need for molecules that can specifically target the inflammatory pathways revealing the intricate mechanisms underlying disease conditions. The evolving landscape of cardiovascular research and the continuous emergence of new challenges, such as drug-induced cardiotoxicity, also underscore the necessity for innovative cardioprotective molecules.

Experimental animal models serve as crucial tools to test and validate these cardioprotective molecules, providing insights into their mechanisms of action, potential side effects, and overall effectiveness. These models help bridge the gap between laboratory findings and clinical applications, offering a platform to assess the translational potential of new cardioprotective agents [5]. Chemically induced experimental models play a pivotal role in unraveling the cardiotoxic effects of specific drugs, including doxorubicin, streptozotocin, 5-Fluorouracil, and Cisplatin. Small rodents like mice and rats are commonly employed due to their genetic similarity to humans and ease of handling. larger animals, including rabbits, dogs, and pigs, offer advantages in terms of size and physiological relevance. Rabbits are often used to assess both acute and chronic effects, while dogs and pigs provide more intricate monitoring capabilities [6]. These models entail exposing animals to these drugs to systematically examine their repercussions on cardiac functions. The detrimental consequences encompass a diminished capacity of the heart to efficiently pump blood, instigation of oxidative damage, and the induction of irreversible injury to cardiac cells. It can also influence the heart's rhythm, metabolism, and structure, leading to problems like prolonged QT intervals that may cause fainting or dangerous heart rhythms [7]. The use of chemical agents can lead to long-term cardiovascular complications and, in severe cases, even death. This toxicity is associated with issues like blood clot formation due to damage to blood vessel linings, heart muscle oxygen depletion leading to ischemia, spasms in coronary arteries after ischemia, and reduced oxygen transfer by red blood cells, causing further heart ischemia. Such experimental models provide a controlled environment to meticulously study and comprehend the intricate mechanisms underlying drug-induced cardiotoxicity [8-10].

The necessity of animal models in the realm of cardiotoxicity is rooted in the rigorous scientific demands of developing new drugs, encompassing both herbal and synthetic cardioprotective agents. These models serve as indispensable tools for elucidating the intricate interplay between novel compounds and the cardiovascular system [11, 12]. Through systematic studies in animals, researchers can meticulously assess the safety profile of emerging drugs, delineate their mechanisms of action, and ascertain their potential efficacy in preventing or mitigating heart damage [13]. Furthermore, animal models facilitate the optimization of dosage regimens, enabling the identification of the most effective and tolerable concentrations. Importantly, the translation of preclinical findings to human relevance is a critical aspect addressed by animal models, aiding in the anticipation of potential risks and therapeutic benefits in clinical settings. Regulatory bodies mandate

comprehensive preclinical testing, including animal studies, to ensure the validity of safety and efficacy claims, thereby contributing to the eventual approval of new drugs. The incorporation of animal models in the investigation of cardiotoxicity aligns with rigorous scientific principles and serves as an indispensable step in the development and evaluation of new drugs and cardioprotective agents [14-16].

Drug-induced cardiotoxicity models in experimental animals

Drug-induced cardiotoxicity is a significant concern in drug development and safety evaluation. Experimental animal models play a crucial role in understanding the mechanisms of cardiotoxicity and assessing the potential cardiovascular risks of new drugs. Several chemotherapeutic agents, including 5-fluorouracil, streptozotocin, cisplatin, and doxorubicin, are known to cause cardiotoxicity and are frequently used to induce cardiac injury in animal models.

Doxorubicin-induced cardiotoxicity model

Doxorubicin is frequently employed to induce cardiotoxicity in rats or mice as a standardized model for evaluating cardioprotective drugs. This anthracycline chemotherapeutic agent is known to cause adverse effects on the heart, closely mirroring clinical manifestations observed in cancer patients [17-19]. Researchers utilize doxorubicin-induced cardiotoxicity due to its well-established and reproducible nature, allowing for consistent evaluation of potential cardioprotective interventions. The dose-dependent effects of doxorubicin enable researchers to modulate the severity of cardiac damage, facilitating the study of both acute and chronic cardiotoxicity [20, 21]. The multifactorial mechanisms involved, such as oxidative stress, mitochondrial dysfunction, and apoptosis, provide a comprehensive platform to assess the efficacy of cardioprotective drugs targeting specific pathways [22]. Additionally, the quantifiable endpoints, including changes in cardiac function, histopathological alterations, and molecular markers, offer objective measures for evaluating the effectiveness of interventions. However, the clinical use of doxorubicin is limited due to its dose-dependent progressive cardiotoxicity, including DNA damage, formation of free active oxygen radicals, apoptosis, etc [97]. The use of doxorubicin in rodents provides a clinically relevant and robust model to advance the understanding of cardiotoxicity, fostering the development of novel therapeutics for mitigating damage induced by chemotherapy and other cardiac toxicities [23-26].

The mechanism involved in doxorubicin-induced cardiotoxicity model

Oxidative stress in response to doxorubicin

Doxorubicin induces oxidative stress, a primary contributor to cardiotoxicity, by disrupting the balance between Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). This imbalance results in damage to subcellular structures, ultimately leading to regulated cell death. NADPH Oxidase (NOX) enzymes, particularly NOX2, play a role in ROS production during doxorubicin stimulation. Inhibition of NOX4 has shown promise in mitigating doxorubicin-induced cardiac injury. Doxorubicin also induces the expression of Inducible Nitric Oxide Synthase (iNOS), leading to the production of nitric oxide and superoxide anions, contributing to oxidative stress and DNA damage [27-34].

Doxorubicin-induced cell death during cardio-toxicity

Apoptosis, autophagy, pyroptosis, and ferroptosis are among the genetically characterized cell death mechanisms that are implicated in doxorubicin-induced acute cardiotoxicity.

Apoptosis

Activation of p53 is essential for the induction of apoptosis in response to doxorubicin. Additionally, the enzyme Poly ADP-Ribose Polymerase (PARP) is implicated in doxorubicin-induced cardiac apoptosis. The oxidative stress provoked by doxorubicin leads to the cleavage of PARP, releasing fragments that contribute to apoptosis and eventual cell loss. This cascade of events underscores the intricate molecular mechanisms involved in doxorubicin-induced cardiotoxicity [36-37].

Pyroptosis

Another type of cell death that contributes to the development of doxorubicin-induced cardiotoxicity is pyroptosis. In cardiomyocytes, doxorubicin causes cleavage of Gasdermin E (GSDME) and activation of caspase-3, leading to membrane rupture and pyroptosis. This is achieved by upregulating the production of the BH3-only protein Bcl-2/adenovirus E1B 19-kDa-interacting protein 3 (Bnip3) in myocytes [38-39]. Moreover, doxorubicin-induced the production of NLRP3 inflammasomes and activated Toll-Like Receptor 4 (TLR4), which in turn activated caspase-1 and gastrin D (GSDMD), facilitating the pyroptosis event [40].

Ferroptosis

Ferroptosis, a recently identified form of cell death, emerges as a contributor to the cardiotoxicity induced by doxorubicin. Upon doxorubicin treatment, there is a release of Fe2+and the formation of a doxorubicin-Fe2+complex within mitochondria, leading to an elevation in ROS levels and triggering ferroptosis, a process dependent on lipid peroxidation. Additionally, doxorubicin treatment inhibits the activity of Acyl-Coa Thioesterase 1 (Acot1), a key enzyme in lipid metabolism [41]. This dual impact of doxorubicin on mitochondrial function and lipid metabolism highlights the intricate interplay of molecular events leading to ferroptotic cell death in the context of cardiotoxicity.

Doxorubicin therapy also causes the immune system to release an assortment of pro-inflammatory facilitators such as interleukin-1, 6, 7, Tumor Necrosis Factor (TNF) receptor 2, vascular endothelial growth factor/VEGF, matrix metalloproteinases/MMP2); it also hinders the maturation of macrophages, stops Natural Killer (NK) cells from activating, and initiates responses from cytotoxic T lymphocytes [50]. Cardiomyopathy develops when doxorubicin elevates oxidative stress, which is linked to an increase in Toll-like receptors 2. Additionally, the TLR4 causes a rise in the amount of TNF-α [42, 43].

Animal models of doxorubicin-induced cardiotoxicity

Dulf *et al.*, (2023) investigated autophagy and oxidative stress indicators as potential mechanisms of myocardial toxicity induced by doxorubicin, utilizing echocardiography and electrocardiography for assessment. The findings revealed disturbances in autophagy and oxidative homeostasis as early as 7 d post-doxorubicin administration, preceding a significant increase in N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), a clinical marker of heart failure. Additionally, notable changes were observed in the electrocardiograms and echocardiograms of treated rats. Doxorubicin-induced cardiac cell injury was revealed as congested blood vessels, edema, a decrease in several nuclei, and fragmentation with necrosis. These results suggest that doxorubicin-induced myocardial toxicity may represent an initial stage in the progression of heart damage early in the therapy course [44].

Qi *et al.*, (2020) study showcased the induction of cardiotoxicity in male C57BL/6 J mice through a four-week protocol of intraperitoneal injections of doxorubicin administered at a dosage of 5 mg/kg per week. The cardiotoxic effects of doxorubicin were evident in the observed apoptosis and inflammatory response in cardiomyocytes. This was characterized by the upregulation of Caspase-3 and Bax expression, accompanied by a decrease in Bcl-2 expression levels.

Additionally, the Nuclear Factor-Kb (NF-κB) signaling pathways were enhanced, further contributing to the inflammatory response in the heart tissue of mice subjected to the doxorubicin-induced animal model of cardiotoxicity. The study demonstrated that the drug, through the suppression of the Nrf2 signaling pathway, heightened oxidative stress by promoting the production of ROS and elevating malondialdehyde levels. This increase in oxidative stress correlated with an augmentation in apoptosis and inflammatory responses within the hearts of the mice [45].

Desai *et al.*, (2012) developed a mouse model of chronic cardiotoxicity induced by doxorubicin to identify early predictive indicators of cardiac tissue damage incidents. Male B6C3F1 mice received weekly intravenous injections of doxorubicin for 4, 6, 8, 10, 12, and 14 weeks at a body weight-based dose of 3 mg/kg, resulting in cumulative doses ranging from 12 to 42 mg/kg. Mice exposed to doxorubicin for at least one week exhibited a significant decrease in body weight growth. Moreover, mice receiving cumulative doxorubicin doses of 24 mg/kg and higher displayed a dose-related increase in the severity of heart lesions. Mice with cumulative doxorubicin doses of 30 mg/kg and above showed a significant decrease in heart rate, suggesting potential drug-induced cardiac dysfunction. These findings collectively demonstrate the development of doxorubicin-induced chronic cardiotoxicity in B6C3F1 mice, providing valuable insights into the progression and severity of cardiac lesions in response to cumulative doxorubicin exposure [46].

Streptozotocin-induced cardiotoxicity model

Streptozotocin is a compound known to induce Diabetic Cardiomyopathy (DCM) in experimental models, particularly in both type I and type II diabetes. DCM is characterized by morphological and functional changes in the left ventricle, leading to left ventricular collapse, especially in diabetic individuals [47]. The pathogenesis of streptozotocin-induced cardiotoxicity involves various mechanisms that contribute to the development of DCM. One notable effect of streptozotocin is ventricular hyperplasia, a condition characterized by abnormal growth and development of heart tissue. Metabolic disorders and deviations in the extracellular matrix further contribute to the structural and functional alterations in the left ventricle. Coronary microvascular dysfunction is another consequence of streptozotocin-induced cardiotoxicity [48]. This dysfunction impairs the blood flow to the heart muscle, exacerbating the overall cardiac impairment. Oxidative stress, a condition where there is an imbalance between the production of ROS and the ability of the body to detoxify them, is a crucial factor in streptozotocin-induced cardiotoxicity. This oxidative stress can lead to tissue necrosis and damage. Myocardial injury caused by streptozotocin results in the release of Cardiac Troponins (cTn) from damaged myocytes. These troponins serve as biomarkers for cardiac damage and are indicative of the extent of myocardial injury. Streptozotocin-induced cardiotoxicity is also associated with the production of free radicals. Free radicals are highly reactive molecules that can cause damage to cells and tissues [49]. In the context of diabetes and streptozotocin-induced cardiotoxicity, free radicals are implicated in heart disease and can contribute to cell autophagy, a process of programmed cell death. Researchers have observed that hyperglycemia induces the cardiac muscle to generate excessive amounts of ROS. This increased oxidative stress plays a role in triggering apoptosis (programmed cell death) in the diabetic heart, contributing to the progression of diabetic cardiomyopathy. Streptozotocin-induced cardiotoxicity involves multiple interconnected processes, including ventricular hyperplasia, metabolic disorders, extracellular matrix deviations, coronary microvascular dysfunction, oxidative stress, tissue necrosis, and apoptosis. Understanding these mechanisms is crucial for developing potential therapeutic strategies to mitigate the adverse effects of DCM and other cardiac disorders [50-52].

The mechanism involved in the streptozotocin-induced cardiotoxicity model

Role of MAPK pathway in streptozotocin-induced cardiotoxicity

The Mitogen-Activated Protein Kinase (MAPK) pathway plays a pivotal role in the complex mechanism underlying streptozotocin-induced cardiotoxicity. Activation of the MAPK pathway is implicated in several key aspects of streptozotocin-induced cardiotoxicity. MAPK activation is linked to the inflammatory response observed in this condition. Streptozotocin-induced inflammation activates MAPK signaling, leading to the release of pro-inflammatory cytokines that contribute to myocardial damage [53]. Additionally, the MAPK pathway is intertwined with oxidative stress, a hallmark of streptozotocin-induced cardiotoxicity. ROS generated in response to streptozotocin can activate MAPK signaling, initiating a cascade that exacerbates oxidative damage to cardiac tissues. Moreover, the MAPK pathway is implicated in the regulation of apoptosis and cell death. Streptozotocin-induced cardiotoxicity is characterized by increased apoptosis in cardiac cells, and MAPK activation has been associated with the modulation of apoptotic pathways. Therefore, the MAPK pathway appears to play a critical role in mediating the inflammatory responses, oxidative stress, and apoptotic processes that contribute to the overall pathogenesis of streptozotocin-induced cardiotoxicity [54].

Role of ROS formation in streptozotocin-induced cardiotoxicity

Streptozotocin, commonly employed to induce diabetes in experimental models, elicits a robust generation of ROS in cardiac tissues, contributing significantly to the pathogenesis of cardiotoxicity. Elevated levels of ROS, including superoxide radicals and hydrogen peroxide, instigate oxidative stress, a condition marked by an imbalance between the production of these reactive molecules and the ability of cellular antioxidant defenses to neutralize them. ROS directly targets cellular components, including lipids, proteins, and DNA, inducing oxidative damage. lipid peroxidation, protein carbonylation, and DNA strand breaks are among the detrimental consequences of ROS accumulation. Such oxidative modifications compromise the structural integrity and functional capacity of cardiac cells, ultimately contributing to myocardial injury [55, 56].

Animal models of streptozotocin-induced cardiotoxicity

In a study conducted by Sabahi *et al.*, in 2021, diabetes was induced in rats through a single intraperitoneal dose of streptozotocin at 60 mg/kg. This induction of diabetes led to elevated levels of Creatine Kinase Isoenzyme (CK-MB) and lactate Dehydrogenase (LDH) in the serum, along with changes in Cardiac Catalase (CAT) and Superoxide Dismutase (SOD) activity. Additionally, diabetes prompted an increase in cardiac Thiobarbituric Acid Reactive Substances (TBARs) and carbonylated protein. Despite a slight increase in ROS production associated with diabetes, this stimulated the elevation of CAT and SOD activities in the cardiac tissue [57].

Alshehri *et al.*, (2021) delved into the potential of kaempferol in mitigating oxidative, inflammatory, and fibrotic damage in the left Ventricles (LVs) of streptozotocin-induced diabetic rats. The administration of streptozotocin significantly disrupted both systolic and diastolic functions in the lVs, leading to notable increases in ventricular collagen deposition, infiltration of inflammatory cells, and expression of pro-apoptotic proteins such as Bcl2-associated X protein (Bax) and cytochrome-C. Streptozotocin-induced diabetes was associated with a decline in body weight, elevated fasting glucose levels, and suppressed fasting insulin levels. Additionally, streptozotocin exposure heightened the levels of ROS, malondialdehyde, TNF-α, and interleukin-6. The study also revealed upregulation of Transforming Growth Factor-β1 (TGF-β1) and increased nuclear levels of NF-kB p65. Kaempferol attenuated DCM in streptozotocin-treated rats through its hypoglycemic and insulin-releasing effects, as well as a cardiac-independent mechanism that involves the activation of sirtuin 1 (SIRT1) [58].

In their study, Moore *et al.,* (2014) hypothesized that injections of streptozotocin were utilized to induce diabetes in CD1 mice of both sexes. Within 8 weeks of streptozotocin-induced diabetes, diastolic dysfunction was seen in female diabetic mice that were measured using echocardiography for functional and dimensional characteristics. Significantly higher levels of pro-apoptotic Caspase-3, microRNA-1, and microRNA-208a, and significantly lower levels of pro-survival Pim-1 were linked to this. At this moment, there were no significant alterations seen in male diabetic mice ($P<0.05$ compared to female diabetic mice) [68]. Furthermore, after 12 and 16 weeks of streptozotocin-induced diabetes, female diabetic mice showed a substantial dilatation of the left ventricle, a lower ejection fraction, and poor contractility ($P<0.05$) compared to male diabetic mice. These results indicate a speedier beginning of ventricular remodeling in these mice. Molecular examination of human diabetic heart tissues validated pre-clinical study findings, demonstrating a significant downregulation of Pim-1 in the female diabetic heart ($P<0.05$ compared to the male diabetic). In diabetic cardiomyocytes,

the female disadvantage was finally restored by the *in vitro* restoration of Pim-1 [59].

According to Wang *et al.*, 2020, the goal of their current study was to evaluate piperine's effects on rats that had streptozotocin-induced diabetic cardiomyopathy. Sprague-Dawley rats were divided into seven distinct groups after intraperitoneal administration of streptozotocin was used to develop diabetes in the animals. Piperine treatment substantially ($p<0.05$) reversed hemodynamic changes, suppressed cardiac markers, and repaired abnormal myocardial functions. Piperine therapy effectively ($p<0.05$) reduced the high degree of cardiac oxido-nitrosative stress and lowered cardiac Na-K-ATPase concentration following streptozotocin delivery. Additionally, piperine significantly ($p<0.05$) raised the activity of mitochondrial enzymes in the heart. Piperine therapy significantly ($p<0.05$) corrected the streptozotocin-induced modification in cardiac mRNA expression of Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), cTn-I, Bcl2, Bax/Bcl2, and caspase 3. The histopathological abnormalities caused by streptozotocin were reduced by piperine treatment. In conclusion, the current study indicates that piperine modulates the caspase-3, Bcl2, and Bax/Bcl2 pathways to attenuate streptozotocin-induced DCM [60].

5-Fluorouracil-induced cardiotoxicity

5-Fluorouracil is a widely used chemotherapeutic agent primarily employed in the treatment of various solid tumors, including colorectal, breast, and head and neck cancers. While effective against cancer cells, 5-fluorouracil is associated with cardiotoxic side effects that have led to increased interest in studying its impact on the cardiovascular system using rodent models. To investigate 5-fluorouracil-induced cardiotoxicity in rodents, researchers typically utilize mice or rats. The experimental design involves administering 5-fluorouracil to rodents through various routes, such as intravenous or intraperitoneal injection, to mimic clinical treatment scenarios. The dosage and duration of 5-fluorouracil administration are critical factors influencing the severity of cardiotoxic effects [61, 62].

5-Fluorouracil-induced cardiotoxicity involves a complex interplay of various cellular and molecular mechanisms, elucidating the intricate processes that lead to adverse effects on the cardiovascular system. One significant facet is endothelial dysfunction, whereby 5-fluorouracil impairs the function of the inner lining of blood vessels, compromising NO bioavailability and causing vasoconstriction. Concurrently, the drug induces oxidative stress by generating ROS within cardiac tissues, resulting in damage to lipids, proteins, and DNA. Furthermore, 5-fluorouracil triggers an inflammatory response in the heart, marked by the release of pro-inflammatory cytokines like TNF-α and interleukin-1β, exacerbating cardiotoxic effects. Thrombogenic effects are evident, increasing the risk of thromboembolic events [63]. Direct myocardial toxicity is also a key aspect, with 5-fluorouracil inducing apoptosis and cell death in cardiomyocytes, contributing to myocardial injury. Additionally, the drug disrupts mitochondrial function, impairs calcium homeostasis, interferes with DNA synthesis and repair, and activates programmed cell death pathways in cardiac cells. The potential interference with cardiac ion channels and electrophysiological properties adds another layer of complexity, possibly leading to arrhythmias. Understanding these multifaceted mechanisms is pivotal for the development of cardioprotective drug interventions designed to alleviate 5-fluorouracil-induced cardiotoxicity [64].

The mechanism involved in 5-fluorouracil-induced cardiotoxicity model

Role of 5-fluorouracil on cardiac functions and inflammatory markers

Currently, the primary mechanisms underlying 5-fluorouracil cardiotoxicity are believed to involve coronary artery spasm, endothelial injury-induced thrombosis, and oxidative stress. However, these proposed mechanisms are mainly derived from limited experimental studies, and there is a lack of standardized criteria for diagnosing and preventing 5-fluorouracil cardiotoxicity. Therefore, further in-depth research using animal models is necessary [65]. A single or several intravenous injections have been used by the majority of researchers to produce 5-fluorouracil cardiotoxicity in animal models, according to the literature currently available which closely resembles clinical application but may increase the risk of phlebitis. Commonly used experimental animals include rabbits and rats, as they allow for better observation of cardiac changes.

Some studies have employed multiple intravenous or intraperitoneal injections of 5-fluorouracil at varying cumulative doses to induce cardiotoxicity in rat models. These studies have reported symptoms such as depression, severe diarrhea, and loss of appetite in rats, along with extensive separation and distortion of myocardial fibers, accompanied by inflammatory cell infiltration around the cells. Additionally, markers of myocardial injury, including Creatine Kinase (CK), C-Reactive Protein (CRP), TNF-α, and interleukin-1β, were found to be elevated, indicating myocardial injury induced by 5-fluorouracil. Other investigations have utilized single intravenous or multiple injections of 5-fluorouracil in rabbit models to induce cardiotoxicity. These studies have observed large areas of hemorrhagic infarction in the rabbit left ventricular wall, multifocal necrosis of myocardial cells, and increased thickness of the left ventricular wall, indicating left ventricular dysfunction [66].

Studies of the myocardial antioxidant system in 5-fluorouracil-induced cardiotoxicity

Durak *et al.* conducted a study to investigate the impact of 5-fluorouracil treatment on the antioxidant system in myocardial tissue. They observed decreased activities of superoxide dismutase and glutathione peroxidase, along with increased CAT activity in female guinea pigs treated with 5-fluorouracil. In 5-fluorouracil-treated rats, the capacity for antioxidants was lower than in control animals, despite an increase in malondialdehyde levels. Reduced α-hydroxybutyrate dehydrogenase activity and a marginally elevated intramuscular malondialdehyde level were found. One study noted a 20% increase in iron levels in 5-fluorouracil-treated rat myocardial tissue compared to controls, while another study on open-chest guinea pigs did not find elevated iron levels in the myocardium following 5-fluorouracil infusion. Despite employing similar methods for iron content determination, the two studies utilized different species and dosages. Additionally, both studies found that copper levels in myocardial tissue remained unaffected by 5-fluorouracil treatment [67].

5-Fluorouracil-induced vasoconstriction

Three studies have demonstrated 5-fluorouracil-induced vasoconstriction. In two of these studies, vasoconstriction of the brachial artery was observed in patients immediately after 5-fluorouracil infusion. This vasoconstriction was transient, recurred with repeated injections of 5-fluorouracil, and was reversed by glycerol nitrate. Three out of the 31 patients treated with 5-fluorouracil had chest pain, according to Salepci *et al.*, but Südhoff *et al.* stated that none of the patients had signs of cardiotoxicity. The study by Salepci *et al.* found abnormalities in the electrocardiogram of five out of thirty-one individuals; however, the study by Südhoff *et al.* did not record electrocardiogram data. Mosseri *et al.*, used isolated rabbit aorta rings to study 5-fluorouracil-induced vasoconstriction *in vitro* [68]. They found that the prevalence and magnitude of vasoconstriction correlated with the molar concentration of 5-fluorouracil, regardless of the endothelial function of the aorta rings. Moreover, nitroglycerin abolished 5-fluorouracil-induced vasoconstriction, and acetylcholine-induced endothelium-dependent relaxation remained unaffected by 5-fluorouracil treatment. It appears from these data that endothelial relaxation pathways have no role in the vasoconstriction caused by 5-fluorouracil. Furthermore, pre-treatment with the Protein Kinase-C (PK-C) inhibitor staurosporine decreased the amount of 5-fluorouracil-induced vasoconstriction, but pre-treatment with the PK-C activator phorbol-12,13 dibutyrate enhanced the amount of 5-fluorouracil-induced vasoconstriction [69].

Animal models of cardiotoxicity using 5-fluorouracil

Studies by Safarpour *et al.,* (2022) and Refaie*et al.,* (2022) respectively demonstrated that administration of 5-fluorouracil (100 mg/kg) on the first day of a 14 d investigation and 5-

fluorouracil at a dose of 150 mg/kg on the 5th day of a 7 d experiment through intraperitoneal injection resulted in significant cardiotoxic effects in rats. Both studies found elevated levels of cardiac injury biomarkers, including aspartate aminotransferase (AST), Alanine Aminotransferase (ALT), lDH, CK-MB, and troponin I following 5-fluorouracil treatment, indicating damage to myocardial tissues [70, 71]. Oxidative stress markers such as malondialdehyde were increased, while antioxidants, like Reduced Glutathione (GSH) and Total Antioxidant Capacity (TAC), were diminished after 5-fluorouracil administration, suggesting the presence of oxidative damage. Refaie *et al.* also reported increases in inflammation markers like TLR4, MyD88, and NFκB. Apoptotic markers, including caspase 3 and endothelin receptors, were heightened, pointing to increased cardiomyocyte death. Histopathological examinations uncovered multifocal myofiber necrosis, pericarditis, hemorrhage, hyperemia, and other structural abnormalities, especially in the left ventricle. Overall, these findings from both studies demonstrate that 5-fluorouracil treatment induces oxidative damage, inflammation, apoptosis, and functional impairment in rat hearts, underlining the cardiotoxicity of this commonly used chemotherapeutic agent. In a 14 d study by Safarpour *et al.*, (2022), a single intraperitoneal injection of 5-fluorouracil (100 mg/kg) on the first day induced substantial cardiotoxicity, evidenced by elevated cardiac enzyme levels and increased expression of cyclooxygenase-2 and TNF-alpha. Histopathological examinations revealed notable degenerations, including high levels of cardiac intoxication, necrosis, and hyperemia. Furthermore, the treatment with 5-fluorouracil resulted in a decrease in body weight, TAC, CAT values, blood cells, and hemoglobin levels. Electrocardiographic parameters were also affected, displaying an increased elevation in the ST segment and prolonged QRS duration [72].

Gui *et al.,* (2023) conducted a 10 d study involving male Wistar rats, where a dose of 150 mg/kg body weight of 5-fluorouracil was administered *via* intraperitoneal injection on the 8th d. The researchers found that 5-fluorouracil exposure led to marked increases in serum and cardiac levels of cTn-I, CK, malondialdehyde, TNF-α, interleukin-1β, 6, NO, inducible iNOS, NF-κB and caspase 3 compared to control rats. Histological analysis revealed myocardial hemorrhage, cardiomyocyte necrosis, and infiltration of inflammatory cells. In another 5 d study, Rafai *et al.,* (2004) administered a single peritoneal injection of 5-fluorouracil at 150 mg/kg to male albino rats on day 1. They reported substantial increases in serum levels of cardiac enzymes, and tell-like receptors. IL16, Myeloid Differentiation Factor 88 (MYD88), heart weight to body ratio, malondialdehyde, and Sodium-Glucose Cotransporter 2 (SGLT2). Meanwhile, reduced GSH and TAC were markedly decreased. These observations collectively demonstrate that 5-fluorouracil induced extensive cardiac damage involving inflammation, oxidative stress, apoptosis, and compromised antioxidant defenses as evidenced by biochemical, histopathological, and physiological alterations [73].

Cisplatin-induced cardiotoxicity

Cisplatin, a widely employed chemotherapeutic agent effective against various cancers, is recognized for its efficacy in treating solid tumors. Despite its clinical success, the use of cisplatin is linked to notable side effects, including nephrotoxicity, ototoxicity, and cardiotoxicity. Given its potential for inducing cardiac toxicity, researchers have delved into drug-induced experimental cardiotoxicity in rodents to comprehend the underlying mechanisms and investigate potential protective strategies. In these experimental models, rodents such as mice or rats receive cisplatin *via* intraperitoneal administration, mirroring the clinical context. The parameters of cisplatin administration, encompassing dose, frequency, and duration, play a pivotal role in determining the extent and severity of cardiotoxic effects. Understanding these factors is crucial for elucidating the mechanisms at play and exploring interventions that could mitigate cisplatin-induced cardiotoxicity [74].

Cisplatin-induced cardiotoxicity involves intricate mechanisms that contribute to significant cardiac damage and dysfunction. A key factor is oxidative stress, culminating in lipid peroxidation of cardiac membranes and the degeneration and necrosis of cardiac tissue. Another critical aspect is the upregulation of transmembrane calcium transport by cisplatin, disrupting cardiac function. Additionally, cisplatin-induced DNA damage instigates apoptosis and necrosis of cardiac cells, with ensuing inflammation intensifying cardiac damage. Furthermore, the impact of cisplatin on neuregulin-1β signaling can lead to myofibrillar disarray, contributing to cardiac toxicity. Understanding these mechanisms is vital for developing strategies to mitigate cisplatin-induced cardiotoxic effects [75].

Mechanism involved in cisplatin-induced cardiotoxicity model

Studies have revealed that cisplatin cardiotoxicity arises from its cytotoxic effects, oxidative stress, and inflammatory processes. However, the precise mechanisms remain poorly understood, and there is currently no established protective agent against cisplatin-induced cardiotoxicity, necessitating further research using animal models. Despite limited literature on the establishment of animal models for cisplatin cardiotoxicity, additional studies are warranted for refinement [76].

Some researchers have mimicked cisplatin cardiotoxicity in animal models by administering intraperitoneal injections of the drug multiple times, with cumulative doses ranging from 12 mg/kg to 120 mg/kg, or by administering the injection once with a cumulative dose of 7 mg/kg. These models have demonstrated various signs of myocardial injury in mice, including cTnI, lDH, and CK-MB at elevated levels, myocardial fiber degenerative conditions and rupture, myocardial cell edema, vacuole-like degeneration, elevated myocardial apoptosis, and these conditions. Additionally, a rat model of cisplatin cardiotoxicity was established using a single intraperitoneal injection of cisplatin with a cumulative dose of 20 mg/kg, which resulted in increased levels of cTnI and lDH, suggesting myocardial damage in rats [77].

Animal models of cardiotoxicity using cisplatin

In a 10 d study by Turkmen *et al.*, (2022), a single dose of 7 mg/kg cisplatin was administered intraperitoneally in rats to induce Myocardial Infarction (MI). Cisplatin induction in the disease group led to a significant increase in the TBARS while SOD, CAT, glutathione peroxidase activities and total GSH levels were decreased significantly. According to the histological examination, histopathological differences such as necrosis, mononuclear cell infiltration, hemorrhage, and vascular occlusion were observed and the cardiac damage score was also increased in the cisplatin-treated group [78].

In another investigation, MI was induced through a solitary intraperitoneal administration of cisplatin in rats at a dosage of 12 mg/kg on the initial day of the experiment. Subsequently, saline was administered orally daily for 14 days. The impact of cisplatin manifested as a notable rise in lipid peroxidation and NO, levels, coupled with a significant reduction in GSH levels and Na+, K+-ATPase activity. Furthermore, heightened serum levels of cardiac marker enzymes such as CK-MB and cTnT were observed. Cardiac malondialdehyde demonstrated an increase, while SOD levels exhibited a decrease. Cytokines such as IL-1ß and TNF-α levels were also elevated. In another investigation, MI was induced by a single intraperitoneal injection of cisplatin in rats at a dose of 12 mg/kg on the first day of the experiment. Subsequently, saline was administered orally daily for 14 d. The impact of cisplatin manifested as a notable rise in lipid peroxidation, and NO, levels, accompanied by a notable decrease in GSH levels and Na+, K+-ATPase activity. Moreover, elevated serum levels of cardiac marker enzymes, including CK-MB and cTnT, were observed. Cardiac malondialdehyde demonstrated an increase, while SOD levels exhibited a decrease. Additionally, cytokines such as interleukin-1ß and TNF-α levels were found to be elevated [79].

Bayrak *et al.*, and Ibrahim *et al.*, respectively, demonstrated the cardiotoxic effects of a single intraperitoneal injection of cisplatin in rats at doses of 16 mg/kg on the 11th day of an 18 d study and in mice at a dose of 7 mg/kg on the 27th day of a 30 d study. The injections resulted in significant increases in Troponin I, CPK, CK-MB, malondialdehyde, and NO levels, coupled with reductions in GPx, SOD, Bcl-2 levels, and CAT [95]. Cisplatin administration induced disruptions in cardiac muscle fibers, loss of striations,

absence of intercalated discs, and pyknotic nuclei. Histopathological changes included degeneration, cardiomyocyte necrosis, fibrous tissue reaction, degenerative alterations, vacuolated cytoplasm, and engorgement of blood vessels [80, 81].

Adali *et al.* conducted a study where a single intraperitoneal injection of cisplatin was administered to rats at a dose of 15 mg/kg on the third day of a 5 d investigation. In the cisplatin-treated group, significant cardiac damage was evident, characterized by congestion, edema, and abnormal nuclei in myocardial fibers. The study observed a considerable decrease in the expression of the antiapoptotic protein Bcl-2 in the cisplatin group. Furthermore, the number of apoptotic cardiomyocytes was notably higher in the cisplatin-treated group. These findings collectively emphasize the detrimental impact of cisplatin on various cardiac parameters and structural integrity, providing insights into its potential cardiotoxic effects in experimental animals [82].

Isoprenaline-induced cardiotoxicity model

The sympathetic nervous system is responsible for preserving cardiovascular homeostasis and is primarily regulated by endogenous catecholamines such as noradrenaline and adrenaline. Catecholamines, however, have the potential to cause further cardiac problems because they are cardiotoxic under certain conditions. Arrhythmias, stress cardiomyopathy, acute MI, and chronic heart failure are among the recognized incidences [83, 84]. Catecholamines alone have the potential to cause infarctions, which is why they are used in experiments as a model of acute MI [83, 84]. Remarkably, compared to endogenous catecholamines, a synthetic catecholamine called isoprenaline with nonselective β-adrenergic agonistic activity has shown a higher capacity to simulate acute MI in experimental animals [85, 98].

The pathogenesis of isoprenaline-induced cardiac dysfunction is mostly understood to include the b-adrenergic receptor as well as catecholamines and their redox cycling, which includes the generation of ROS and a series of their oxidation products [86]. The first event in pathophysiology is the overstimulation of both β-adrenergic receptors in the cardiovascular system, even though oxidative stress is significant. Prolonged exposure to high levels of isoprenaline can induce oxidative stress, generating ROS and causing damage to cellular components. This oxidative stress, coupled with alterations in calcium handling, can lead to apoptotic and necrotic cell death pathways in cardiac myocytes, exacerbating myocardial injury. Additionally, isoprenaline-induced myocardial damage triggers an inflammatory response characterized by the release of pro-inflammatory cytokines and immune cell infiltration into the myocardium, further contributing to tissue damage [87, 89].

Animal models of isoprenaline-induced cardiotoxicity

Wu *et al.,* (2023) conducted a study involving 72 six-week-old wild-type female mice (C57BL/6). They were divided randomly into groups: a control group receiving normal saline and groups treated with increasing doses of isoprenaline (5, 10, 25, 50, and 100 mg/kg isoprenaline via intraperitoneal injections daily for 14 days). The 25 and 50 mg/kg isoprenaline groups showed significant weight changes and lower mortality compared to the control. These groups also exhibited reduced autonomous activity in the open-field test. Echocardiography revealed balloon-like apexes of the heart and left ventricular dyskinesia in the 25 and 50 mg/kg isoprenaline groups. Electrocardiography showed increased ST segment amplitude, QT interval, and Q amplitude in these groups. Histological examination of heart tissue showed a disordered arrangement of myocardial cells, dissolution of myocardial fibers, widened myocardial cell space, edema, and hyperemia in the interstitium, while control group tissue remained structurally intact. Additionally, the 25 and 50 mg/kg isoprenaline groups exhibited significantly higher levels of cortisol, BNP, cTn-T, and CRP compared to the control group. The study successfully established a high-incidence, low-mortality SC model by administering 25 and 50 mg/kg isoprenaline, which may serve as a basis for developing other animal models of SC [90].

Hosseini *et al.,* (2023) employed a subcutaneous injection of isoprenaline at a daily dosage of 85 mg/kg for two consecutive days (on days 8 and 9). The histopathological examination revealed that isoprenaline induced degenerative changes in the myocardium, along with inflammation and hemorrhage, resulting in an increased release of cardiac markers such as cTnT, lDH, CK-MB, and CPK, as well as elevated levels of malondialdehyde in cardiac tissue. Significant cellular damage, edema, congestion, tiny regions of bleeding, and focal infiltration of inflammatory cells, including neutrophils, lymphocytes, and macrophages, were observed upon microscopic assessment of the isoprenaline-treated group. Furthermore, the administration of isoprenaline resulted in a decrease in the concentrations of thiol content, CAT, and SOD. It also raised the levels of triglycerides, low-Density lipoprotein Cholesterol (LDL-C), and Very-Low-Density lipoprotein Cholesterol (VLDL-C), while concurrently decreasing the levels of High-Density lipoprotein Cholesterol (HDL-C). According to the study, enhanced adipose tissue lipid mobilization elevated cardiac cytosolic calcium levels, and heightened cyclic adenosine monophosphate levels could be the cause of the rise in serum lipids in rats after isoprenaline injection [91].

Abdelhalim *et al.,* (2021) conducted a study where rats were subjected to subcutaneous injection of isoprenaline at a dose of 100 mg/kg for 2 consecutive days to induce MI. The cardiac muscle of rats treated with isoprenaline exhibited a localized area of coagulative necrosis, as evidenced by the histological investigation. In addition, these rats' myofibers showed signs of MI induction, including thrombosis in blood vessels, loss of striation, hypereosinophilia, karyopyknosis, and macrophage infiltration in the interstitium. Moreover, the plasma concentrations of troponin-I and malondialdehyde were markedly increased with isoproterenol administration. Additionally, there was a noticeable rise in the activity of enzymes such as creatine kinase, lDH, and ALT. On the other hand, the cardiac homogenates of rats given isoprenaline had considerably lower concentrations of GSH and SOD activity. The generation of ROS by isoprenaline resulted in damage to cellular tissue structure, causing the release of enzymes such as CK, AST, ALT, and lDH into the bloodstream, thereby increasing their concentrations in the serum [92].

In a research study by Wang *et al.,*(2016), Incubation with different doses ranging from 0.015 to 0.0025 mol per liter for 24 h. isoprenaline-induced oxidative stress and apoptosis in H9c2 cardiomyocytes. The levels of SOD and GPx were downregulated as well as the levels of malondialdehyde were upregulated in isoprenaline-induced H9c2 cardiomyocytes. A further mechanism study indicated the induction of mitochondria-dependent apoptotic pathways and reduction of the expression levels of the Bcl-2 family. Isoprenaline significantly increases apoptotic rate compared with the control group. They found that when H9c2 cardiomyocytes were treated with isoprenaline, the expression levels of the pro-apoptotic proteins Bax and p53 were much higher than those of the control group, whereas the expression levels of the anti-apoptotic protein Bcl-2 were lower. Using western blot, they were able to identify both total and phosphorylated (active form)c-Jun N-terminal Kinase(JNK), Extracellular Signal-Regulated Kinase (ERK), and P38 MAPK. Following treatment with isoprenaline, there was a significant rise in the expression levels of p-ERK and p-P38. There are many parallels between human heart failure and isoprenaline-induced cardiac hypertrophy in rats [93].

Ojha *et al.,* (2010) demonstrated an isoprenaline-induced cardiotoxicity rat model in which an isoprenaline control group consisting of 15 rats was administered with saline p. o. with isoprenaline of dose 85 mg per kg s. c. for induction of myocardial necrosis in rats. In rats, the myocardial SOD, CAT, and GPx enzyme activity were significantly reduced with the treatment of isoprenaline. Because superoxide anions can be detrimental to the myocardium, increased generation of superoxide anions or inadequate clearance of superoxide anions was the cause of decreased SOD activity in isoprenaline control animals in this investigation. Through the process of neutralizing free radicals, the cellular tripeptide glutamyl cysteinyl glycine, or GSH, inhibits peroxidative damage. After the isoprenaline was administered, there was a noticeable drop in GSH. Free radicals produced in ischemia tissues were known to induce metabolic stressors, which in turn led to the breakdown of the tissue defense mechanism and subsequent cardiac damage and necrosisMoreover, after the injection of isoprenaline, we noticed a reduction in the myocyte injury marker

CK-MB isoenzyme and lDH, which indicate the degree of necrotic damage to the cardiac membrane caused by isoprenaline. MI can be diagnosed by looking for the leakage of the enzymes lDH and CK-MB. Determining the CK-MB isoenzyme and lDH is therefore a helpful metric for evaluating myocardial injury. Moreover, a histological analysis of the isoprenaline control group's heart cells revealed increased necrosis, edema, and inflammation [94].

Trastuzumab-induced cardiotoxicity

Trastuzumab is a type of medicine that targets a protein called Human Epidermal Growth Factor Receptor-2 (HER2), found on the surface of certain cancer cells. This medicine works by binding to the HER2 protein, which is produced by the HER-2 gene. This gene is associated with the growth of cancer cells. Trastuzumab is a humanized monoclonal antibody designed to combat tumor growth by specifically attaching the HER-2 protein on the surface of cancer cells. The potential effects of trastuzumab on the cardiac tissue were studied utilizing the model of cardiotoxicity in experimental rats. Varying amounts of trastuzumab were injected into the rats through the intraperitoneal route. This resulted in cumulative doses of 15.75 mg/kg, 48 mg/kg, and 60 mg/kg. The observed cardiac manifestations in the rats included myocardial fibrosis, reduced left Ventricular Ejection Fraction (LVEF) and Fractional Shortening (FS), increased left Ventricular End-Diastolic Diameter (LVDD), and End-Systolic Volume (ESV). Additionally, the rats exhibited elevated levels of serum lDH and cTnI, indicative of potential heart issues. In addition, a similar cardiotoxicity model was replicated in rabbits by injecting trastuzumab under the skin (subcutaneous injection) at a cumulative dose of 26 mg/kg. This caused infiltration of lymphocytes and macrophages around heart muscle cells, along with a decrease in lVEF, indicating impaired left ventricular function in rabbits [95]. Cardiac dysfunction with trastuzumab is often asymptomatic but can be symptomatic as well and the cardiotoxicity is aggravated with the prior use of chemotherapeutic agents like anthracyclines. Previously published literature showed that cancer therapy-related cardiac dysfunctions range from 13%-17% with trastuzumab [96].

Table 1: Overview of chemical-induced cardiac toxicity models in experimental animals

Model	Animal species used	Method	General condition	Cardiac structure and functions	Myocardial injury	Pathological changes of the myocardium	References
Doxorubicin	Mice	Single i. p. injection of 25 mg/kg	Chemotherapy	LVEF, FS↓	Heart failure and interstitial swelling	LDH↑, CK MB↑	[27]
Doxorubicin	Rat	A single i. p. injection of 10 mg/kg, 20 mg/kg in the tail vein	Decreased diet and activity, weight loss, and diarrhea	LVESV, lVEDV↑, lVEF↓	Cardiac fibers are twisted and injured, and myocardial cells are necrotic.	BNP, lDH, cTnT↑	[32]
Doxorubicin	Mice	Multiple i. p. injections of 4 mg/kg/w with an accumulative dose of 24 mg/kg	Weight loss	LVESV, lVEDV↑, lVEF↓	Collagen deposition and interstitial fibrosis in the heart	cTnI↑	[36]
5-Fluorouracil	Rat	A single intraperitoneal injection of 150 mg/kg or several intravenous doses of 8 mg/kg/d with a cumulative dose of 40 mg/kg or numerous intraperitoneal injections of 50 mg/kg/w with a cumulative dose of 300 mg/kg	Depression, severe diarrhea, loss of appetite	-	The myocardial cells are surrounded by inflammatory cells, and the myocardial fibers are severely twisted and divided.	CK, CRP, TNF-α, IL 1β↑	[61]
5-Fluorouracil	Rabbit	50 mg/kg intravenously as a single shot or 15 mg/kg/w with a total dose of 60 mg/kg		LVWT↑	The cardiomyocytes have lymphocytes and neutrophils infiltrating them, and they show multifocal necrosis.		[65]
Cisplatin	Mice	Four i. p. injections of mg/kg every two days, with a cumulative dosage of mg/kg, mg/kg, or mg/kg/2d, and a cumulative dose of mg/kg	-	-	Vacuum valvular degeneration, cardiac edema, cardiac fiber degeneration and rupture, and increased myocardial cell apoptosis	CK-MB, lDH,cTnI↑	[75]
Trastuzumab	Rat	A series of intraperitoneal injections at a dose of 2.25 mg/kg/d with a cumulative dose of 15.75 mg/kg or 6 mg/kg/d with a cumulative dose of 48 mg/kg, 20 mg/kg/w, or 60 mg/kg	-	LVEF, FS↓, lVDD, ESV↑	Myocardial fibrosis	LDH,cTnI↑	[95]

CONCLUSION

Utilizing chemicals like streptozotocin, isoprenaline, and anticancer medications such as cisplatin, doxorubicin, and 5-fluorouracil in experimental setups is crucial for comprehending their mechanisms in inducing cardiac damage in rodent subjects. These models reveal that anticancer drugs can damage the heart in different ways, including oxidative stress, DNA damage, and problems with mitochondria. For example, 5-fluorouracil harms the heart by causing various issues like inflammation, blood clotting, and directly damaging heart cells and ion channels. Streptozotocin models help us understand diabetic heart problems by showing how metabolic disorders and blood vessel issues lead to heart damage.

Isoprenaline models help study sudden heart injuries like heart attacks, aiding in finding treatments to protect the heart. Overall, these models are vital for testing drug safety and effectiveness and developing treatments to protect the heart.

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CONFLICT OF INTERESTS

The authors have no conflict of interest.

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