Chapter

Experimental Model of Cardiotoxicity

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Abstract

The occurrence of heart electrophysiology dysfunction or/and muscle damage is referred to as cardiotoxicity. The heart weakens and becomes less efficient at pumping and hence circulating blood. Cardiomyopathy can be caused by a variety of factors, including viral infections, diseases such as diabetes, ischemia, hypertension, obesity, radiation therapy, antipsychotic drugs, cytotoxic drugs, most notably chemotherapeutic agents; antitumor antibiotics, monoclonal antibodies, tyrosine kinase inhibitors, platinum-based compounds, microtubule inhibitors, vinca alkaloids, antimetabolites, proteasome inhibitors, topoisomerase inhibitors, alkylating agents, corticosteroids. This chapter focuses on the mechanisms of cardiotoxicity, animal models and transgenic methods used in studies, and the effects of therapeutic agents on cardiotoxicity.

Keywords: cardiotoxicity, cardiomyopathy, chemotherapeutics, diabetes, ischemia, radiation therapy, toxicants, transgenic animal models

1. Introduction

Globally, heart disease is responsible for a third of all deaths [1]. Cardiotoxicity occurs when the heart, in whole or in part, is damaged as a result of factors such as obesity, chemotherapy (CT), alcohol exposure, anorexia, neurosis, unconscious drug use, occupational and environmental heavy metal exposure [2–4].

Toxicants impair pumping efficiency by reducing the number of active myocytes, cause oxidative damage and lipid peroxidation, which results in cell swelling, altered Ca^{2+} homeostasis, and irreversible myocyte injury, alter aerobic metabolism, myocardial conduction, cell membrane function, directly damaged myocardium, and induce vascular changes [5]. They also cause QT interval prolongation and ionic channel blockage, which can lead to syncope and ventricular fibrillation. The heart weakens and becomes less efficient at pumping and thus circulating blood. Because of the high energy demands of the heart, it is susceptible to toxins that interfere with oxygen availability, carbohydrate metabolism, and oxidative phosphorylation [6, 7].

Cardiotoxicity is characterized by cardiac dysfunctions, arrhythmia (changes in heart rhythm), hypotension, tachypnea, edema, heart muscle damage (cardiomyopathy), changes in transmission pathways, and toxic effects on the heart [3]. Cardiotoxicity includes changes in resting cardiac measurements as well as dynamic functional evaluations of the cardiovascular (CV) systems [3, 5, 6]. The formation of oxygen free radicals and calcium overload in myocytes, a deficiency

of antioxidant systems such as catalase and superoxide dismutase, and a possible immunological reaction triggered by the drug are the main pathophysiological processes of cardiotoxicity [8]. Acute or subacute heart damage includes changes in the ventricular repolarization phase, the duration of the QT interval, arrhythmias, ischemia, acute heart failure (HF), and myocarditis-pericarditis-like syndrome. As a result of chronic (early/late) conditions, patients may have symptoms such as left ventricular (LV) dysfunction, systolic/diastolic impotence, and cardiac death [9, 10].

Cardiotoxicity is a well-known side effect of many cytotoxic drugs that can result in long-term morbidity.

2. Chemotherapy-induced cardiotoxicity (CIC)

The development of cancer screening methods, early diagnosis, and the widespread use of adjuvant chemotherapy can result in a significantly higher positive response rate in cancer treatment. Cancer drugs destroy cancerous cells in a variety of ways. These actions usually result in cell death (cytotoxicity), but they can also prevent the cell from growing without killing it (cytostatic action) [11].

Chemotherapeutics have a variety of modes of action, including alkylation of DNA, disruption of DNA and RNA synthesis by intercalating between base pairs, inhibition of DNA polymerase, stimulation of apoptosis, inhibition of DNA topoisomerase II, and preventing mitosis via altering tubulin polymerization. With this higher positive response, however, the number of people exposed to chemotherapy's early and late cardiac side effects emerges [12]. A wide range of adverse effects of chemotherapy and radiation on cardiac structure, hemostasis and thrombosis, cardiac dysfunctions and arrhythmias, and toxic effects on the heart have been well-documented [1, 13].

Side effects are common among cytotoxic drugs, notably chemotherapeutic agents; antitumor antibiotics, monoclonal antibodies, tyrosine kinase inhibitors, platinum-based compounds, microtubule inhibitors, vinca alkaloids, antimetabolites, proteasome inhibitors, topoisomerase inhibitors, alkylating agents, corticosteroids, and other drugs. They have the potential to cause long-term morbidity. They are linked to irreversible dilated cardiomyopathy and dose-dependent cardiotoxicity [14, 15].

Anthracyclines, a class of antibiotics derived from Streptomyces spp, have been used to treat a variety of cancers over the last 50 years, including lymphoma, leukemia, bladder cancer, breast cancer, and other metastatic cancers [16, 17]. Cardiotoxicity is a growing concern in clinical oncology due to the increasing use of anthracyclines, the introduction of new antitumor agents with potentially cardiotoxic properties, and the use of combined treatments that may have adverse effects on the heart [18, 19].

Anthracyclines catalyze intracellular oxygen radicals via enzymatic reactions in mitochondria, as well as non-enzymatic iron-mediated free radical reactions which damage DNA. They induce apoptosis in vascular cells and cardiomyocytes by activating caspases and degrading internucleosomal DNA [20]. When compared to other tissues, cardiomyocytes have a 35–40% larger amount of mitochondria. Cardiomyocytes use 90% of the ATP produced by mitochondria [21]. Due to bio-energetic failure, genotoxic stress, and oxidative stress, adenosine monophosphate-activated protein kinase (AMPK) signaling is suppressed during treatment, resulting in increased energy stress and hypertrophy [21]. Serum troponin levels in anthracycline-treated patients are also observed to be higher, indicating cell death [22, 23].

Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, and valrubicin are some of the most commonly used anthracyclines [17]. These drugs have similar effects on cardiotoxicity [24–26]. Following the existence of targeted therapy, doxorubicin is still widely used in cancer treatment today [10, 27]. However, anthracycline's medical use is limited due to dose-dependent and cumulative cardiotoxicity. The clinical efficacy of this drug is restricted due to its side effects, particularly cardiotoxicity when doses exceed 400–700 mg/m^2 for adults and 300 mg/m^2 for children [6, 7, 28]. Doxorubicin cardiomyopathy is more likely at 400 mg/m^2 (5%), at 550 mg/m^2 (26%), and at 700 mg/m^2, where the risk is as high as 48% [14].

A primary cause of doxorubicin-induced cardiomyocyte damage is assumed to be ROS (reactive oxygen species) generation and lipid peroxidation by inhibition of mitochondrial membrane potential and mitochondrial permeability transition pore [29]. To interfere with DNA replication, doxorubicin inhibits DNA topoisomerase 2-beta (Top2β) whereas a doxorubicin-Top2β DNA complex prevents the repair of damaged DNA and leads to cell death [27, 30, 31]. Doxorubicin also affects adrenergic function and adenylate cyclase inhibition of sarcoplasmic reticulum Ca^{2+} release, inhibits Ca^{2+}-ATPase activities causing diastolic dysfunction, reduces expression of cardiac-specific genes and down-regulates expression of a variety of cardiac muscle-specific proteins including mitochondrial proteins, contractile proteins, sarcoplasmic reticulum proteins [29]. Treatment with doxorubicin induces the immune system to generate a variety of inflammatory mediators (IL-1, IL-6, IL-7, TNF receptor 2, vascular endothelial growth factor/VEGF, matrix metalloproteinases/MMP2); natural killer cells stop functioning, cytotoxic T lymphocytes responses are triggered, and macrophage differentiation is inhibited [32, 33]. Doxorubicin cardiomyopathy increases oxidative stress, which is connected to an increase in Toll-like receptors 2, induces nuclear factor kappa B (NF-κB), and finally leads to apoptosis [34]. There is also an increase in the level of tumor necrosis factor (TNF-α) due to the toll-like receptor 4 [35].

The human epidermal growth factor receptor 2 (ERBB2) is a transmembrane tyrosine kinase receptor that plays in a variety of cellular processes, including cell survival in normal healthy tissue [36]. As a humanized monoclonal antibody, trastuzumab targets ERBB2 on the surface of tumor cells that overexpress ERBB2 [37]. Trastuzumab-induced cardiac damage was detected in metastatic breast cancer trials for the first time. It is the most common chemotherapeutic agent related to left ventricular dysfunction [38]. Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) activity in patients with metastatic colorectal cancer, non-small cell lung cancer, and breast cancer. Although, congestive heart failure (CHF) has been reported in a study, its overall incidence and relative risk are still unknown [39].

Tyrosine kinase (TK) inhibitors (TKI) are molecules designed to target TKs that are overexpressed in cancer cells, but they also inhibit normal variants of tyrosine kinases in non-cancerous cells, which can cause severe side effects such as left ventricular failure [40].

Imatinib is an ATP-competitive small-molecule ABL kinase inhibitor that was developed primarily for the treatment of malignancies such as chronic myeloid leukemia (CML) [41, 42]. It has been shown that imatinib leads to significant mitochondrial damage, including loss of membrane potential, the release of cytochrome C, and markedly reduced energy production with significant declines in ATP concentration, in studies on cultured cardiomyocytes [43, 44]. Other tyrosine-kinase inhibitors such as dasatinib, nilotinib, sunitinib, sorafenib, and lapatinib have been related to drug-induced cardiotoxicity, although the true extent of the damage remains unknown. The literature mentions only a few cases of asymptomatic QT prolongation, pericardial effusion, acute coronary syndromes [45].

Anticancer drugs based on platinum bind to DNA, causing it to crosslink. End result: cancer cells die through apoptosis because of the crosslinks, which interfere with DNA repair and synthesis in the cancer cells. Cisplatin, carboplatin, and oxaliplatin, platinum-based compounds with severe nephrotoxic, neurotoxic, and ototoxic properties, are frequently used in the treatment of human neoplasms [46, 47]. Vascular toxicity, hypertension, dyslipidemia, early atherosclerosis, and coronary artery disease are the most serious late effects of cisplatin-based chemotherapy in patients [48].

Taxanes (paclitaxel, docetaxel, cabazitaxel, Nab-paclitaxel) are microtubule inhibitors (MIT) or mitotic inhibitors that play an important role in mitosis and have lower cardiotoxicity than anthracyclines. Vinca alkaloids such as vinblastine, vincristine, liposomal vincristine, and vinorelbine are also mitotic inhibitors that are used to treat a variety of cancers such as breast, lung, myelomas, lymphomas, and leukemia. As a result, several trials have been conducted to evaluate their use in combination with anthracyclines [49–52].

Antimetabolites such as 5-fluorouracil (5-FU), capecitabine, azacitidine, cytarabine, gemcitabine, methotrexate, hydroxyurea, and pentostatin which are commonly used to treat leukemia, ovarian, breast, gastrointestinal, and other solid tumors, damage proliferating cells during the S phase of mitosis by substituting the normal DNA/RNA building blocks [53]. Endothelial injury followed by thrombosis; energy depletion and myocardial ischemia; coronary arterial spasm following myocardial ischemia; and decreased ability of red blood cells to transfer oxygen leading to myocardial ischemia are all associated with antimetabolite toxicity [54, 55].

Proteasome inhibitors (PI), which primarily function as immunosuppressants and inhibit bone resorption, such as bortezomib, carfilzomib, and ixazomib, are a promising new class of drugs for the treatment of multiple myeloma, and they are also being studied for other types of cancer [56]. As non-proliferative cells with increased proteasome activity, cardiomyocytes are particularly sensitive to proteasome inhibition.

DNA topoisomerases (type I and type II) are the enzymes responsible for DNA unlinking, and play critical roles in a variety of biological processes involving DNA. Several topoisomerase I inhibitors (also known as camptothecins) include irinotecan, topotecan, and camptothecin, while topoisomerase II inhibitors (also known as epipodophyllotoxins) include etoposide, mitoxantrone, and teniposide [57]. Topoisomerase inhibitors cause the release of ROS, lead to DNA breaks and prevent ligase repair. The enzymes catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are antioxidant enzymes in oxidative stress modulation, crucial for efficient removal of ROS. Cardiomyocytes are particularly vulnerable to damage because they have low levels of antioxidant enzymes required to detoxify ROS [58].

Cells are also prevented from reproducing by alkylating agents such as cisplatin, busulfan, mechlorethamine, temozolomide, dacarbazine, streptozocin, which damage their DNA [59].

Following are a few examples of *in vivo* models of chemotherapy-induced cardiotoxicity and protective agents based on the literature;

To explore cardiotoxic effects, animal models are being studied, and therapeutic approaches developed. Because considerable pharmacokinetic and pharmacodynamic data from studies examining the anticancer efficacy of drugs are available, rodents are an attractive model for studying cardiotoxicity.

In the initial periods of cardiotoxicity studies, rabbits were thought to be the standard model. In a study, scientists evaluated the protective effect of ICRF-187 (dexrazoxane, a drug used to prevent anthracycline-induced cardiotoxicity) in rabbits against chronic daunorubicin cardiotoxicity. For the experimental model, twenty-four male white rabbits were divided into four groups (group1; 25 mg ICRF-187/kg and 3.2 mg daunorubicin/kg, group2; daunorubicin (3.2mg/kg), group3;

ICRF-187 (25 mg/kg), group4; placebo). They treated animals six times at 3-week intervals over an 18-week period. Significantly different cardiotoxic effects were observed in animals treated only with daunorubicin and those treated only with daunorubicin + ICRF-187. Anthracycline cardiotoxicity was significantly reduced by pretreatment with ICRF-187 [60].

In another study, Zhang et al. divided 50 male Sprague-Dawley rats into three groups for a 15-day experiment: control (saline), doxorubicin (3 mg/kg), and doxorubicin+oxymatrine (12.5, 25, and 50 mg/kg) to detect oxymatrine's protective effects on cardiovascular diseases. Specifically, they found that oxymatrine pretreatment protected against doxorubicin-induced cardiotoxicity in rats' hearts by inhibiting the apoptotic pathway [61].

Zilinyi et al. investigated metformin's (anti-diabetic drug) protective role and its effect on autophagy in doxorubicin-induced cardiotoxicity. In the first group of four Sprague-Dawley rats, doxorubicin (3 mg/kg every second day) was administered intraperitoneally, metformin (250 mg/kg/day) was administered via gavage, and the third group received doxorubicin + metformin, while the fourth group was a control group for two weeks. Doxorubicin-treated myocytes were significantly thinner than those in the control group. Myocyte diameters in the doxorubicin + metformin group were nearly identical to those in the control group. According to the histopathological examination of heart tissue samples, metformin normalized autophagy [62].

In a doxorubicin-induced cardiomyopathy model, Erbaş and his colleagues described the therapeutic effects of liraglutide (LIR), oxytocin, and granulocyte colony-stimulating factor. Four groups of 32 rats were given, respectively, group I; placebo 0.9% NaCl saline solution at a dose of 1 ml/kg/day i.p. (doxorubicin + saline), group II; 1.8 mg/kg/day of liraglutide i.p. (doxorubicin + LIR), group III; 160 μg/kg/day oxytocin i.p. (doxorubicin + OX), group IV; 100 μg/kg/day filgrastim i.p. (doxorubicin + G-CSF (Granulocyte colony-stimulating factor)). It was revealed through the study's findings inflammatory activity and improved tissue integrity were found to be decreased in response to oxytocin treatment. Besides, LIR reduces levels of proinflammatory cytokines, lipid peroxidation products, troponin T, pro-BNP levels, and CASPASE-3 in doxorubicin-treated rats [63].

Arsenic trioxide and imatinib mesilate cardiotoxicity were examined in male Wistar rats. In the experiment, for ten days, arsenic trioxide (5 mg/kg) and imatinib mesilate (30 mg/kg) was given intraperitoneally and orally, respectively. As a result, the cardiac tissue of the combination-treated group showed fibroblastic proliferation, myocardial disorganization, and myocardial necrosis [64].

According to a study by Saleh et al., tadalafil (Tad) might protect against cardiac and vascular damage caused by the chemotherapy drug cisplatin (CDDP). Seventy-two male albino rats were divided into four groups: the control group, the CDDP (4 mg/kg) i.p. group, the Tad (0.4 mg/kg BW Tad i.p. daily) group, and the Tad +CDDP (0.4 mg/kg BW Tad i.p. + 4 mg/kg BW CDDP i.p) group. In the heart homogenate sample from CDDP treated rats, Tad was able to reduce blood pressure, heart rate, and levels of cardiac troponin, malondialdehyde (MDA), while increasing levels of reduced glutathione (GSH) and nitric oxide (NO) [65].

3. Radiation therapy-induced cardiotoxicity

Cardiotoxicity caused by radiation therapy (RT) is not only seen in adults, but also in children. High radiation exposure, being female, higher anthracycline cumulative dose, trisomy 21, and race are all risk factors for cardiotoxicity in children [66]. Since the early 1900s, ionizing radiation therapy has been utilized to treat cancer [67]. Along with medical advancements, the role of imaging modalities

in the administration of the treatment process has gradually increased, in addition to surgical and systematic treatment [68, 69]. Considering the significance of these procedures in the treatment process and in enhancing survival, heart problems from radiotherapy remain a risk [69]. Radiation-induced heart disease (RIHD) is an important cause of long-term non-cancer death after thoracic irradiation [70]. Studies have shown that people who live at least 5 years after diagnosis have a high rate of cardiovascular death [71]. Studies have shown that significant cardiovascular events usually occur within 10–15 years [72]. Lung cancer, mediastinal lymphoma, and breast cancer are cancers that are proximal to the heart and have the highest prevalence of RT, which means they have a significant risk of cardiotoxicity [73]. When Saika et al. looked at breast cancer radiotherapy treatment and heart failure risk, they discovered that women who had RT for breast cancer had a 10 times higher risk of heart failure than the control group, regardless of age or cancer type [74]. Cardiotoxicity from RT causes a worsening of cardiac function in a variety of illnesses, including cardiomyopathy, pericardial injury, coronary artery disease, and heart disease [75, 76].

The effects of factors such as the total radiation volume applied to the patient, the patient's age, the radiation exposure process, and the simultaneous use of cardiotoxic chemotherapeutic drugs such as anthracyclines are seen in radiation-induced heart diseases [1, 4]. Symptoms of these diseases include pericardial and myocardial fibrosis, rhythm disorders, conduction abnormalities, atherosclerosis, and heart valve injuries. Although, cardiac issues do not manifest themselves until later in life in people, evidence of cardiac toxicity can be found after 10–15 years of follow-up [1, 77]. It has been stated in the literature that RT may have detrimental effects on several important tissues in the heart [68]. In studies, it has been explained that the basis of the mechanism of cardiac damage caused by RT is related to microvascular changes and inflammation that causes longer-term fibrotic changes [1, 68, 78].

Following are a few examples of *in vivo* models of radiation-induced cardiotoxicity and protective agents based on the literature;

In the studies carried out so far, models have been created with different animals to create experimental animal models of cardiotoxicity. Some of these models are Male Albino rats [79, 80], Male Sprague-Dawley rats [63], Albino Wistar rats [81], male C57/BL6 mice [82].

Mezzaroma et al. used three-month-old C57BL/6J male mice in their study, and 12 of them were irradiated with a single 20 Gray (Gy) dose of radiation therapy, while the other six underwent sham-irradiation. They found that when compared to sham non-irradiated mice, radiation therapy-treated mice exhibited a 2-fold higher rate of myocardial interstitial fibrosis after six months [83].

Using Mast cell-deficient rats (Ws/Ws) and mast cell–competent littermate controls (+/+), researchers exposed the rats for six months to 18 Gy localized single-dose irradiation to investigate cardiac function. They found that mast cell–deficient rats had a higher upward/leftward shift in the left ventricular (LV) diastolic pressure-volume relationship, a decrease in vivo LV diastolic area, and a greater rise in the thickness of the LV posterior wall [84].

Dreyfuss et al. in their study aimed to develop a new mouse model to investigate the pathophysiological mechanism of RT-induced cardiotoxicity and to detect clinically targetable biomarkers of cardiac damage. They used 9–11 weeks of female C57BL/6 mice to form the model. Single radiation doses of 20, 40 or 60 Gy were given to the selected mice, with or without the adjacent lung tissue, using conformal radiation therapy to the cardiac apex. When the results were analyzed, perivascular fibrosis was seen 8 and 24 weeks after RT. The developed model can be utilized to incorporate radiomic and biochemical markers of cardiotoxicity to guide early treatment intervention and human translation studies [85].

In another study, Ibrahim et al. aimed to detect cardiac magnetic resonance (CMR) imaging markers of early RT-induced cardiac dysfunction. In the study, the effect of CMR on global and regional cardiac function and myocardial T1/T2 values at 2-time points after RT with the use of CMR in a localized cardiac RT rat model was investigated. Rats that received 24 Gy radiation, whole-heart radiation were compared to sham-treated rats. They concluded that MRI regional myocardial strain is sensitive imaging diagnostic for detecting RT-induced subclinical cardiac damage before global cardiac function was compromised [86].

4. Ischemic cardiomyopathy

Ischemia is another of the most typical cardiotoxic effects [87]. This term comes from the Greek language (isch means restriction and haema means blood) and refers to a situation where there is an imbalance between the demand for blood and the supply in the tissue [88]. Cardiomyocytes, unlike other tissue cells, do not store energy in the form of glycogen, hence the relationship between myocardial oxygen use and the amount of oxygen given to the myocardial cells is extremely delicate. Cardiovascular problems are further increased by myocardial ischemia [89]. Stress, aging, alcohol consumption, and poor nutrition are all risk factors [90]. 5-fluorouracil (5-FU), cisplatin, and capecitabine are the most common chemotherapeutic agents that cause cardiac ischemia as a cardiotoxic side effect [88, 91, 92]. Isoproterenol (ISP) is another drug that is commonly used to treat bradycardia and heart block, but it can cause myocardial ischemia [92]. 5-FU is a common anticancer drug that can cause cardiotoxicity and is related to myocardial ischemia. In this case, the potential mechanism that occurs in myocardial ischemia is indirectly induced coronary vasospasm. Coronary vasospasm may be caused by the synthesis of vasoactive compounds, intimal hyperplasia which results in hyperactive coronary arteries, or it can be myocardial cell damage that occurs as an autoimmune reaction in individuals who are susceptible to 5-FU. Eskilsson et al. investigated verapamil to see if it could protect against 5-FU-induced cardiac ischemia, but the results were not significant [88]. Capecitabine, another agent that is used in chemotherapy, is the oral prodrug of 5-FU. In other words, it is the inactive form of 5-FU, which is activated by thymidine phosphorylase in tumor cells. It is used for its advantages compared to 5-FU. However, capecitabine cardiotoxicity is also known to be reported in the literature [92]. In a case of cardiac ischemia associated with capecitabine-induced cardiotoxicity, acute onset of severe anterior chest pain is observed. The development of chest pain and ischemic changes on ECG is no more observed after capecitabine is ceased [93].

Isoproterenol (ISP) is a medication used to treat conditions such as bradycardia, Torsades de pointes (TdP), and heart block. However, ISP also generates free radicals, which cause oxidative stress. Underlying molecular mechanisms in ISP-induced cardiotoxicity include oxidative stress, the renin-angiotensin system (RAS), apoptosis, and DNA damage. All of these causes cell death and, as a result, cardiac injury, including ischemia [90].

Cisplatin is an antineoplastic drug based on platinum. It is used to treat tumors of the lung, ovary, sarcoma, and lymphoma. The most common cardiotoxic complications caused by cisplatin are thromboembolic events, including myocardial ischemia and infarction [94]. Depolarization of the mitochondrial membrane due to structural abnormalities is one of the mechanisms involved in cisplatin-induced myocardial dysfunction. Furthermore, the endoplasmic reticulum stress response is activated, and apoptosis and caspase-3 activity are increased in cardiomyocytes [95].

Arsenic trioxide (As_2O_3) is an anticancer agent used in patients with acute promyelocytic leukemia. Arsenic is a chemical element that can be consumed or absorbed through the environment, such as through water and air. Arsenic-related cardiopathological consequences include heart failure and arrhythmia. Caspase activation, mitochondrial disruption, and the pk53 and MAPK signaling pathways all contribute to apoptosis in arsenic cardiotoxicity [96].

Following are a few examples of *in vivo* models of ischemic cardiomyopathy and protective agents based on the literature;

Paclitaxel, a taxoloid drug, is a cardiotoxicity-inducing drug that causes ischemia, with mechanisms including oxidative stress and apoptosis [97]. Studies on mice have shown that L-glutamine protects against the cardiotoxicity of the anticancer drug cantharidin, which is similar to ischemia in its mechanism of action [98]. ISP is used in protective drug research to create acute or progressive cardiotoxicity in animal models. Curcumin, quercetin, coriander, Momordica, and Withania somnifera are plant-based agents that have been shown to reduce myocardial ischemia in ISP models [90]. The extract of the Spondias mombin plant was used as a treatment in an ISP model on rats. The findings strongly imply that the plant could be used as a cardioprotective treatment. Spondias mombin improves the contractility of the ISP model rat hearts, which are unable to pump blood due to ischemia [99]. Another ISP model investigation was conducted by Jain et al., and ferulic acid was found to be a cardioprotective agent for ISP-induced cardiotoxicity [100]. Pituitrin, like ISP, induces myocardial ischemia. Another rat model for cardiotoxicity is being investigated, and a flavonoid named latifolin derived from Lignum dalbergiae odoriferae was shown to protect against acute myocardial ischemia induced by pituitrin and ISP [101]. Zhang et al. investigated latifolin's cardioprotective effects on doxorubicin-induced cardiotoxicity. They determined that latifolin protects against the cardiotoxic effects of doxorubicin [102].

5. Diabetic cardiomyopathy

Diabetes mellitus (DM) is a heterogeneous metabolic disease characterized by chronic hyperglycemia resulting from defects in insulin action, insulin secretion, or both. Although, some of the patients die from acute metabolic complications such as ketoacidosis, hyperosmolar hyperglycemic state, and hypoglycemia, the main problem is the increased morbidity and mortality resulting from long-term complications of diabetes. Morbidity and mortality are related to decreased life expectancy and decreased quality of life due to diabetes-related complications [103]. The main cause of morbidity and mortality in diabetic patients is cardiovascular complications [104].

40% of DM patients have heart failure and cardiotoxicity. The increase in the incidence of these conditions is because insulin resistance is a risk factor [105]. Insulin desensitization greatly diminishes the important effects of insulin on heart tissue. It is expressed on many cell surfaces, including cardiomyocytes, where insulin receptor, ligand binding, and insulin receptor substrates (IRS) 1 and 2 are taken up. In addition to IRS1 and IRS2, regulation of the PI3K/Akt pathway is also important in the ERK and MAP kinase cascade. They provide control of metabolism and cell survival. One of the Akt isoforms, AKT1 is involved in the survival of cardiomyocytes; AKT2 is required for the modulation of genes involved in cardiac metabolism. AKT2 promotes glucose uptake through mobilization and fusion of GLU4-containing vesicles to the plasma membrane. Short-term activation of AKT shows cardioprotective effects, can increase glycolysis, and decrease oxidative phosphorylation. The long-term activity of AKT1 in the adult heart is associated with a higher risk of cardiac complications and reduced mitochondrial function [106].

Following insulin stimulation, AKT1 phosphorylates and blocks FOXO1 nuclear translocation, inhibiting the expression of proapoptotic proteins belonging to the Bcl-2 family. FOXO1 has emerged as one of the key players in chronic metabolic diseases, promoting hyperglycemia and glucose intolerance [107]. In physiological conditions, pro-survival stimuli were induced by insulin-suppressing FOXO1 activity via the PI3K/AKT1 pathway. Following stress stimuli, FOXO1 translocates in the nucleus and causes negative feedback on the insulin pathway via a JNK-dependent mechanism that greatly reduces IRS-1 activity [108].

The heart of healthy people without DM obtains 60–90% of its energy from free fatty acids (FFA) oxidation and the rest from lactate and glucose [109]. In patients with DM, glucose uptake is greatly reduced, FFA uptake is increased, and the metabolic balance shifts to lipid oxidation. Increased FFA oxidation is complicated by lipotoxicity and high levels of triglyceride synthesis causing myocyte apoptosis. Additionally, in the diabetic heart, increased lipid oxidation increases mitochondrial dissociation and oxidative stress, which can lead to decreased myocardial energy production and myocardial contractile dysfunction [110]. Hyperglycemia is an important component in diabetes-associated cardiotoxicity because glucotoxicity leads to cardiac dysfunction by inducing oxidative stress and producing enhanced glycation end products. In addition, hyperglycemia may activate the renin-angiotensin-aldosterone system (RAAS) and cause an increase in cell necrosis and fibrosis [111]. Another important component is the inflammation that occurs in diabetes. Expression of inflammatory cytokines such as tissue necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) is increased in the myocardium associated with myocardial contractile dysfunction [112]. In a study by Stentz et al., it was reported that acute hyperglycemic crises such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are associated with the inflammatory state and independently cause changes in proinflammatory cytokines, oxidative stress, and cardiovascular markers [113].

Increased leukocytes in the myocardium also contribute to the relationship between diabetes and cardiotoxicity. Pathological stresses such as hyperglycemia, hyperlipidemia, high RAAS, and advanced glycation end products (AGEs) stimulate the secretion of proinflammatory molecules, adhesion molecules, and danger-associated molecular patterns (DAMPs) from leukocytes. In addition, these triggers induce ROS-mediated endothelial dysfunction, which also causes cardiac remodeling. Secreted proinflammatory cytokines bind to receptors such as TLR4-MyD88 complex, the receptor for AGEs (RAGE), and IL-1R and initiate intracellular signaling pathways. These pathways activate NF-kB, resulting in transcriptional upregulation of inflammatory cytokines and NLRP3 inflammasome. NF-kB activation and increased oxidative stress mature IL-1B and IL-18 with induction of pyroptosis. At the same time, stressed and damaged cardiomyocytes contribute to inflammatory cascades by releasing pro-inflammatory cytokines and DAMPs. The chronic inflammatory cytokine-induced intracellular response causes pathological cardiac remodeling and cardiac dysfunction [114].

In summary, it involves complex and multifactorial mechanisms such as hyperglycemia, hyperinsulinemia, insulin resistance, increased free fatty acids, microvascular damage and inflammatory cytokines, changes cellular metabolic pathways in cardiomyocytes and contributes to cardiotoxicity by impairing heart function.

Following are a few examples of *in vivo* models of diabetic cardiomyopathy and protective agents based on the literature;

Rodent models of type 1 and type 2 diabetes share many features with human diabetic cardiomyopathy and have greatly advanced our understanding of the underlying pathology of diabetic cardiomyopathy. Each model has certain limitations, and there is no perfect model that fully phenotypes the human condition. Genetic heterogeneity and lifestyle differences among people make it difficult to produce a suitable model. Some studies with these models are given below.

In one study, empagliflozin treatment was applied to investigate the cardiac metabolic profile of Zucker diabetic fatty rats, which is an early-stage DMT2 model. This treatment activated the cardioprotective master regulator of cellular energy homeostasis, AMP-activated protein kinase, and decreased IL-6 and cardiac mRNA levels while increasing autophagy at the cardiac level. In addition, it reduced cardiac levels of the essential glucose mediators 2,3-bisphosphoglycerate and phosphoenolpyruvate, and regulated several amino acids important in the metabolic control of cardiac function, such as glutamic acid. Therefore, it has been proven that empagliflozin has a protective effect on the development of cardiometabolic diseases associated with cardiac bioenergetic dysregulation and cardiac lipidoma dysregulation [115].

In a study at the ERBAS Institute of Experimental Medicine, 12 rats were used to create a diabetic model after receiving an i.p injection of streptozocin. Rats were randomly assigned to one of two groups: the diabetes group, received 1 mL/kg saline, and the second one received 160 g/kg/day i.p oxytocin for 28 days. They found that oxytocin treatment reduced cardiac myocyte thicknesses significantly over a 4-week period. Besides, as plasma TGF-β levels increased in diabetic rats, oxytocin application significantly decreased plasma TGF-β levels [116].

In another study, rats with and without diabetes were used as models. The hearts of those predisposed to diabetes exhibited depressed contractility and ventricular relaxation at high filling pressures, and abnormalities in the contractile performance of these hearts were observed [117].

Diabetic patients suffer from dual stress on the heart: (1) diabetic cardiomyopathy caused by hyperglycemia and (2) cardiotoxicity caused by anti-diabetic drugs. The following drugs are used as a solution to cardiotoxicity [118].

Metformin (Met) is an oral biguanide antihyperglycemic drug commonly used in the treatment of type 2 diabetes. It activates AMPK and induces cardiac autophagy through the AMPK signaling pathway and improves cardiac functions. In other words, metformin activates AMP-activated protein kinases that play an important role in insulin signaling and fat and glucose metabolism [119]. Kobashigawa and colleagues demonstrated that the cardioprotective effect of metformin against DOX-induced toxicity is mediated through the upregulation of AMPK and its downstream target molecules [120]. However, treatment with high doses of metformin induces the same change in the AMPK pathway, but its protective effect is lost. The authors suggested that this may be due to the downregulation of the platelet-derived growth factor receptor. Moreover, silencing of adiponectin receptors suppressed AMPK activation and cell viability in metformin and DOX-treated cells [121]. In another study, metformin was able to activate AMPK, restore autophagy, and improve heart function [122].

Another drug, Pio, is hyperglycemic drug; it is FDA (Food and Drug Administration) approved and does not show liver toxicity, but cardiotoxicity. It stimulates the peroxisome proliferator-activated receptor (PPAR) γ, which controls the storage of fatty acids and glucose metabolism [123].

One study shows that curcumin has the potential to reverse cardiotoxicity caused by the anti-diabetic drugs Pio and Met. It confirms the generation of ROS in cardiomyoblasts upon treatment with anti-diabetic drugs that Pio is more toxic than Met. Curcumin significantly reduced the oxidative stress caused by anti-diabetic drugs and strengthened the built-in oxidative machinery. It also reduces mitochondrial changes and thus reduces apoptotic cell death of cardiomyoblasts *in vitro* [118].

6. Antipsychotic drug-induced cardiotoxicity

Antipsychotic drugs have been used to treat psychosis caused by a variety of disorders such as bipolar disorder, delirium, paranoia, schizophrenia,

substance-induced psychosis, Tourette's syndrome, dementia, Huntington's disease, multiple sclerosis, and parkinsonism. They come in a variety of forms and affect dopamine, serotonin, and other receptors as well as physiological systems. This can cause a wide range of negative effects, such as palpitations, akathisia, dystonia, tardive dyskinesia, orthostatic hypotension, tachycardia, arrhythmias, and heart failure [124]. Antipsychotics are grouped into two types: first-generation (typical, conventional or neuroleptics) antipsychotics (FGAs) such as butyrophenones, chlorpromazine, haloperidol, phenothiazines, thioridazine, and thiothixene, and second-generation (atypical) antipsychotics (SGAs) such as aripiprazole, asenapine, brexpiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidon, quetiapine, risperidone, ziprasidone. They can have a variety of effects on cardiovascular function, including direct effects such as blocking cardiac muscarinic receptors, blocking 1-adrenoceptors, blocking sodium, potassium, and calcium channels, and blocking calmodulin, causing QT prolongation as well as indirect effects such as blocking 2-adrenoceptors in the central nervous system (CNS). Antipsychotic drug-induced toxic cardiomyopathy has also frequently been linked to myocardial infarction [125, 126].

Clozapine, the only drug approved for resistant schizophrenia, comes with a warning for an increased risk of fatal myocarditis [124, 127].

Cyclic antidepressants, such as tricyclic and tetracyclic forms, were among the first antidepressants to be developed. TCAs (tricyclic antidepressants) inhibit norepinephrine and serotonin reuptake, leading to an overproduction of these neurotransmitters in the presynaptic cleft [128]. They also inhibit postsynaptic histamine, alpha-1 adrenergic, and muscarinic-acetylcholine receptors [129]. These tricyclic antidepressants were approved by the FDA for the treatment of depression and anxiety disorders: amitriptyline, amoxapine, desipramine, doxepin, Imipramine, nortriptyline, protriptyline, and trimipramine [130].

Most mortality from arrhythmias, hypotension, QTc prolongation, myocardial depression, and ventricular fibrillation is caused by cardiac toxicity, which is the most common side effect of TCAs. TCAs lengthen the cardiac action potential by inhibiting cardiac sodium channels and slowing phase 0 depolarization [131].

Amitriptyline (AMT) intoxication is the third most prevalent cause of mortality among prescription medication-related toxicities, after sedative-hypnotic drugs and analgesic drugs [132].

Following are a few examples of *in vivo* models of antipsychotic drug-induced cardiotoxicity and protective agents based on the literature;

In a study conducted at the ERBAS Institute of Experimental Medicine, they investigated and compared the electrophysiological, immunohistochemical, and biochemical effects of metoprolol, lipid emulsion, and $MgSO_4$ on AMT-induced cardiotoxicity. Thirty male Sprague-Dawley rats were used in the study. Five groups were given the following treatments: saline intraperitoneally (i.p.); AMT 100 mg/kg per os (p.o.) and saline i.p.; AMT 100 mg/kg p.o. and 5 mg/kg metoprolol i.p.; AMT 100 mg/kg p.o. and 20 ml/kg lipid emulsion. As a result of the study, the QT intervals were significantly prolonged in the AMT + saline group than in the other groups. The QT interval was significantly reduced in all the other groups when compared to the AMT + saline group. They reported that AMT has severe cardiotoxic effects and manifests with ECG abnormalities such as prolongation of QTc duration, which is crucial in cardiotoxicity. The study's findings also demonstrated that $MgSO_4$ was more potent than other treatments in AMT-toxic rats in terms of shortness of QTc prolongation and immunohistochemical/biochemical effects [133].

In their research, Erbas and his colleague examined the impact of metoprolol and diltiazem on ziprasidone-induced QTc prolongation. For the experiment, 24 rats were divided equally into four groups: I, control, II, 3 mg/kg ziprasidone and

saline, III, 3 mg/kg ziprasidone and 1 mg/kg metoprolol, IV, and 3 mg/kg ziprasidone and 2 mg/kg diltiazem. As a result, they observed that rats treated solely with antipsychotic drugs developed ECG abnormalities. When the QTc intervals of the four groups were compared, the QTc of the second group (ziprasidone + saline) was significantly prolonged than that of the control group. Moreover, in the study, metoprolol and diltiazem were found to have a beneficial effect on a prolonged QT interval [134].

A study on clozapine-induced cardiotoxicity was conducted using young male Wistar rats that were given clozapine (10, 15, and 25 mg/kg/day, i.p.) for 21 days. Clozapine, particularly at relatively high doses, was found to have a clear cardiotoxic effect after haemodynamic and echocardiographic studies were performed to assess cardiac functions. An increase in the serum activity of CK-MB (creatine kinase-myocardial band) and LDH (lactate dehydrogenase), two markers of cardiotoxicity, supported these findings [135].

7. Transgenic methods in cardiotoxicity research

Cardiotoxicity develops later as a result of stress, chronic diseases, cancer therapies, and immunotherapies in general, but it can occur *in vivo* and *in vitro* if the necessary genetic facilities are available. Mimicking proteomic and genetic disorders, in particular, can cause cardiomyopathies, cardiac transmission problems, and a variety of heart diseases. These models are created using a variety of transgenic methods. The method to be used in a study also varies depending on the pathophysiological mechanisms being studied.

The main methods for creating transgenic models are TALEN (transcription activation-like effector nucleases), CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9), sleeping beauty, piggyBac (PB), pronuclear microinjection (PMI), viral transgenesis, RNAi (RNA interference), and hiPSC (human induced pluripotent stem cells). Numerous studies are currently being conducted in which these methods are being used not only to create pathological models, but also to develop new treatment methods.

Following are a few examples of *in vivo* models of *transgenic methods* based on the literature;

Genetically modified cell lines are frequently used due to their ease of maintenance and manipulation. Unfortunately, cell culture results do not always accurately reflect human physiology.

hPSCs (human pluripotent stem cells) can be genetically reprogrammed and converted into iPSCs (induced pluripotent stem cells), which can then be used for functional analysis in a variety of studies. Isogenic hPSC lines derived from ZFNs (zinc-finger nucleases), TALENs, or CRISPR/Cas9 add to our understanding of a variety of cardiovascular diseases, particularly cardiomyopathies and electrophysiological disorders [136].

Disease models can be created in a matter of weeks using current gene-editing methods, including knock-in, knock-out or mutation of certain genes in experimental animals, such as rats. CRISPR/Cas9 systems have recently been used to edit DNA more efficiently based on direct injection of genome editing machines into single-celled mouse embryos. Various cardiovascular diseases have been studied in mammalian models, including but not limited to rats, rabbits, and pigs, to date. Even in zebrafish models alone, various cardiac development, cardiac regeneration, vascular development, and hereditary cardiomyopathy were studied. In addition to single-cell embryo studies, it has been demonstrated that somatic *in vivo* genome

editing studies in adult animals using CRISPR/Cas9 delivery via viral vectors and lipid nanoparticles are possible. Adenovirus and adeno-associated viruses (AAVs) are viral vectors that can be used to efficiently present genetic material in adult animals [136].

Several transgenic models of inherited arrhythmias have been described. Long-QT syndrome (LQTS-1/2/3/8/15), Atrial fibrillation (AF), Brugada Syndrome, and Catecholaminergic polymorphic ventricular tachycardia (CPVT) are just a few of the inherited arrhythmias that have been created using the hPSC [137].

LQTS: Ion channel genes KCNQ1 and KCNH2 with dominant-negative mutations that cause LQTS Type 1 and 2, respectively, were successfully integrated into the AAVS1 locus, which is considered a safe haven using ZFN technology and created an LQTS model in a study on iPSC-CMs (iPSC-Cardiomyocytes). The potential duration of action in regulated iPSC-CMs was significantly longer than in control cells that were not regulated as characteristic phenotypes of the long-QT syndrome, according to patch-clamp results [138].

Dermal fibroblasts from two people in a family with LQTS-1 and two healthy people were infected with retroviral vectors encoding the human transcription factors OCT3/4, SOX2, KLF4, and c-MYC and converted into hPSCs in another study [139]. Another research examined the therapeutic potential of new IKs activators in LQTS using dermal fibroblasts differentiated into hPSCs [140].

To create the LQT15 model, an electrophysiological study mimicked mutations in CALM2 from the CALM1, CALM2, and CALM3 genes that encode Calmodulin, a Ca^{2+} sensor on hPSC [141].

Transgenic models are also frequently used in studies on other types of Long QT Syndrome [142–147].

Brugada Syndrome: a large class of arrhythmias caused by a mutation in SCN5A (sodium voltage-gated channel alpha subunit 5), a cardiac sodium channel gene. Brugada Syndrome, Bradycardia, Atrioventricular (AV) Blocks, and Ventricular Fibrillation are few examples (VF).

A scn5a+/− (heterozygous knock-out) transgenic rat model was created for therapeutic evaluation, and the Brugada Syndrome phenotype was mimicked in a study [148]. The models created in a study targeting the SCN5A gene demonstrate cardiac conduction slowdowns and ventricular tachycardia (VT) [149].

In an *in vitro* study, dermal fibroblasts from two patients with Brugada Syndrome and two healthy individuals were differentiated to iPSC-CMs using Sendai virus (SeV) [150].

CPVT: The mutation in the RYR2 gene, which encodes the cardiac ryanodine receptor and is associated with CPVT cases, is modeled on hiPSCs differentiated from dermal fibroblasts via retrovirus [151].

The main cardiomyopathies investigated by developing transgenic models are dilate cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and restrictive cardiomyopathy (RCM).

Dilate cardiomyopathy: A study focused on striated muscle alpha-tropomyosin (α-TM), an essential thin filament protein involved in the pathogenesis of both dilate and hypertrophic cardiomyopathy. The Glu54Lys mutation, one of two prominent mutations in this protein (Glu40Lys and Glu54Lys), was expressed in transgenic rats. In echocardiography examinations, the successful dilate cardiomyopathy phenotype was observed [152].

In an iPSC-based study, an iPSC-CMs model was created from dermal fibroblasts from patients in a DCM family with a spot mutation (R173W) on the gene encoding cardiac troponin T (cTnT), a sarcomric protein [153].

In a study targeting Leiomodin proteins, which play a vital role in muscle thin filament length, the Lmod2 mutation was modeled in rats using the piggyBac transposon. It has been demonstrated that these rats with ventricular arrhythmias and increased postnatal mortality have a typical DCM phenotype [154].

In a recent study, a knock-in mouse model was created in which endogenous genes were altered to include the deletion of three base pairs encoded in cardiac troponin T for K210 in dilate cardiomyopathy patients [155].

In a study focusing on the titin protein, preserved blood samples from three DCM patients with the dominant TTN mutation were reprogrammed, and high-quality iPSC clones were expanded, differentiated, and enriched by metabolic selection to create a culture with >% iPSC-CMs. To analyze the effects of titin mutation on sarcoma structure, the iPSC-CMs method was created [156].

Hypertrophic cardiomyopathy: A transgenic hypertrophic cardiomyopathy model based on the erasure of 468–527 amino acids, which is bridged by the addition of a point mutation (G1445A) and 9 nonmyosin amino acids (SerSerLeuProHisLeuLysLeu) resulting in Arg403Gln, was created in a study targeting two mutations in the myosin heavy chain gene. Transgenic sequences were shown to be extracted from prokaryotic vector sequences, purified on agarose gels, and injected into the pronuclei of fertilized rat eggs [157].

In a comparative study, two different mutations (R92Q and E163R) in the TNNT2 gene, which encodes cardiac troponin T, were used. Echocardiography showed left ventricular hypertrophy, increased contractility, and diastolic dysfunction in both models. These phenotypes, however, were found to be more pronounced in R92Q mice [158]. HCM rat models with these two mutations had previously been described [159, 160].

In a study on the actin protein, the molecular mechanisms of apical hypertrophic changes were tried to be clarified in rat models created by a mutation (E99K) in the cardiac actin gene (ACTC). The phenotypic investigation of the created models was carried out using echocardiography, electrocardiography, magnetic resonance imaging, and a conductance catheter [161].

In a study examining the central role of calcium-related disorders in the disease pathogenesis in HCM, the iPSC-CMs model was created using fibroblasts derived from HCM patients with the Arg663His mutation in the MYH7 gene, which encodes the heavy chain of myosin [162].

A recent study used transgenic mouse models with the cardiac troponin-I mutation ($cTnI^{Gly146}$) to try to demonstrate that the exosomally derived Y-RNA fragment could regress the HCM clinic [163].

Restrictive cardiomyopathy: Mogensen and colleagues first described six different TnI C-terminal mutations linked to restrictive cardiomyopathy (L144Q, R145W, A171T, K178E, D190G, and R192H) in 2003 [164, 165].

In a study in RCM examining troponin mutations, transgenic rat models were explained by focusing on $cTnI^{193His}$ (R193H) and R145W mutations [165].

Numerous transgenic methods from the past to the present have developed *in vivo* and *in vitro* models that are commonly utilized to describe the pathophysiology of the disease. Aside from these studies, which look at the phenotypic manifestations of disease molecular mechanisms, the fact that transgenic approaches give hope for the treatment of numerous diseases has sparked a lot of research. Transgenic methods have therapeutic potential, particularly for cardiotoxic conditions induced by proteomic and genetic disorders that cannot be treated with drugs.

Besides these, R14del mutation in the phospholamban gene (PLN) is another important cause of cardiomyopathy development. Correcting this mutation on induced cardiomyocytes (iCMs) using the TALEN vector method resulted in improved Ca^{2+} handling, hypertrophic phenotype regression, and homogeneous

reticular distribution of phospholamban [166]. In another study using 3D human engineering heart tissue technology, the PLN R14del mutation disrupts cardiac contractility; however, the contractile function is restored in this model with TALEN-mediated genetic correction [167].

A study of the human embryo revealed that the heterozygous MYBPC3 mutation associated with HCM is corrected by an endogenous, germline-specific DNA repair response using the homology-directed repair (HDR) with CRISPR/Cas9, an up-to-date genome editing method [168].

Long QT syndrome is caused by three major mutations: KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) [169]. These mutations disrupt potassium flow or prolong inward storage flows, prolonging the potential duration of cardiac action and reducing repolarization reserve. According to a study that modeled the E637K mutation in KCNH2, potassium currents were also corrected to relatively close levels after transfection with an optimized siRNA targeted against the mutant potassium channel [170].

A study of CASQ2 knockout rat models reported that exogenous CASQ2 expression, provided via intraperitoneal adeno-associated virus serotype 9 (AAV9) vector, improves CPVT phenotype by correcting arrhythmogenic phenotype and ultrastructural abnormalities [171].

In addition to these models, studies on the therapeutic potentials of transgenic studies for heart failure (HF) have been conducted. An earlier study revealed that overexpression of SERCA2a in cells isolated from HF patients improved myocyte contractile function [172]. Furthermore, genetic therapies for Duchenne muscular dystrophy (DMD), which causes HF with cardiomyopathy, were emphasized. Previous research tried to improve dystrophin mutations using transgenic methods such as ZFN, TALEN, and meganucleases [173–177]. Even more recently, the CRISPR/Cas9 method was used with AAV to treat mice with dystrophin deficiency induced by a spontaneous mutation in the dystrophin gene [178]. The aim was to remove exon 23 from the dystrophin gene, provide partial functional dystrophin expression in skeletal myofibers and heart muscle, and increase muscle strength [179–181].

8. Conclusion

Cardiomyopathy is a serious disease in which the heart muscle becomes inflamed and does not work as well as it should. Although, that drug administration and radiation therapy for the disease have a higher positive response, the number of patients experiencing early and late cardiac side effects is growing. There are dozens of diseases related to cardiotoxicity described in the literature, each with dozens of distinct proteomic/genetic mechanisms. The difficulty in modeling and treating diseases stems from the fact that disease mechanisms emerge from a variety of causes that interact with one another in a complex structure. New therapeutic agents, advanced genetic editing technologies and the effective revelation of molecular mechanisms every day, however, are a beacon of hope for humanity to overcome these diseases.

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