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EVIDENCE FOR CARDIOTOXICITY ASSOCIATED WITH SERTRALINE IN RATS

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ABSTRACT

Sertraline is an antidepressant that is frequently prescribed to treat depression, obsessive-compulsive disorder, panic disorder, and anxiety. This drug had a safe cardiotoxicity profile, until the reporting of cases of sertraline-associated cardiotoxicities in the early 2000s. Since then, there have been conflicting results on the cardiotoxicity of this drug. In the study reported here we aimed to identify the cardiotoxic effects of sertraline by evaluating serum cardiac biomarkers, such as serum aspartate aminotransferase (AST), creatinine phosphokinase-myoglobin band (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin T (cTn-T) levels as well as electrocardiographic parameters, DNA damage in cardiomyocytes, and histological findings of heart tissue in rats that were administered oral doses of 5, 10, or 20 mg/kg of sertraline for 28 days. Additionally, to investigate possible mechanisms underlying cardiotoxicity, glutathione and malondialdehyde levels in cardiac tissue were determined to evaluate oxidative stress. According to our results, AST, LDH, and cTn-T levels were significantly increased in the 10 and 20 mg/kg sertraline groups when compared to the control group. Heart rates were increased, PR intervals prolonged, short QTc value was observed, and T-wave amplitudes were decreased significantly in the 20 mg/kg sertraline group when compared to the control group. Significant DNA damage was observed in the high-dose groups. Histopathological investigations also revealed some degenerative changes in the 10 and 20 mg/kg sertraline groups. Glutathione levels were significantly decreased in the 10 and 20 mg/kg sertraline groups when compared with the control group. In conclusion, our findings support the cardiotoxic potential of sertraline and also suggest that oxidative stress may play a role in the toxicity of sertraline.

Keywords: Sertraline, cardiotoxicity, cardiac biomarkers, ECG, DNA damage, oxidative stress

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INTRODUCTION

Drug-induced cardiotoxic effects are difficult to determine in the early stages of the drug development process. Therefore, cardiotoxicity is one of the most important reasons for the withdrawal of drugs from the market.[1] As it is known, the heart is physiologically and structurally very sensitive to the adverse effects of drugs. A large proportion of frequently used drugs have cardiotoxic effects.[2] In particular, patients with cardiovascular diseases are more susceptible to drug-induced cardiotoxic effects.[3, 4]

Patients with cardiovascular disease experience more depression and anxiety than the general population.[5-8] It is also known that patients with depression and anxiety are at risk of developing cardiovascular disease.[6, 7, 9, 10] Additionally, drugs that are used in the treatment of depression and anxiety have cardiotoxic adverse effects, including hypertension, orthostatic hypotension, tachycardia, bradycardia, blood pressure abnormalities, and abnormalities in the electrical activity of the heart.[11, 12] Although selective serotonin reuptake inhibitor (SSRI) antidepressant drugs are known to have safer cardiotoxicity profiles than tricyclic antidepressants, there is evidence in the literature that SSRIs have the potential for mild bradycardia, insignificant prolongation of QT intervals, dysrhythmia syncope, and orthostatic hypotension.[13-16] According to Beach et al (2014), SSRIs have given rise to slight QT interval prolongation, which is statistically significant and dose-dependent.[17] Recently, fluoxetine, paroxetine, and sertraline (SRT) were included in Group 4 of drug-induced arrhythmia classifications.[18] But, SRT does not have any significant electrocardiographic effects. Vascular effects of SRT include infrequent hypertension, postural hypotension, and, rarely, strokes.[19, 20] Studies show potentially clinically significant QT prolongation and electrocardiographic abnormalities only when SRT is taken concomitantly with other QT-prolonging medications or with SRT overdose.[21-23] Otherwise, it has been emphasized that CYP2B6 and CYP2C19 genetic polymorphisms in patients may influence SRT metabolism. Patients who have low enzyme activities will potentially be at a higher risk of adverse drug reactions, including cardiovascular adverse effects.[24-26]

Therefore, unlike studies performed previously, we evaluated cardiotoxicity by determining levels of cardiac biomarkers, such as serum aspartate transaminase (AST), creatine kinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin T (cTn-T) levels, ECG parameters, DNA damage in cardiomyocytes, and histological findings of heart tissue after SRT exposure at repeated pharmacological doses to rats in the present study. In

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addition, the effect of oxidative status, which has an important role in drug-induced cardiotoxicity, was determined.

MATERIALS METHODS

Materials

SRT was a kind gift from IE Ulagay-Menarini Group, (Istanbul, Turkey). The chemical used for anesthesia was obtained from the following source: urethane (Sigma-Aldrich, Steinheim, Germany). The kits used were obtained from the following sources: LDH Assay Kit (BioAssay Systems, CA, USA), CK-MB Assay Kit (BioCheck, CA, USA), AST (Cusabio Life Science, Hubei, PR China), Malondialdehyde (MDA) ELISA Kit (Cusabio Life Science, Hubei, PR China), Glutathione (GSH) ELISA Kit (Cusabio Life Science, Hubei, PR China), Rat Cardiac Troponin-T (cTn-T) ELISA Kit (Cusabio Life Science, Hubei, PR China).

Animals

Male Wistar rats weighing 200-250 g and 8-10 weeks old were obtained from Anadolu University Research Center for Animal Experiments. The rats were housed in a room with controlled temperature (24°C) for 12-h light/12-h dark cycle (lights on at 08:00 h) with free access to standard rat food and water. Animals were acclimatized to the laboratory environment for at least 48 h before the experimental session. The experimental protocol was approved by the Local Ethical Committee on Animal Experimentation of Anadolu University, Eskisehir, Turkey in adherence with the National Institutes of Health Guidelines for the Use of Laboratory Animals (File Registration No: 2014-15).

Experimental groups

The rats were assigned randomly into following treatment groups: *Control group*: animals received distilled water orally for 28 days (n=8). *SRT-5 group*: animals received 5 mg/kg dose of SRT orally for 28 days (n=8). *SRT-10 group*: animals received 10 mg/kg dose of SRT orally for 28 days (n=8). *SRT-20 group*: animals received 20 mg/kg dose of SRT orally for 28 days (n=8). The doses of SRT were determined according to the previous studies[27-29] investigating SRT-induced antidepressant and anxiolytic effects to obtain a dose-response relationship in therapeutic concentrations of SRT in rats and these doses were in accordance with the guidelines extrapolating human doses to animal doses.[30] All drugs were administered at a volume of 1 mL/100 g by dissolving in distilled water.

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At the end of 28 days, the animals were anesthetized by intraperitoneal injection of 1.5 g kg^{-} urethane.[31]

ECG recordings

ECGs were recorded through needle electrodes which were located right wrist, right ankle and left ankle (Lead II) using Biopac MP36 data acquisition system (Biopac Systems, Santa Barbara, CA). The changes in heart rate, PR interval, QT interval, QRS interval, QRS amplitude, and T-wave amplitude were determined from ECG in all groups. As known that, QT interval is dependent on heart rate, so the appropriate correction formula is used for resolving this problem. We calculated the corrected QT interval (QTc) according to normalized Bazett's formula that is QTc= QT / (RR / f)$^{1/2}$ suggested by Kmecova and Klimas.[32] The stored records were analyzed off-line and included measures of PR interval (from the beginning of the P wave to the beginning of the QRS complex; reflects conduction through the AV node), QRS complex (from the beginning of the Q wave to the end of the S wave; represents depolarization of the ventricles), QT interval (extends from the beginning of the QRS complex to the end of the T wave; reflects duration of ventricular depolarization and repolarization), and T wave (from the beginning of the QRS complex to the apex of the T wave; represents repolarizations of ventricles).[33]

Determination of serum cardiac biomarker levels

Blood samples for cardiac biomarker analysis (AST, CK-MB, LDH, and cTn-T) were collected via cardiac puncture from right ventricle of the anesthetized animals by using a syringe. After 30 min of drawing the blood to allow clotting, blood samples from rats were centrifuged at 1,000 g for 15 min at 4°C, and serum was separated. AST, CK-MB, LDH, and cTn-T levels were assayed according to the manufacturer's instructions.

The animals were euthanized via withdrawal of large amounts of blood from the right ventricle. Heart tissues were removed and cleaned of blood in a phosphate buffer solution (PBS) (composition: NaCl: 8 g/L, KCl: 0.2 g/L, KH_2PO_4: 0.2 g/L and Na_2HPO_4: 1.14 g/L at pH: 7.4). The heart specimens were stored in a refrigerator at –80 ºC until they were used in determining levels of GSH and MDA.

Determination of DNA damage in cardiomyocytes

The heart specimens were homogenized in a Potter Elvehjem homogenizator in 1.5 mL ice-cold Merchant's medium (pH 7.4). Aliquots of cell suspensions were then rapidly embedded

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in agarose. The comet assay was performed essentially according to the procedure described by Singh et al. (1988).[34] Frosted microscope slides were covered with 1% normal melting point agarose in phosphate-buffered saline. Heart cells (10 µL) containing 1 x 10^5 cell/ml was suspended in 75 µL of 1% (w/v) low melting point agarose. 85 µL of this suspension was applied to the surface of a microscope slide (pre-coated with 1% normal melting point agarose) to form a microgel and allowed to set at 4 °C for 5 min. The slides were immersed in a freshly prepared lysing solution (2.5 mM NaCl, 100 mM Na_2EDTA, 10 mM tris, 1% triton X-100, and 10% DMSO, pH 10) for 1 hour at 4°C. After lysis, the slides were immersed in electrophoretic buffer (1 mM Na_2EDTA, 300 mM NaOH, pH 12.5) for 20 min to allow the DNA to unwind and the alkali-labile damage to be expressed. The slides were then placed side-by-side in a horizontal gel electrophoresis tank filled with fresh electrophoretic buffer. After electrophoresis (24V, 300 mA, 20 minutes), the slides were washed for 5 minutes with a 0.4 M Tris buffer to neutralize the excess alkali, and were then stained with SYBR Green I (1:10.000) for 1 hour and covered with coverslips. Slides were viewed using an Olympus BX (Olympus, Tokyo, Japan) 50 fluorescence microscope. All measurement data were analyzed using BS 200 ProP with software image analysis (BS 200 ProP, BAB Imaging System, Ankara, Turkey). One hundred cells were scored on each slide. Results of the comet assay are expressed as extent tail moment, a product of the tail length and the tail DNA% (extent tail moment = tail length x tail DNA% / 100).[35]

Histological analysis of heart tissue

The heart specimens were fixed in paraformaldehyde (4%) in phosphate buffer pH 7.2 for 2 hours at 20 to 22 °C. They were dehydrated in a graded series of alcohols. In order to improve infiltration, the samples were treated with a mixture of LR White (Electron Microscopy Sciences, FT Washington PA) and 70% ethanol (2:1) (v:v) for 1 hour at 20 to 22 °C. The samples were then embedded in LR White and sectioned at 700 nm (0.7 microns) thickness by using a Leica EM UC7 ultramicrotome. Semi-thin sections were stained with 1% toluidine blue/borax (pH 8.4) for 2 minutes and observed under a Leica DM 750 light microscope.[36]

Determination of GSH and MDA levels in heart tissue

The heart specimens were diluted at the ratio of 1:20 (w:v) with cold buffer (50 mM MES, pH 6-7, containing 1 mM EDTA) and were homogenized. The homogenates were centrifuged at 10000 x for 15 minutes at +4 °C. The supernatants were removed and were deproteinized. Then, the samples were used for total GSH assay.

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The specimens were diluted 1:20 (w:v) with cold buffer (i.e., 0.25 M sodium phosphate buffer, pH 7.4, containing 0.05 M sucrose) and were homogenized. The homogenates were centrifuged at 10,000 g x for 15 minutes at +4 °C. The supernatants were used for MDA assay.

Statistical analysis

All data were expressed as mean ± standard error. Statistical analyses of the groups were performed on SigmaPlot v.10 package program (Systat Software, USA). All values were verified to be normally distributed. In the other experiments, One-way ANOVA followed by Tukey test as post hoc test was performed. $P < 0.05$ was considered statistically significant.

RESULTS

Effects of SRT administration on ECG parameters

According to our ECG recordings, heart rate was significantly increased in SRT-10 and SRT-20 groups compared to the control group. In the SRT-20 group, PR interval was significantly prolonged compared to the control group and also SRT-5 group. Although statistically significant differences were not observed between groups in terms of QT intervals, significantly decrease of the QTc value was determined in the SRT-20 group according to the control group. Furthermore, T-wave amplitudes of SRT-10 and SRT-20 groups were significantly decreased compared to the control group. Also, this decrease in SRT-20 group was significantly different from the SRT-5 group (**Table 1**).

Effects of SRT administration on serum cardiac biomarkers

When the groups were compared with control group in terms of serum AST levels, significantly increases were obtained in the SRT-administered groups. No significant differences were obtained among the SRT-administered groups (**Table 2**).

When serum CK-MB levels were compared between the groups, no significant differences were found between the SRT-administered groups compared to the control group (**Table 2**).

In the present study, serum LDH levels were significantly increased in 10 and 20 mg/kg SRT-administered groups compared to the control group. No significant differences were obtained among the SRT-administered groups. (**Table 2**).

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Compared to the control group, significantly increases were found in terms of serum cTn-T levels in the 10 and 20 mg/kg SRT-administered groups. No significant differences were found between the SRT-administered groups (**Table 2**).

Effects of SRT administration on cardiomyocyte DNA

Values of extent tail moment were as the following; 4.41 ±0.24, 4.65 ±0.22, 5.05 ±0.21 and 6.42 ±0.42 (mean ±standard error) for the control group, SRT-5, SRT-10 and SRT-20 groups, respectively. The control group and SRT-5 group did not show any significant damage. Exposure to 10 and 20 mg/kg SRT increased the tail moment when compared to the control group (**Figure 1**).

Effects of SRT administration on the cardiac histology

Microscopic examination of heart tissues from the control group and SRT-5 group revealed normal histological architecture and cardiac muscle structure. On the other hand, heart tissues from the SRT-10 group showed mild inflammation and few extravasation of red blood cells accompanying interstitial edema. Degenerative changes including irregular myofibrils, myofibrillar loss, inflammation, deformation of blood vessels and scattered extravasation of red blood cells accompanying intracellular and interstitial edema were observed in cardiac tissues of SRT-20 group (**Figure 2**).

Effects of SRT administration on GSH and MDA levels in cardiac tissue

GSH levels of heart tissues were decreased in the SRT-administered groups, this difference was significant in the SRT-10 and SRT-20 groups compared to the control group. There was no difference between the SRT-administered groups (**Table 3**).

When the groups were compared in terms of MDA levels in cardiac tissue, identical levels were obtained both in the control group and the SRT-administered groups (**Table 3**).

DISCUSSION

The cardiovascular adverse effects of SRT were investigated in repeated pharmacological doses in our study, which we performed independent of other risk factors related to cardiotoxicity. Pathological cardiovascular symptoms attracted attention in the 10 and 20 mg/kg SRT groups, especially in the 20 mg/kg SRT group. In our study, it was determined that serum AST, LDH, and cTn-T levels and heart rate were increased; PR interval was

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prolonged; short the QTc value was determined; the amplitude of T-wave were decreased; and DNA damage was induced with SRT administration in cardiomyocytes, dose-dependently. Hypertrophy, myofibrillar loss, deformation of blood vessels, edema, inflammation, and fibrosis were observed in the histological sections of the heart tissue in the 20 mg/kg SRT group, while mild inflammation, few extravasation of red blood cells, and interstitial edema were observed in the histological sections of the heart tissue in the 10 mg/kg SRT group. On the other hand, when the oxidative status in the heart tissue after SRT administration was evaluated, it was found that GSH level were decreased. Consequently, it could be concluded that detected cardiac toxicity findings were accompanied by oxidative stress in the cardiac tissue.

Myocardial injury is mostly caused by the deficiency of oxygen or glucose due to sudden reduction in blood flow in the coronary arteries; specific biomarkers from myocardial cells are then released to blood.[37] AST, LDH, total CK, and troponins are used to determine this damage and the elevation of these biomarkers is interpreted as a sign of myocardial injury.[38-40] Although alanine aminotransferase (ALT) and AST are known as biomarkers of hepatotoxicity, both of them, especially AST, are located in skeletal and cardiac muscles.[41] After a myocardial ischemia, blood AST level increases and remains at the elevated level for several days. Also, blood LDH level gains wide clinical acceptance. However, because this enzyme was also present in other tissues than the myocardium, its diagnostic specificity was limited. In spite of the limitation of LDH measurement it is clinically used because LDH concentrations remained elevated for up to a week after a myocardial injury.[42] On the other hand, cardiac troponins have the desired specificity, they have replaced the other enzymes for diagnosing myocardial ischemia and infarction.[42,43] In terms of serum AST, LDH and cTn-T levels were observed to be significantly increased after high doses SRT in our study. According to these results, it can be concluded that SRT administration induced myocardial injury, dose-dependently. Furthermore, this finding was also supported by myocardial hypertrophy and fibrosis, which are prognostic indicators of the myocardial injury observed in the heart tissues of the 20 mg/kg SRT group.

A heartbeat consists of myocardial contraction a depolarization (systolic) phase, and then a repolarization (diastole) phase, which is the stage of relaxation and other pulsation.[44] In our study, heart rate significantly increased in the high dose SRT group. Similarly, there are some studies that indicated SRT-induced tachycardia.[45-51] ECG is routinely used in the determination of cardiotoxicity induced by various agents.[1] An ECG is a recording of the heart's electrical activity as a graph consisting of PQRST complexes.[52] Anomalies in an ECG,

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such as prolonged PR interval, long QT, changes in T waves, and ST segments, are used for the detection of cardiac issues.[53] Our ECG recordings indicated that the PR interval prolonged, the QTc value shortens, and the T-wave amplitude decreased after high-doses SRT administration. The PR interval is the required time for an electrical impulse to be conveyed from the sinoatrial node via the atrioventricular-node to the Purkinje fibers.[54] Alterations in the PR interval may be physiological or may represent abnormal progression of electrical conduction from the atria to the ventricles through the atrioventricular-node. Prolongation of the PR interval is mainly related to a delayed impulse in the atrioventricular-node as well as delayed impulses in the atrium, His bundle, bundle branches, and Purkinje fibers.[54,55] Additionally, prolongation of the PR interval may indicate a first-degree heart block. The known causes of first-degree atrioventricular block are numerous, including ischemic heart disease and degenerative conduction system disease.[56] Furthermore, it is well known that prolongation of the PR interval is associated with an adverse outcome in structural cardiac abnormalities.[56, 57] Hypertrophic cardiomyopathy, which was observed in the rats that were administered high dose SRT, may have caused the prolongation of the PR interval. The QT interval reflects the total duration of ventricular myocardial depolarization and repolarization.[58] It varies with heart rate, and therefore a correction must be made before its interpretation.[59] Normalized Bazett's formula is one of the commonest formulas used for calculating QTc value.[60,61] As known that, drug-induced prolonged QTc is recognized as an important finding of cardiotoxicity by authorities. Recently, the concern is emerging about the pro-arrhythmic risk associated with QTc shortening. As compared with QTc prolongation, QTc shortening remains elusive. QTc shortening can predict arrhythmia and warrants further investigation.[62,63] Furthermore, change at repolarization phase such as T-wave abnormalities as a common marker of proarrhythmia[63] were observed in our study. Short QTc can cause depolarization and repolarization faster than normal in the heart muscle, leading to abnormal heart rhythms including atrial fibrillation, ventricular tachycardia, and ventricular fibrillation.[59,64] T-wave amplitude is a marker of ventricular repolarization. T-wave amplitude changes are associated with some ischemic conditions.[65-67] T-wave amplitude anomalies may also be a sign of the effect of myocardial hypertrophy on the repolarization phase.[68] Therefore, it should be emphasized that the hypertrophic changes observed in the myocardial structure of the 20 mg/kg SRT group may be the reason for the decreased T-wave amplitude. Furthermore, tachycardia may cause a decrease in T-wave amplitude by shortening the interbeat interval.[69]

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As with biochemical and ECG parameters, DNA damage in cardiac tissue is also used as a biomarker to determine xenobiotic-induced cardiotoxicity.[70-74] We performed the comet assay, one of the standard methods for assessing DNA damages, which includes single and double strand DNA breaks. Our results showed that SRT administration caused a significant increase in DNA damage in cardiomyocytes, dose-dependently. SRT-induced DNA damage may be due to the increased oxidative stress in cardiac tissue. Like other macro-molecules, such as lipids and proteins, DNA is also affected by oxidative stress, which results in oxidative DNA damage. Oxidative stress is known to be an important mechanism of xenobiotic-induced cardiotoxicity.[75-79] The heart is susceptible to oxidative stress because of its high energy metabolism, which causes the production of excessive free radicals, and its lower antioxidant mechanisms activity relative to other organs.[75] Oxidative stress occurs as a result of the imbalance between free radicals and antioxidants in the organism.[80] Our results showed that GSH levels in cardiac tissues after SRT administration were decreased, dose-dependently. The depleted level of cardiac GSH could be related to the increased utilization of this biomolecule for the detoxification process. Also, after excessive production of reactive species in myocardial cells could lead to cardiac GSH depletion. As known that, myocardial injury can be induced by the release of reactive species due to the infiltration of neutrophils, which produces reactive oxygen species and cytokines. [81] At this point, it could be emphasized that SRT administration did not affect MDA level in cardiac tissue. However, GSH comprises a system that maintains the intracellular reducing environment and acts as primary defense against excessive generation of harmful reactive species. So, determination of GSH level in tissue or blood after xenobiotic exposure can be accepted the most important biomarker to indicate oxidative status.[82-84]

In conclusion, our study, which investigated the effects of repeated SRT administration on cardiac parameters, indicated that SRT administration at high doses might have the potential to cause cardiotoxic effects. Therefore, the presence of cardiovascular risk factors such as sex, age, cardiovascular disease history, and electrolyte anomalies may be more critical for patients undergoing SRT therapy. Furthermore, patients who are poor metabolizers due to decreased CYP2B6 and CYP2C19 activities, which may have an impact on SRT metabolism, are at risk for developing cardiotoxic effects during SRT treatment. Therefore, it may be important to adjust SRT doses in the presence of these risk factors.

AUTHOR CONTRIBUTIONS

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SI conceived of the study, carried out the experimental design and drafted the manuscript. SI, participated in in animal handling and dissection, recording ECG, blood sample collection, biochemical assays and evaluation of the results. MB participated in animal handling and dissection, recording ECG, blood sample collection, biochemical assays and statistical analysis. GK participated in comet assay, histological analysis, evaluation of results and helped to draft the manuscript. VK participated in animal handling and dissection, comet assay, histopathological analysis, statistical analysis and evaluation of the results. SU participated in animal handling and dissection, comet assay and histopathological analysis. BD participated in animal handling, dissection, biochemical assays and statistical analysis. OA carried out the experimental design and coordination. OA participated in animal handling and dissection, recording ECG, blood sample collection, biochemical assays and evaluation of the results. OA helped to draft the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Table 1. Effects of sertraline administration on ECG parameters

	C	SRT-5	SRT-10	SRT-20
Heart rate (Beats/min)	280.33 ±3.97	279.00 ±3.92	299.57 ±1.70 (*)	399.86 ±3.44 (***, +)
PR interval (msec)	55.58 ±0.38	53.43 ±0.53	55.43 ±0.62	62.29 ±0.49 (*, +)
QT interval (msec)	59.67 ±0.35	54.50 ±0.67	60.16 ±0.27	63.00 ±0.45
QTc	43.84 ±1.00	41.22 ±1.22	42.03 ±0.63	38.85 ±1.77 (*)
QRS amplitude (mV)	1.16 ±0.02	1.13 ±0.01	1.13 ±0.01	1.18 ±0.01
QRS interval (msec)	13.00 ±0.14	14.50 ±0.37	13.25 ±0.09	12.71 ±0.15
T wave amplitude (mV)	0.34 ±0.003	0.36 ±0.01	0.26 ±0.01 (*)	0.18 ±0.004 (*, +)

C: Control group; SRT-5: 5 mg/kg sertraline administered rats for 28 days group; SRT-10: 10 mg/kg sertraline administered rats for 28 days group; SRT-20: 20 mg/kg sertraline administered rats for 28 days group.

All data were expressed as mean ± standard error.

* Significant differences when compared with control group ($P < 0.05$).

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*** Significant differences when compared with control group ($P < 0.001$).

+ Significant differences when compared with SRT-5 group ($P < 0.05$).

Table 2. Effects of sertraline administration on serum cardiac biomarkers

	C	SRT-5	SRT-10	SRT-20
AST (mU ml^{-})	197.10 ±0.68	267.25 ±7.62 (*)	266.15 ±5.91 (*)	302.52 ±1.50 (****)
CK-MB (ng ml^{-})	5.11 ±0.10	5.06 ±0.11	5.53 ±0.17	5.05 ±0.23
LDH (mU ml^{-})	20.30 ±0.82	44.80 ±2.23 (*)	51.95 ±1.09 (***)	36.86 ±1.58 (*, !)
cTn-T **(pg ml^{-})**	0.68 ±0.10	2.6 ±0.12 (*)	2.07 ±0.02 (*)	2.85 ±0.16 (*)

AST: Aspartate transaminase; CK-MB: creatine kinase-myocardial band; LDH: Lactate dehydrogenase; cTn-T; Cardiac troponin T. C: Control group; SRT-5: 5 mg/kg sertraline administered rats for 28 days group; SRT-10: 10 mg/kg sertraline administered rats for 28 days group; SRT-20: 20 mg/kg sertraline administered rats for 28 days group.

All data were expressed as mean ± standard error.

* Significant differences when compared with control group ($P < 0.05$).

*** Significant differences when compared with control group ($P < 0.001$).

Table 3. Effects of sertraline administration on GSH and MDA levels in cardiac tissue

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	C	SRT-5	SRT-10	SRT-20
MDA (nmol ml⁻)	1401.79 ±22.60	1240.76 ±7.93	1242.85 ±9.45	1201.02 ±11.92
GSH (µM)	54.67 ±1.67	45.19 ±1.31	35.35 ±2.72 (*)	39.52 ±0.76 (*)

GSH: glutathione; MDA: malondialdehyde. C: Control group; SRT-5: 5 mg/kg sertraline administered rats for 28 days group; SRT-10: 10 mg/kg sertraline administered rats for 28 days group; SRT-20: 20 mg/kg sertraline administered rats for 28 days group.

All data were expressed as mean ± standard error.

* Significant differences when compared with control group ($P < 0.05$).

Figure legends

Figure 1. Effects of sertraline administration on cardiomyocyte DNA

(a) Tissue comet assay photo of control group; (b) tissue comet assay photo of SRT-5; (c) Tissue comet assay photo of SRT-10 (d) Tissue comet assay photo of SRT-20; (e) Tail moment graph: C: Control group; SRT-5: 5 mg/kg sertraline administered rats for 28 days group; SRT-10: 10 mg/kg sertraline administered rats for 28 days group; SRT-20: 20 mg/kg sertraline administered rats for 28 days group. (Scale bars: 10 µm in a-d)

*Significant differences when compared with control group ($P < 0.05$)

+ Significant differences when compared with SRT-5 ($P < 0.05$)

Significant differences when compared with SRT-10 ($P < 0.05$)

Figure 2. Effects of sertraline administration on the cardiac histology

Longitudinal (a, b, c, d) and cross (e, f, g, h) sections of cardiac muscle in control and experimental group rats. (a, e) Control group demonstrating normal histological architure. (b, f) 5 mg/kg SRT administered rats with no observable pathology. (c, g) 10 mg/kg SRT administered rats showing mild inflammation and few extravasation of red blood cells (arrowhead) accompanying interstitial edema. (arrow) (d, h) 20 mg/kg SRT administered rats showing hypertrophy and irregular myofibrils (*), myofibrillar loss (arrow), deformation of blood vessels (short arrow), edema, inflammation and fibrosis (arrowhead). (Scale bar: 30 µm)

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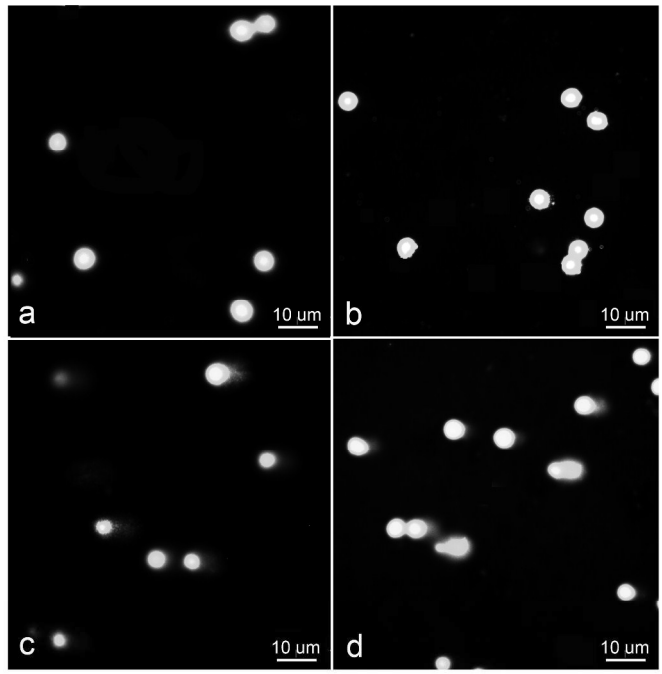

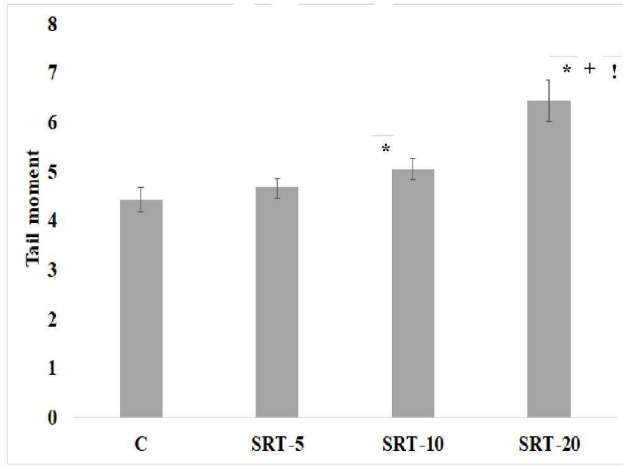

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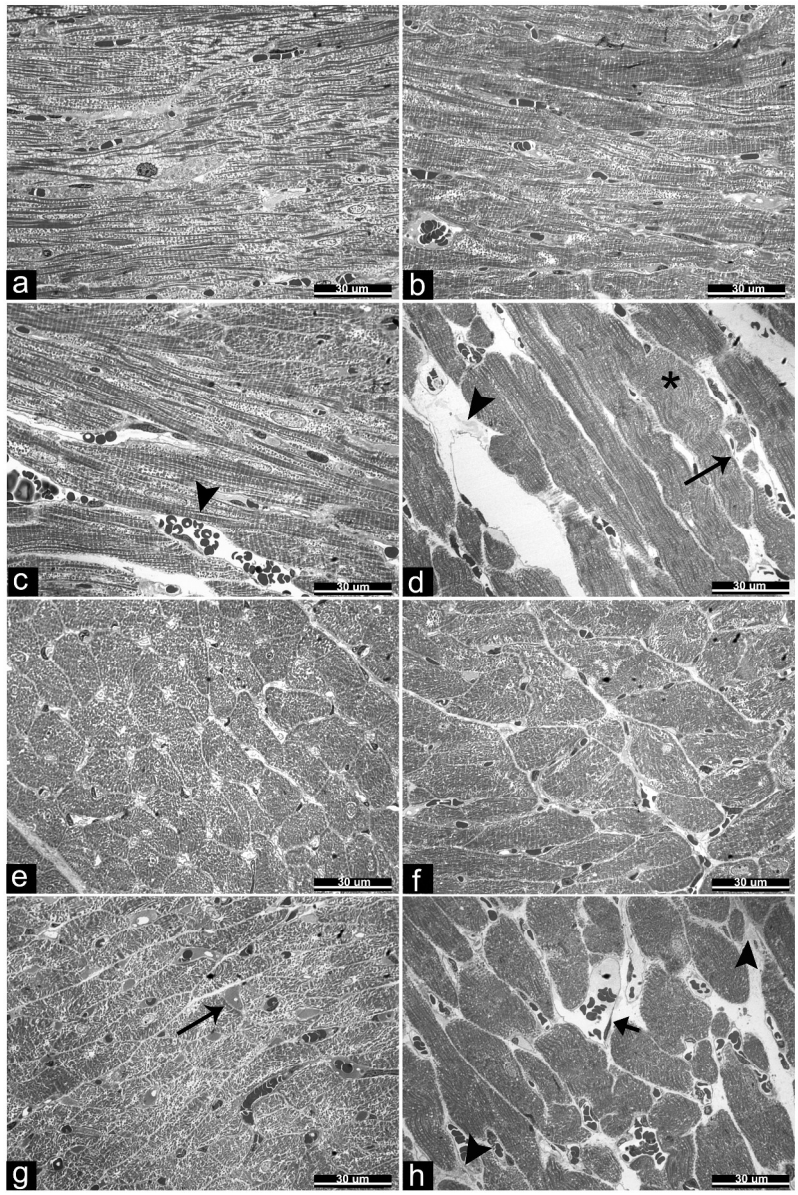

Figure 2

226x338mm (300 x 300 DPI)