Review Article

A Review on Effects of Cardiotoxic Drugs in Animal Models

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ABSTRACT

The major types of Cardiotoxicity in humans are mainly drug-induced, trauma, and stress-induced. Animal models for drug-induced Cardiotoxicity are generated by using various categories of drugs including anticancer, antiretroviral and antidiabetic, etc. Many of these drugs induce Cardiotoxicity via altering 'redox homeostasis' by rising the generation of oxygen radicals. Apart from this, many other drugs utilize a different pathway to promote cardiac damage. Here we describe the various categories of drugs that produce Cardiotoxicity by different mechanisms in various animals and cell line methods. Each category of the drug utilizes different pathways to induce Cardiotoxicity, leads to change in the enzyme level and *in vivo* parameters which can be used as biomarkers. This review gives an idea to the investigator for the section of appropriate animal models to achieve the objectives of the experiment. Identification of lead molecules and selection of a correct drug to induce Cardiotoxicity by using experimental data may allow the investigator to come out with desired outcomes.

KEY WORDS: Animal models, drug-induced Cardiotoxicity, biomarkers

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INTRODUCTION

A condition when there is the manifestation of electrophysiological dysfunction or impairment of heart muscles leads to Cardiotoxicity. Various pathological signs indicated in Cardiotoxicity are alteration in blood pressure and rhythm of heart, cardiac ischemia, and/ or myocyte death, which results in heart failure. Cardiotoxicity is caused due to administration of chemotherapeutic agents or other medications to control a group of diseases or disorders and incorrect drug administration. Adverse effects due to heavy metals consumption, if Cardiotoxicity becomes extreme which may lead to cardiomyopathy is also a cause of Cardiotoxicity[1].

From the preceding 5 decades, the meaning and finding of Cardiotoxicity have been unaffected; periodically Cardiotoxicity depends on the rate of heart failure and an indication of fall in left-ventricular ejection fraction (LVEF) [2]. The National Cancer Institute specifies Cardiotoxicity as "toxicity that affects the heart" [3]. Most accurately cardiac review and evaluation committee is overviewing the clinical trials define Cardiotoxicity as: "a) cardiomyopathy in terms of a decrease in left ventricular ejection fraction (LVEF), either global or more severe in the septum; b) symptoms associated with heart failure (HF); c) signs associated with HF, such as S3 gallop (ventricular gallop), tachycardia, or both; d) reduction in LVEF from a baseline that is in the range of less than or equal to 5% to less than 55% with accompanying signs and symptoms of HF" [1].

Cardiotoxic drugs are classified as primary and secondary cardiotoxic drugs. Primary cardiotoxic drugs produce expected dose-dependent and time-dependent cardiovascular adverse effects while secondary cardiotoxic drug which stimulates the cardiovascular adverse effect unexpectedly, often in patients with cardiovascular comorbidities. From 1994 to 2006- 45% of drugs were withdrawn due to adverse effects of the drug-like cardiac arrhythmia and cardiac ischemia-related side effects etc. viz rosiglitazone also sibutramine[4-6].

This review focuses on the various categories of the drugs that lead to Cardiotoxicity at the therapeutic dose level by distinct mechanisms. We will emphasize the various *in vivo* and *in vitro* parameters that fluctuate during Cardiotoxicity. Scientists across the globe use the battery of screening tests to understand the Cardiotoxicity of drugs. This review covers the various categories of drugs that produce Cardiotoxicity at the therapeutic dose level along with their mechanism of action of Cardiotoxicity. Moreover, the present review also focuses on the various suitable experimental models of Cardiotoxicity and also outlines the various parameters which alter during the experiment.

Drug-Induced Cardiotoxicity:

Classification of cardiotoxic drugs:

I) ***Anticancer drugs:***

A) Cytotoxic drugs:

1. Anthracycline and its analogs: Doxorubicin
2. Antimetabolite:
   a) Pyrimidine Antagonists: Fluropyrimidines
3. Anti-microtubules: (Taxans and vinca Alkaloids)
4. Alkylating Agent: Cisplatin

B) New targeted therapies

   a) Tyrosine-protein kinase inhibitors
   b) Monoclonal Antibody

II) Antiretroviral drugs: Zidovudine

III) Anesthetic drugs: Bupivacaine

IV) Antidiabetic drugs

   a) Thiazolidinediones: Rosiglitazone

b) Sulphonyal ureas: Glibenclamide

V) Antipsychotics

VI) Other drugs: cocaine, alcohol

Mechanism of drug-induced Cardiotoxicity:

I) Anticancer drugs:

Most of the anti-cancer drugs cause Cardiotoxicity/ cardiac dysfunction by mitochondrial dysfunction, free radical stress, and calcium overload, the immunological reaction after the oxidative stress[7].

A. Cytotoxic drugs:

1. Anthracycline and its analogs

This class includes the anticancer antibiotic doxorubicin and its analogs. Anthracyclins are the most consumed drug globally for cancer but it may lead to dose-dependent and schedule-dependent congestive heart failure (CHF) and also left ventricular dysfunction usually seen in women and patients with a history of cardiovascular complications[8].

Anthracycline-induced Cardiotoxicity occurs due to many mechanisms. Reductive activation of one or two electrons leads to the formation of semiquinone free radicals after the reduction of one electron from the quinone moiety. Quinone moiety again regenerates its parent quinone by reducing molecular oxygen to superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and reactive oxygen species (ROS). Generated free radicals cause an increase in oxidative stress and energy exhaustion, further disturbances the balance in -between prooxidant/antioxidant levels.

Copper-zinc and manganese, superoxide dismutase (SODs), catalase (CAT), and glutathione peroxidase cause elevated production of reactive oxygen species and reactive nitrogen (RNS) species, or both, in response to declining concentrations of anti-oxidant enzymes[9,10].

The reduction of two-electron from side-chain moiety leads to the conversion of anthracyclines to secondary alcohol-metabolites which is considered less active at redox cycling but very effective to dysregulate iron-calcium homeostasis[11].

Mitochondrial DNA damage might be the major contribution to the development of heart failure due to the accumulation of anthracycline drugs in mitochondria which then intercalated with the mitochondrial DNA, binds with its biomolecules leading to DNA oxidation and production of intramitochondrial ROS and RNA also inhibits topoisomerase II[12].

2. Antimetabolite:

(a) Pyrimidine antagonist

1. Fluoropyrimidines:

The cardiotoxic mechanism of 5-fluorouracil is not known exactly but according to some studies, fluoropyrimidines can cause a hemorrhagic infarction, interstitial fibrosis, and inflammatory reaction in the myocardium. It shows toxic effects on endothelial nitric oxide (NO) synthase of vascular endothelium which is the main reason to cause coronary spasm through protein kinase C and reduced capacity of RBCs to transfer oxygen[13-14]. Fluoropyrimidines enhance the metabolism of the myocardium that may cause energy diminution and ischemia. Fluoropyrimidines can cause cellular damage due to oxidative stress as a result of improved superoxide anion levels and reduced antioxidant capacity.

3. Antimicrotubules (Taxans & vinca alkaloids)

It has a novel mechanism of Cardiotoxicity. Antimicrotubules include drugs like paclitaxel or vinca alkaloids that show Cardiotoxicity by stimulating histamine release by acting on the receptor in cardiac tissues which leads to disturbances in rhythmic conduction of the heart ultimately turns into arrhythmia. Antimicrotubules may also show cardiotoxic effects like sinus bradycardia and ventricular tachycardia, atrioventricular(AV) node blockage, fall in the blood pressure, congestive heart failure, and myocardial ischemia, etc[15].

4. Alkylating agents

Alkylating agents like cisplatin elevates mitochondrial oxidative stress and mitochondrial membrane depolarization which induces cardiac dysfunction[16]. Cisplatin also changes endoplasmic reticulum function by stimulating stress response, augmenting caspase 3 activities, and increasing the apoptosis rate[17]. The alkylating agent cisplatin can cause an increase in thromboxane production by platelets to initiate aggregation of platelets, and trigger arachidonic-acid pathways in platelets[18].

"The cardiotoxic effect of cyclophosphamide is due to toxic endothelial injury followed by linkage of toxic metabolites which causes myocyte damage, interstitial hemorrhage, and edema" [19].

B. New targeted therapies

1. ***Tyrosine-protein kinase inhibitors:***

Imatinib mesylate, sorafenib, and sunitinib are a few examples of tyrosine kinase inhibitors that are indicated in gastrointestinal stromal tumors, renal cancer, and chronic myeloid leukemia.

It has been reported that individuals treated with tyrosine kinase inhibitors have developed cardiotoxicities that include CHF, cardiomyopathy, rhythmical disturbances, an extension of QT intervals, myocytes injury, and acute coronary syndromes". Hypertension and sudden death are most common to develop systolic dysfunction and cardiomyopathy"[20-24].

According to the research done on cardiotoxic effect caused by tyrosine kinase inhibitors(TKIs), it is observed that many proliferative pathways of cancerous cells play a vital role in cardiac muscles including homeostasis of mitochondrial and sarcoplasmic-reticulum (SR), electrical-impulses and inotropic function, survival signaling. TKIs show their effect on myocardial contractility, gene expression, cell viability, etc.

The endoplasmic reticulum stress response-induced

pro-death pathway that activates c-Jun N-terminal kinases (JNKs) up-regulation may be one probable mechanism for imatinib-induced Cardiotoxicity, leading to a delicate change in mitochondrial function and cardiomyocyte death[25-27].

2. *Monoclonal antibody*

Trastuzumab is a monoclonal antibody that specifically blocks the human-epidermal-growth-factor receptor2 (HER2)[28,29]. This drug is indicated in women suffering from advanced breast cancer where the HER2 protein is overexpressed in tumors.

Trastuzumab shows its cardiotoxic through HER2 blockade which results in disruption of neuregulin-1 (NRG-1) dependent responses leads to structural and functional changes, causes cardiomyocyte death. To tackle the above stress effects cardiac muscles activate the protective pathways through NRG-1 which triggers HER-4/HER-4 homodimerization and HER-4/ HER-2 heterodimerization.

Trastuzumab increases cellular oxidative stress and induces the expression of Bcl-2 and BAX which are pro-apoptotic factors. This results in mitochondrial defect via the opening of MPTP channels and subsequent activation of apoptotic pathways which causes myocardial dysfunction.

II. Antiretroviral drug

Zidovudine is a well-known drug from this class that is specifically used for the management of HIV patients. Zidovudine plays a disrupting role to cause cardiac dysfunction because it disturbs the mitochondrial DNA -polymerase enzyme which is accountable for DNA replication[30]. Few studies propose that it can directly inhibit the mitochondrial transport mechanism particularly mitochondrial ADP/ATP-translocator and mitochondrial-deoxynucleotide carrier as a result there is energy depletion which eventually leads to cardiac dysfunction[31,32].

III. Anesthetics drug

Anesthetics drug-like bupivacaine used as local anesthetics can cause mitochondrial dysfunction because of its action on carnitine-acyl-carnitine translocase which plays a vital role to carry carnitine-fatty acid complexes which give energy to cardiac mitochondria and carnitine which has a cardioprotective role across the inner mitochondrial membrane. Bupivacaine blocks carnitine-acyl-carnitine translocase which prevents entry of long-chain acylcarnitine inside the mitochondrial matrix & also circumvent the comeback of carnitine into the cytoplasm that results in a deficiency of L-carnitine which results in cardiac toxicity[33].

IV. Antidiabetic drug:

A. Thiazolidinediones

Rosiglitazone shows the adverse effect of a speedy increase in LDL-cholesterol and tendency of fluid retention which causes an elevated risk of CHF and myocardial infarction (MI) [34]. Rosiglitazone shows the effects like a fall in the rate of respiration, substrate oxidation rate, reduces glutathione content, suppresses superoxide dismutase, and also elevates malondialdehyde level, protein carbonyl 8-hydroxy-2 deoxyguanosine inside the mitochondria which leads to oxidative stress which causes mitochondrial dysfunction and energy deficiency.

Glitazone is an insulin sensitizer. Glitazone causes degradation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α). PGC-1α plays an important role to control mitochondrial biogenesis and metabolism, blocking of this by Glitazone leads to Cardiotoxicity[35].

B. Sulphonyl urea

Sulfonylureas like glibenclamide act directly on the mKATPs enzyme and inhibit it which is involved in the cardioprotective mechanism resulting in augmented reactive oxygen species (ROS) production and mitochondrial permeability cause necrotic cell death via a shift of mitochondrial permeability transition pore (MPTP)pore opening results in mitochondrial energetic dysfunction[35].

V. Antipsychotic drugs

Antipsychotic drugs including tricyclic anti-depressants (TCAs) show many cardiovascular side effects like sinus tachycardia & postural hypotension, peripheral anti-adrenergic effects, decreases in the force of contraction, adrenergic-α receptors blocking effects. TCAs show their effect on atrioventricular(AV) conduction by extending conduction time in the bundle of His and its branches which leads to delay the duration of the electrocardiographic complex(QRS) and QTc intervals[36]. TCAs show heart blockage due to their anticholinergic and quinidine-like actions by interfering with the re-uptake of mechanisms and myocardial depressant properties[36]. Other factors like elevated triglyceride (TG) and LDL-cholesterol levels, diabetes millets (DM), and weight gain are predisposing factors to cause Cardiotoxicity.

VI. Other drugs

Cocaine

Overactivation of the adrenergic system due to the misuse of cocaine is the major cause of cardiac side effects. Cocaine causes oxidative stress which leads to mitochondrial dysfunction on the molecular level initiated by the metabolism of excess catecholamines[37]. When catecholamine enters into the mitochondria it will go under redox cycling and converts into monochrome and produce a large number of free radicals.

Alcohol

Cardiotoxicity by the alcohol directly occurs by myocardial damage, the non-oxidative metabolism of alcohol produces fatty acid ethyl esters in the heart which dissociate mitochondrial oxidative phosphorylation leads to mitochondrial dysfunctioning[38].

Alcohol dehydrogenase enzyme required for the metabolism of alcohol which is not present in the

cardiac muscle cells but in the liver alcohol undergo oxidative catabolism and metabolized alcohol into acetaldehyde which may drop the production of myocardial protein leading to cardiac muscle cell damage this may lead to disturbance in calcium equilibrium as well as stability and boosting endoplasmic reticulum stress[39,40].

TABLE I: CARDIOTOXIC DRUGS AND THEIR EFFECTS ON ANIMAL MODELS REPORTED IN DIFFERENT STUDIES

Sr No	Drug	Experimental Model	Dose and route of administration	Parameters
1	Doxorubicin	ICR mice	20 mg/kg/bw, (*i.p.*)[41]	- Serum LDH & CK-MB determination - MDA, GSH, Cysteine, Myofibrillar loss and cytoplasmic vacuolization in heart tissue
		Dogs	1 mg/kg/bw (*i.v.*) [42]	- Blood Test: Complete Blood count (CBC), determination of total- protein/ bilirubin/lipids; lipid profile- Albumin/ Globulin/ Triglycerides/ Cholesterol. Urea, nitrogen, Creatinine, Glucose, Direct bilirubin, Uric acid. inorganic content- Sodium, Potassium, Phosphorus Calcium, Chloride. SGPT, LDH, Alkaline phosphatase, SGOT, CPK, Myofibrillar loss, and cytoplasmic vacuolization (Myocardial Alteration)
		Male Wister Rats	15 mg/kg/bw,(*i.p.*)[43]	- In heart tissue: GSH, GSSG, MDA, Protein Carbonyls. CAT, SOD, GSH-Px, GR - Serum: LDH, CK, CK-MB, Troponin, TNF-α, Nitric oxide I - Heart: LV end-diastolic posterior wall thickness and septal thickness (PWT and SWT), LV end-diastolic dimension (LVEDD)
		Spontaneously hypertensive rats	1 mg/kg/bw(*i.v.*)/wk for 12-week[44]	
2.	Daunorubicin (DAU)	Rabbits	3mg/kg/bw (*i.v.*) successively for 10 weeks [45]	- Renal parameters: Creatinine, Urea, Proteins, Albumin, Triglycerides, Cholesterol, Calcium - Blood: cTnT, Leucocytes, Erythrocytes, - Hemoglobin, Hematocrit, Mean Cell volume (MCV), Red cell distribution width (RDW) - Myocardial damage
3.	5-Fluorouracil (5-FU)	Rat cell line (H9c2), (HT-29)	5-FU 400 µM & 4 µM for cell line ((H9c2), (HT-29) respectively [46]	- The rat cardiocytes (H9c2) cell line: Thiobarbituric Acid-Reactive Species (TBARS), Nitrite assay, mitochondrial potential through FACS analysis.
		Guinea pig	400mg/kg/bw/d (*i.p.*), for 5 day[47]	- Heart: susceptibility to oxidation (SO), GSH-Px, CAT, GR Oxidation resistance (OR), Troponin T (cTnT), - Antioxidant potential (AOP) - Erythrocytes: SO, GSH-Px, CAT
4.	Paclitaxel	Male Wistar rats	7.5mg/kg/bw (*i.p.)*, successively for4 weeks [48]	- Serum: Total antioxidant capacity, Creatine-kinase (CK-MB), Malondialdehyde (MDA) - Cardiac tissue: Total nitrate/nitrite content, Histopathological Examinations
5.	Cyclophosphamide	Male Sprague-Dawley	20mg/kg/bw (*i.p.*) successively for3 weeks[49]	- Serum: lactate dehydrogenase (LDH), Creatine-kinase (CK), total cholesterol, triglycerides (TG), creatinine (Cr), urea, tumor-necrosis-factor-α (TNF- α), thiobarbituric acid, total nitrate, adenosine triphosphate (ATP), catalase, glutathione, and glutathione peroxidase. - Heart: Morphological changes
		Male Wistar albino rats	Single dose (200 mg/kg/bw), (*i.p.*) [50]	
6.	Cisplatin	Male Wistar albino rats	7mg/kg/bw, (*i.p*).[51]	- In the heart tissue homogenate: Reduced glutathione (GSH), Malonaldehyde (MDA), Catalase (CAT), Glutathione peroxidase (GSH-Px) - Histopathology of heart: Myocardial changes
			5mg/kg/bw, (*i.p.*) for 5 weeks[52]	Perfused heart: Left ventricular systolic and diastolic pressure, Heart Rate, TBARS, NO_2 level, SOD, Glutathione, CK, LDH, O_2, H_2O_2.
7.	Imatinib Mesylate	Male spontaneously hypertensive rats (SHRs)	50/100 mg/kg/bw for 14 days (*p.o.*) [26]	- Serum: Cardiac troponin - Histopathology: Myocardial lesions
8.	Trastuzumab	Mice	4mg/kg/bw/week, (*i.p.*)[53]	- On the heart: LV end-systolic internal diameter (LVIS), - Interventricular septal thickness (IVS), Posterior wall thickness (PWT), LV fractional shortening (LVFS), LV ejection fraction (LVEF)

9.	Zidovudine[54]	Rats	50 mg/kg/day for 14days	- On heart: ECG changes. - Histopathological studies of heart - Heart tissue (homogenate): ROS determination and effect on DNA, Creatinin phosphate, MDL, Alpha c-actin, Troponin C, Mitochondrial creatine kinase, Malate dehydrogenase
		Transgenic mice (depleted or overexpressed mitochondrial superoxide dismutase)	0.22 mg/day; 0.25ml orally 35 days in drinking water[55]	- Heart: Cardiac mitochondrial H_2O_2, aconitase activity, histology, and ultrastructure, echocardiographically
		Male OF1 mice	10 mg/kg/bw/day, for 35 days supplied in drinking water [56]	- Heart: Heart rate, Left ventricle end-diastolic dimensions (LVEDD), Anterior and posterior wall thickness (AWTH/ PWTH), - Heart homogenate: Oxidative damage- Malonaldehyde, Glutathione, SOD, CAT
10.	Bupivacaine	Male Sprague-Dawley rats	Bupivacaine: 2.0 mg/kg/min (*i.v.*)[57]	- Plasma: L-carnitine
		Dogs	10 mg/kg (*i.v.*)[58]	- Heart: Electrocardiogram (EKG), Arterial blood pressure, Myocardial pH (pHm) & pO2 (pmO_2)
11.	Rosiglitazone	C57BL/6 Mice	10 and 30 µM (isolated hearts)[59]	- Cardiac function and mitochondrial oxidative stress *in vitro* and *in vivo*- PCr, ATP, ATP/ADP ratio. - Heart homogenate: Mitochondrial dysfunction (decreases in respiration and substrate oxidation rates, and activities of complexes I and IV)
		Rat, db/db mice (H9c2 cell line)	50 and 60 µM [60]	- Superoxide dismutase (SOD), Catalase, Glutathione reductase (GR), Glutathione-S-transferase (GST), Glutathione peroxidase (GPx)
12.	Amitriptyline	Rabbits	10 mg/kg/hour (*i.v.*)infusion through marginal ear vein[61]	- Heart: P-R interval, widening of the QRS complex QRS complex, ECG
		Male Wistar rats	0.94 mg/kg/bw/min (*i.v.*) infusion [62]	- Heart: Mean arterial pressure (MAP), Heart rate (HR), QRS duration, the Survival rate
13.	Imipramine	Rabbits	18 mg/kg/hour, infusion through marginal ear vein[61]	- ECG changes: P-R interval, widening of the QRS, QRS complex
14.	Maprotiline	Rabbits	25 mg/kg/hour infusion through marginal ear vein[61]	- ECG changes: P-R interval, widening of the QRS, QRS complex
15.	Mianserin	Rabbits	35 mg/kg/hour infusion through marginal ear vein [61]	- ECG changes: P-R interval, widening of the QRS, QRS complex
16.	Cocaine	Dogs	7.5 mg/kg/bw, cocaine (*i.v.* boluses) [63]	- ECG changes - Serum concentration of cocaine
		Male Wistar albino rats	Intra arterially with cocaine (2 mg/kg/min) [64]	- Myocardial lesions
17.	Alcohol	Dog	Intravenous (*i.v.*) boluses of ethanol (1 gm/kg/bw) [63]	- ECG - Serum concentration of ethanol

CONCLUSION

Animal models for Cardiotoxicity are generated in mice, rats, dogs, and nonhuman primates by using various categories of drugs that recreate similar to the human pathological condition. Although oxidative and nitrosative stress provoked by anticancer drugs can lead to Cardiotoxicity and impair physiological cardiovascular functions. Cardiac dysfunction by mitochondrial membrane depolarization and some structural changes causes a rise in mitochondrial oxidative stress is considered as the major pathway to induce Cardiotoxicity. In the past, successfully many anti-oxidants drugs were tried to tackle drug-induced Cardiotoxicity. One can choose the most suitable drug -induced animal model and biomarker study based upon the character of the lead molecule to achieve the objective of the experiment.

In conclusion, although from the last decade much research is going on for the screening of cardioprotective drugs by implementing the drug-induced Cardiotoxicity models. But the pre-clinical outcome and clinical findings are not exactly parallel so close lab studies and clinical trials are required to be carried out by using some advanced techniques to get the most suitable animal models which resemble the human conditions.

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The author declares that this work was done by him and all liabilities about claim relating to the content of this article.

LIST OF ABBREVIATIONS

ADP: Adenosine diphosphate
AOP: Antioxidant potential
ATP: Adenosine triphosphate
AWTH: Anterior wall thickness
CAT: Catalase
CK-MB: Creatine kinase-MB
CPK: Creatine phosphokinase
cTnT: Troponin T
EKG: Electrocardiogram
FACS: Flow cytometry and fluorescence-activated cell sorting
GPx: Glutathione peroxidase
GSH: Glutathione
GSH-Px: Glutathione peroxidase
GSSG: Glutathione disulfide
H_2O_2: Hydrogen peroxide
HER2: Human Epidermal Growth Factor Receptor-2
HF: Heart Failure
IVS: Interventricular septal thickness
JNKs: c-Jun N-terminal kinases
LDH: Lactate dehydrogenase
LVEDD: Left ventricle end-diastolic dimensions
LVEDD: LV end-diastolic dimension
LVEF: left ventricular ejection fraction
LVESD: LV end-systolic dimension
LVFS: LV fractional shortening
LVIS: LV end-systolic internal diameter
MAP: Mean arterial pressure
MCV: Mean Cell volume
MI: Myocardial Infarction
mKATPs: mitochondrial ATP-sensitive K^+ channel
MPTP: Mitochondrial Permeability Transition Pore
NO: Nitric Oxide
NRG-1: Neuregulin 1
OR: Oxidation resistance
PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PWT: Posterior wall thickness
PWTH: Posterior wall thickness
RNS: Reactive Nitrogen Species
ROS: Reactive Oxygen Species
SGOT: Serum glutamic-oxaloacetic transaminase
SGPT: Serum glutamic pyruvic transaminase
SO: Susceptibility to oxidation
SODs: Superoxide dismutases
SR: Sarcoplasmic reticulum
SWT: Septal wall thickness
TBARS: Thiobarbituric Acid-Reactive Species
TCAs: Tricyclic Anti-Depressants
TKI: Tyrosine Kinase Inhibitors

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