

Cardiotoxic Effect of Chlorpromazine in Adult Male Albino Rats and the Possible Curcumin Cardioprotection (Histological, Histochemical and Immunohistochemical Study)

Manar A. Bashandy¹, Safaa A. Amin² and Hanan Seleem³

¹Anatomy, ²Forensic Medicine & Clinical Toxicology & ³Histology Departments, Faculty of Medicine, Menoufiya University
maalbash@yahoo.com sfamin2007@yahoo.com.

Abstract: Introduction: Chlorpromazine is a centrally acting phenothiazine antipsychotic drug used for the management of psychoses, including schizophrenia, and in the control of severely disturbed or agitated behavior. Several studies reported variable effect of chlorpromazine on myocardial muscle. **Aim of the work:** This study aimed to determine the possible protective effect of curcumin on: chlorpromazine induced histopathological changes in rat heart model. **Material and Methods:** Twenty-eight adult male Albino rats were subjected to experiment for 14 days as follows: Control groups were divided into: group I, Rats in this group were injected intraperitoneally with the same volume of vehicle (normal saline) and group II, were received curcumin (200 mg/kg b.wt./day) orally daily. Group III, was injected intraperitoneally with daily dose (10 mg/kg b.wt) of chlorpromazine. Group IV received curcumin (200 mg/kg b.wt./day) orally daily half an hour before intraperitoneal injection of chlorpromazine. Heart tissue were excised for histological, histochemical and, immunohistochemical studies. **Results:** Histologically and histochemically, myocardial muscles of chlorpromazine treated rats showed pathological changes in the form of some degenerated fragmented muscle fibers with vacuoles. In other areas, wide separation of muscle fibers with areas of myocytolysis can be seen. Some cardiomyocytes nuclei are small and pyknotic and others are fading out. The blood vessels appeared congested with infiltration in between myocardial muscle fibers. There was weak PAS reaction in the degenerated muscle fibers and moderate reaction in other cells. There was increased deposition of collagen fibers in between cardiac muscle and around blood vessels as shown by Masson trichrome stain. Immunohistochemically, in chlorpromazine treated group showed negative immunoreactivity for E cadherin in the cytoplasm of muscle fibers. On the other hand, histological, histochemical and immunohistochemical examination of the prophylactic group displayed nearly normal appearance of most myocardial muscle fibers, but still some muscle fibers appeared widely separated with some vacuolations. **Conclusion:** Chlorpromazine causes myocardial damage in experimental rats. Curcumin could be used as protective agents against long term use of chlorpromazine to ameliorate damaging effects on myocardial muscles as it has positive contribution as a dietary supplement for the prevention of myocardial injury and heart disease.

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1. Introduction

Chlorpromazine is a centrally acting phenothiazine antipsychotic drug used for the management of psychoses, including schizophrenia, and in the control of severely disturbed or agitated behavior (Raj *et al.*, 2005)

Chlorpromazine was originally used as antihistamine and antihypertensive agent (Hollister, 1995). However, long term observation of calming and sedating effect led to its trial in psychiatric patients.

The antipsychotic drugs generally have antiemetic, anti-nausea, analgesic, sedatives and general anesthetic effects (Soliman and Abdel-Maegind, 1999).

Previous studies documented that, long term use of chlorpromazine can adversely affect myocardial muscles, lung structure, Autonomic nervous system (Kodavanti *et al.*, 1990).

Experimental studies exhibited that, chlorpromazine can produce hyperprolactinaemia,

hypospermia, histopathological changes in testis (Petty, 1999 & Raji *et al.*, 2005))

Some researchers reported that, a single dose of chlorpromazine can protect against the myocardial injury caused by ischemia, perfusion or calcium paradox (Saito *et al.*, 1985). On the other hand, Ng *et al.*, 1982 reported only changes in ECG. While, Tri and Combs (1975) observed ventricular tachycardia as a complication of chlorpromazine therapy. More-over, Saito *et al.*, (1985) observed microscopic and ultrastructural myocardial damage in rat model after chronic use of chlorpromazine therapy.

The mechanism of action of chlorpromazine is not completely understood. Its antipsychotic effects are believed to be related to its action in selectively blocking the transmission of nerve impulses from cell to cell in a region of the brain called the limbic system. This part of the brain is involved with emotions and motivation (McEvoy and Bethesda, 2001).

Curcumin or diferuloylmethane extracted from the root of *Curcuma longa* L. (Duvoix *et al.*, 2005).

Although Curcumin is widely used as food flavoring agent, it is also used in Indian medicine and culinary traditions (Hergenhahn *et al.*, 2002).

Curcumin presents strong anti-oxidative, anti-inflammatory, anti-septic (Hergenhahn *et al.*, 2002), antiviral (Mazumder *et al.*, 1995) chemo-therapeutic and chemo- protective properties (Duvoix *et al.*, 2005).

Many previous studies have demonstrated that, curcumin had protective effects in Adriamycin cardiotoxicity (Vankatesan, 1998) and had ability to protect myocardium against isoprenaline-induced oxidative stress (Nirmala & Puvanakrishnan, 1996). It was therefore of interest to determine whether curcumin has protective effect against chlorpromazine cardiotoxicity.

2. Material and Methods:

Materials :

Animals:

Twenty eight adult male Albino rats with a body weight (170-200 grams) were selected for this study. The animals obtained from breeding animal house, Faculty of Medicine, Menofia University (Menofia, Egypt). The animals were acclimated to room temperature (22 - 25° C) for one week before experiment and kept under good hygienic condition. They were feed standard animal food and tap water *ad libitum*.

Drugs and chemicals:

Chlorpromazine hydrochloride Tablets:

Each tablet contain 100 mg of chlorpromazine which obtained from Misr Company for Pharm. Ind. S.A.E. Each 2 tablets (200 mg) were dissolved in 100 ml of sterile non- pyrogenic normal saline to obtain concentration of 2 mg/ml.

Curcumin: powder, 200 mg/kg/day.

Experimental protocol:

Animal experimentations were carried out in an ethical manner following guidelines set by Ethical Committee of Menofia University. The animals were divided into 4 groups, each of 7 rats: **Group I:** Rats in this group were injected intraperitoneally the same volume of vehicle (normal saline) along the duration of the experiment (14 days). **Group II:** Rats in this group were orally administered curcumin (200 mg/kg b.wt./day) orally for 14 days (Vankatesan., 1998). Curcumin was suspended in distilled water for oral administration. **Group III:** Rats in this group were aseptically injected intraperitoneally with daily single dose (10 mg/kg) of chlorpromazine for 14 days (Saito *et al.*, 1985). **Group IV:** Rats in this group were received curcumin (200 mg/kg b.wt./day) orally daily half an hour before intraperitoneal injection of chlorpromazine for 14 days.

On day fifteen, rats were sacrificed after 24 hrs of last dose of drug; the rats were sacrificed by cervical dislocation. Specimen of the left ventricle of the heart

was excised then immersed in normal saline. The tissues were divided and subjected to the following studies:

I- Histopathological evaluation:

The left ventricle of the heart of each animal was dissected out then fixed in 10% formal saline. The specimens were processed to obtain paraffin blocks from which 5 µm thick sections were cut and stained with: haematoxylin & eosin.

II- Histochemical studies:

Paraffin sections were stained with Periodic Acid Scheif (PAS) & Masson Trichrome (MT) stains (Stevens and Wilson, 1996).

III-Immuno-histochemical study:

Paraffin blocks were prepared from specimen already fixed in 4% paraformaldehyde. Sections were dewaxed in xylene, rehydrated and pretreated with 3% hydrogen peroxide (3% H₂O₂ in absolute methyl alcohol) for 10-15 minutes in humidity chamber for blocking of endogenous peroxidase activity. For antigen retrieval: Heat induced epitope retrieval (HIER) procedure was used (New Marker immune histopathology catalogue, 2000). Ultra V Block was applied for 5 minutes. Sections were incubated overnight with monoclonal mouse primary antibody raised against

E-cadherin (diluted at a 1:50), Technofight, code M1681 (Clone 168). After washing with PBS, biotinylated secondary anti-immunoglobulin (LSAB 2 system-HRP, Dakocytomation (Copenhagen) was applied 40 min at room temperature. The specimens were washed in phosphate buffered saline (PBS) and incubated with streptavidin peroxidase for 10 minutes. While the slides were in PBS, the diaminobenzidine (DAB) chromogen substrate was prepared and then, applied on slides for 5 minutes to detect immunoreactivity. Finally, the specimens were counter- stained with Mayer's hematoxylin. Negative control was performed by omitting the primary antibody step consequently no immune-staining occurred (Qi *et al.*, 2006).

3. Results.

Group I: Control group:

Light microscopic examination of the myocardium of left ventricle of control adult male albino rats showed branching and anastomosing cardiac muscle fibers with central oval vesicular nuclei. Capillaries and fibroblasts were seen in the connective tissue between the cardiac muscle fibers (Figs.1&2). Periodic Acid Scheif's (PAS) reaction of the left ventricle showed strong reaction which appeared magenta red in the cytoplasm of cardiac muscle fibers (Fig. 3). Masson's trichrome (M.T) stained reactions of the left ventricle revealed few fine collagen fibers between the cardiac muscle fibers (Fig.4). Immunohistochemical stain for E – cadherin revealed

moderate to strong brown positive immunoreaction in the cytoplasm of cardiac muscle fibers (Fig. 5)

Group II: Curcumin group:

Showed the same light microscopic appearance like control group I.

Group III : Chlorpromazine treated group :

Light microscopic examination of the myocardium of left ventricle of chlorpromazine treated rats showed some degenerated fragmented cardiac muscle fibers with irregular outlines with congested blood capillaries. Some cardiac muscle fibers appeared with vacuoles. Some nuclei appeared with peripherally margined chromatin and infiltration around the congested blood vessels (Figs.6&7) the cardiac muscle fibers showed haphazard orientation. The nuclei of most of the cardiac muscle fibers appeared small and deeply stained (pyknotic) (Fig.8).

Most of the cardiac muscle fibers showed disorientation with large sized vacuoles in between (Fig.9). Some of the cardiac muscle fibers were separated from each other by wide intercellular space with large areas of cell loss (myocytolysis) and extravasation of blood (Fig.10). Other cardiac muscle fibers showed degeneration with rarified cytoplasm. Some nuclei are pyknotic and others are fading out. Marked extravasation of RBCs were also seen (Fig. 11).

PAS reaction of this group showed weak reaction in the degenerated muscle fibers and moderate reactions in other cells (Fig. 12).Masson trichrome stained sections showed an apparent increase in the amounts of collagen fibers between the cardiac muscle fibers and around blood vessels. Focal areas of excessive collagen fiber deposition were also detected (Figs.13&14). Immunohistochemical stain for E-cadherin revealed negative immuno-reactivity in the cytoplasm of the cardiac muscle fibers (Fig. 15).

Group IV: Protective group (Chlorpromazine & curcumin treated group) :

Light microscopic examination of the myocardium of left ventricle of rats that received chlorpromazine and curcumin showed that, the cardiac muscle fibers preserved the normal architecture except for a few degenerated and fragmented cardiomyocytes with extravasation of RBCs (Fig. 16).Some wide separation between the cardiac muscle fibers with pyknotic nuclei were also detected (Fig.17). Some cardiac muscle fibers showed small vacuoles (Fig. 18).

PAS reaction of this group showed strong reaction in some cardiac muscle fibers and moderate reaction in others (Fig. 19).Masson Trichrome stained sections revealed minimal amount of collagen fibers between the cardiac muscle fibers and around blood capillaries (Fig. 20). Immunohistochemical stain for E-cadherin revealed mild to moderate positive immunoreactivity in the cytoplasm of cardiac muscle fibers (Fig.21).

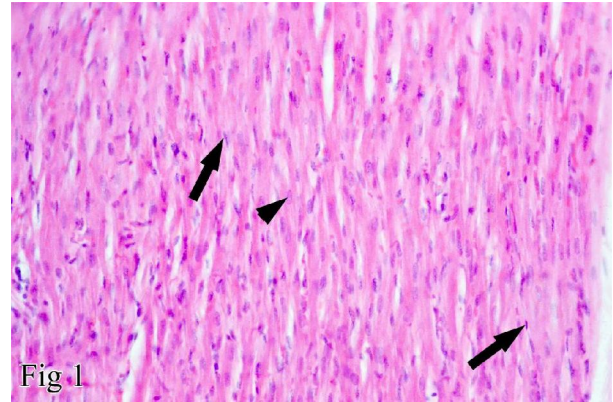


Fig.1. A photomicrograph of a longitudinal section of a control adult rat myocardium showing branching and anastomosing muscle fibers with centrally located nuclei (arrow head). Notice: The flattened nuclei of connective tissue between the cardiac muscle fibers (arrow).
(H & E, X400)

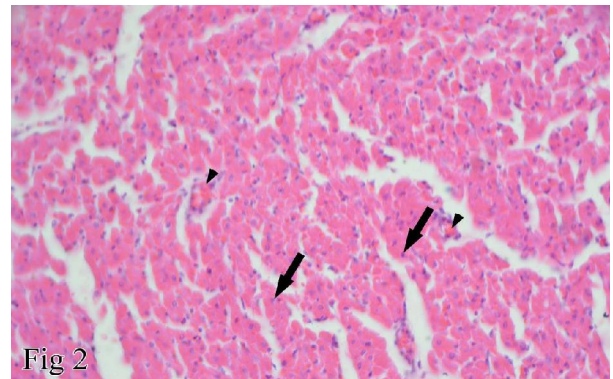


Fig.2. A photomicrograph of a transverse section of a control adult rat myocardium showing bundles of cardiac muscle fibers with central rounded nuclei (arrow). Notice: the presence of small blood capillaries between the muscle fibers (arrow head).
(H & E, X 400)

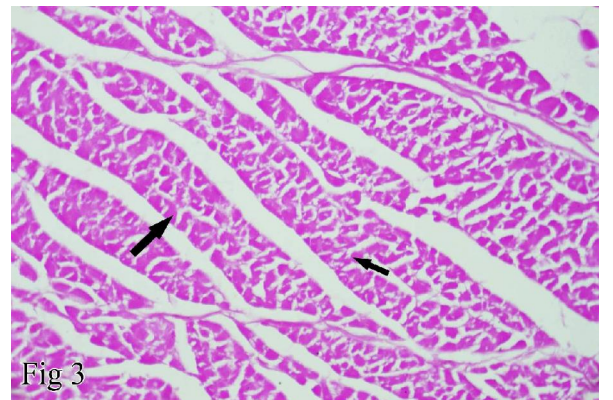


Fig.3. A photomicrograph of a transverse section of myocardium of a control adult rat showing strong PAS reaction (magenta red) in cytoplasm of cardiac muscle fibers (arrow).
(PAS, X 400)

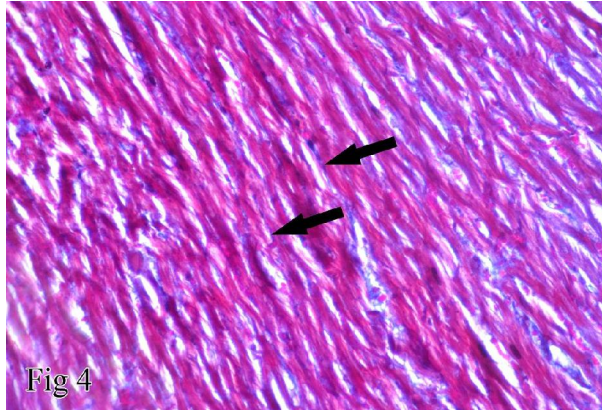


Fig.4. A photomicrograph of a longitudinal section of myocardium of a control adult rat showing few and fine collagen fibers between the cardiac muscle fibers (arrow) (Masson Trichrome's , X 400)

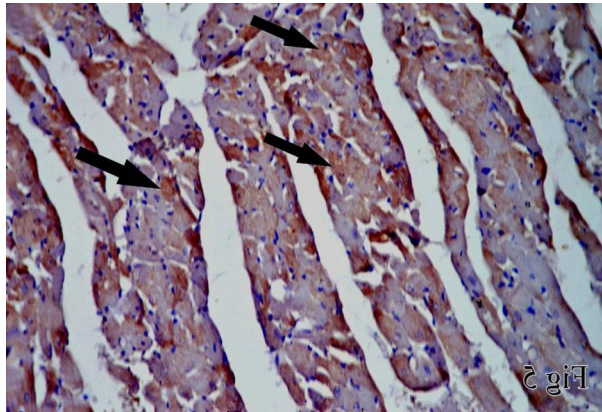


Fig. 5. A photomicrograph of a transverse section of myocardium of a control adult rat showing moderate to strong positive immunoreactivity for E cadherin in the cytoplasm of muscle fibers (arrow) (E cadherin immunostain, X 400).

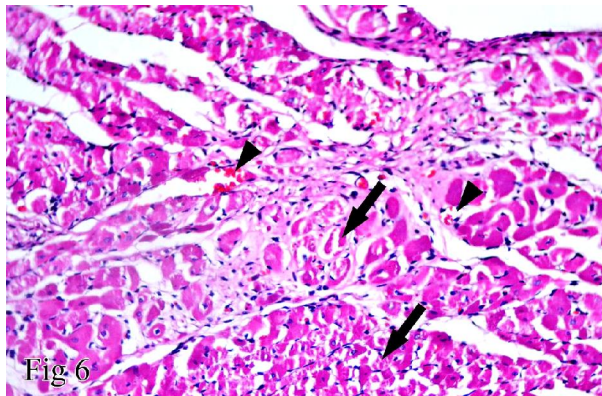


Fig.6. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine showing some degenerated fragmented muscle fibers with irregular outlines (arrow). Notice: the presence of congested blood capillaries (arrow head) (H&E, X 400)

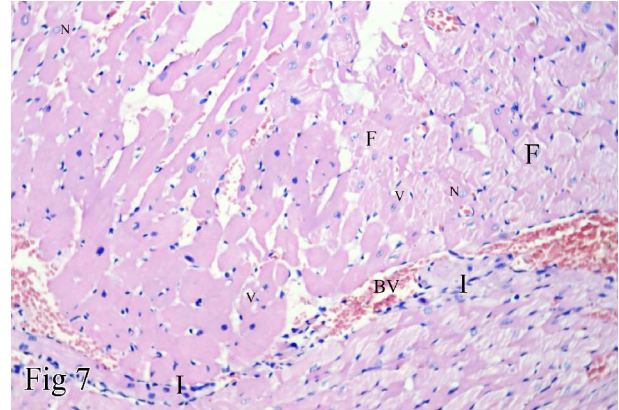


Fig.7. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine showing some muscle fibers with some vacuoles (V) and others degenerated fragmented (F). Notice: The nuclei with peripherally margined chromatin (N). Congested blood vessels (BV) with infiltration (I) (H&E, X 400)

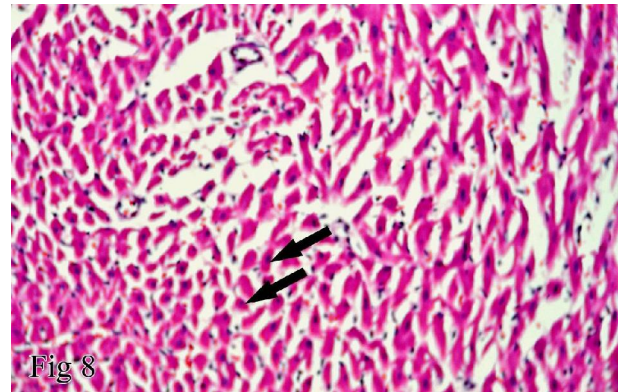


Fig.8. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine showing haphazard orientation of muscle fibers. Some nuclei are small and deeply stained (arrow). (H&E, X 400)

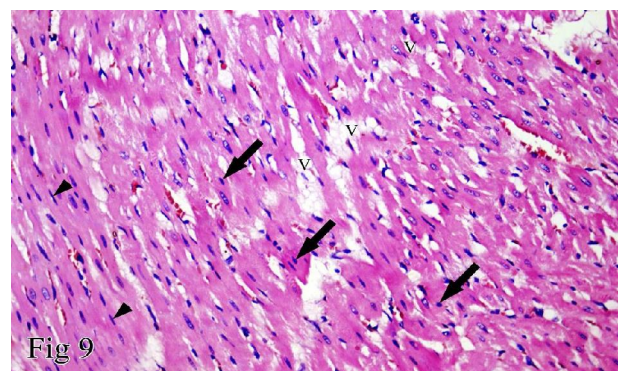


Fig.9. A photomicrograph of a longitudinal section of myocardium of an adult rat treated with chlorpromazine showing disorientation of muscle fibers with large sized vacuoles (V) in between. Some nuclei are small and pyknotic (arrow). Notice: The dark flat nuclei of fibroblasts of endomysium (arrow head.) (H&E, X 400).

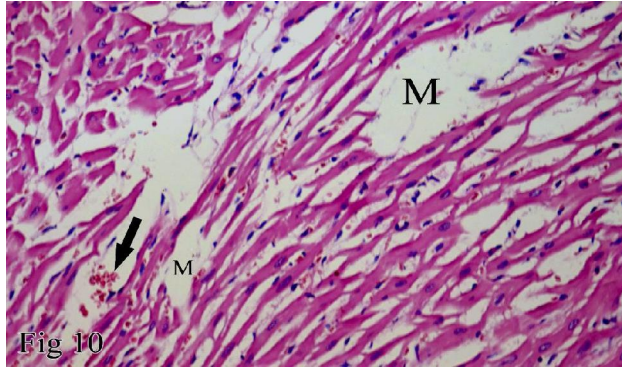


Fig.10. A photomicrograph of a longitudinal section of myocardium of an adult rat treated with chlorpromazine showing wide separation of muscle fibers with areas of myocytolysis (M) denoting cell loss and extravasation of blood (arrow). (H&E, X 400)

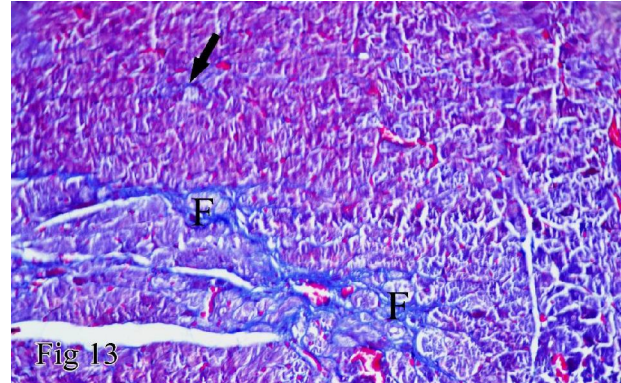


Fig.13. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine showing apparent increase in collagen fibers between the cardiac muscle fibers (arrow). Note: Focal areas of excessive increase in collagen fibers deposition are also seen (F). (Masson Trichrome's, X 400)

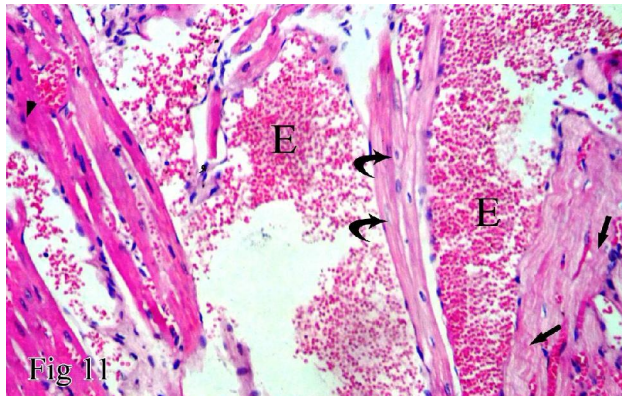


Fig.11. A photomicrograph of a longitudinal section of myocardium of an adult rat treated with chlorpromazine showing degenerated muscle fibers with rarified cytoplasm (arrow). Some nuclei are small and pyknotic (arrow head) and others are fading out (curved arrow). Notice: Marked extravasation of RBCs (E). (H&E, X 400)

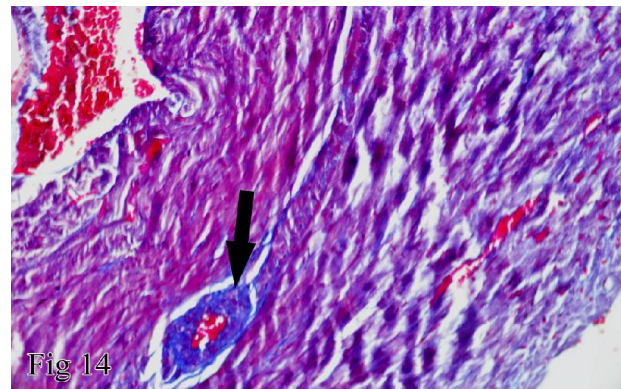


Fig.14. A photomicrograph of a transverse and longitudinal section of myocardium of an adult rat treated with chlorpromazine showing apparent marked increase in collagen fibers around the congested blood capillaries (arrow) (Masson Trichrome's, X 400)

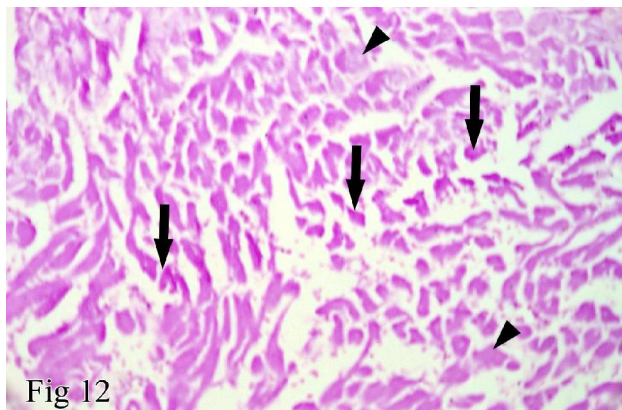


Fig.12. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine showing weak PAS reaction in the degenerated muscle fibers (arrow head) and moderate reaction in other cells (arrow). (PAS, X 400).

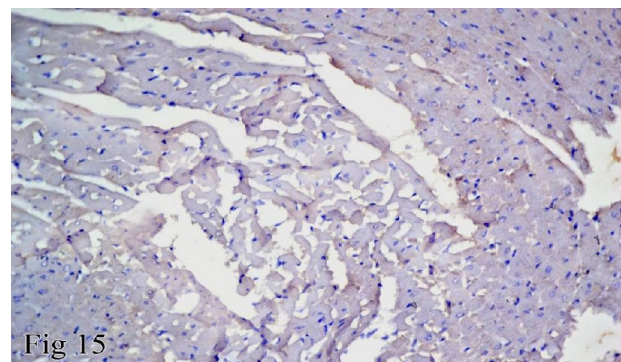


Fig.15. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine showing negative immunoreactivity for E cadherin in the cytoplasm of muscle fibers. (E cadherin immunostain, X 400)

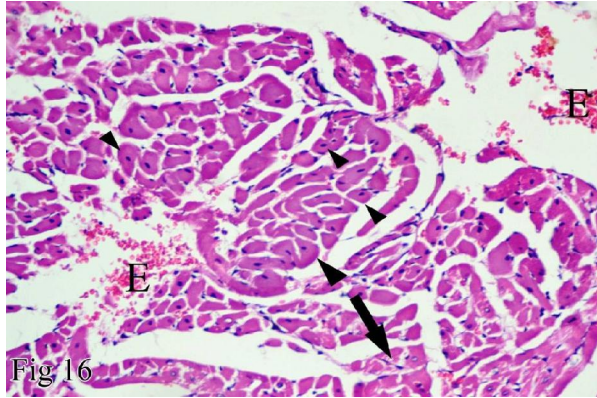


Fig 16

Fig.16. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine and curcumin showing few degenerated and fragmented cardiomyocytes (arrow) with extravasations of RBCs (E). Other parts look normal with normal nuclei (arrow head). (H&E, X 400)

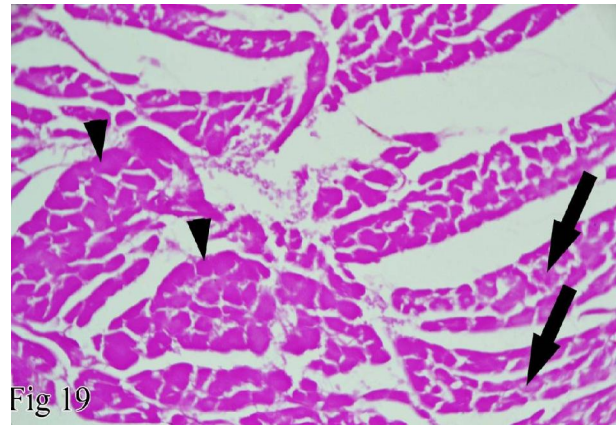


Fig 19

Fig.19. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine and curcumin showing strong PAS reaction (magenta red) in some muscle fibers (arrow head) and moderate reaction in others (arrow). (PAS, X 400)

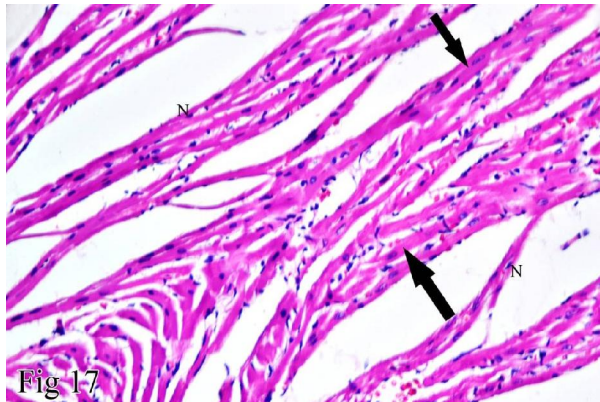


Fig 17

Fig.17. A photomicrograph of a longitudinal section of myocardium of an adult rat treated with chlorpromazine and curcumin showing branching and anatomizing muscle fibers. Some cardiomyocytes appear normal (arrow) and others show wide separation. Some cardiomyocytes nuclei are shrunken and pyknotic (N). (H&E,X 400)

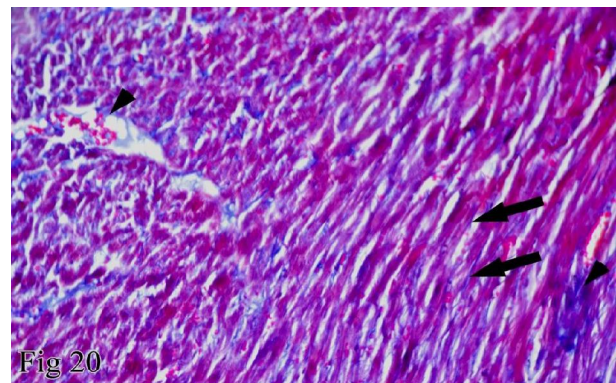


Fig 20

Fig.20. A photomicrograph of a transverse and longitudinal section of myocardium of an adult rat treated with chlorpromazine and curcumin showing minimal amount of collagen fibers between the cardiac muscle fibers (arrow) and around blood vessels (arrow head) (Masson Trichrome's, X 400)

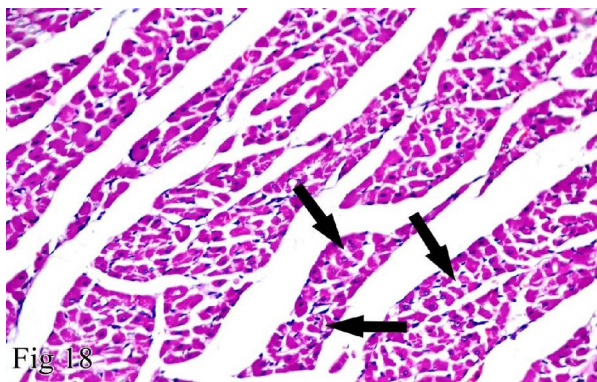


Fig 18

Fig.18. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine and curcumin showing muscle fibers nearly similar to that of control group except some of them show wide separation with small vacuoles (arrow) (H&E, X 400)

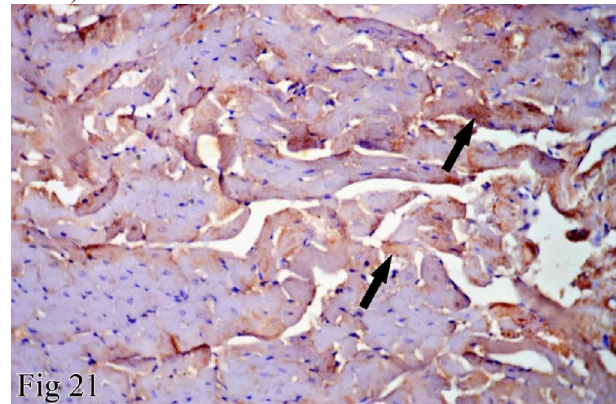


Fig 21

Fig.21. A photomicrograph of a transverse section of myocardium of an adult rat treated with chlorpromazine and curcumin showing mild to moderate immunoreactivity for E cadherin in the cytoplasm of muscle fibers (arrow). (E cadherin immunostain, X 400)

4. Discussion

Chlorpromazine is a centrally acting phenothiazine drug with primary action at subcortical levels as well as on multiple organ systems. It is classified as a low- to moderate-potency antipsychotic and in the past was used in the treatment of both acute and chronic psychoses, including schizophrenia and the manic phase of manic depression as well as amphetamine-induced psychoses (Seeman, 2010).

The present study aimed to clarify the toxic effect of chlorpromazine on rat heart and whether curcumin has a protective effect against chlorpromazine cardiotoxicity or not.

Cardiac muscle of control group shows normal general structure as findings reported by Bas and Kalender, 2011 who described normal cardiac structure during their experiment and this proved that studied animals were healthy.

In the current study, examination of the myocardial sections of chlorpromazine treated rats showed some degenerated fragmented muscle fibers with irregular outlines and rarified cytoplasm. This can be explained by accumulated effect of alpha adrenoceptor blocking property of chlorpromazine. This agreed with Kilian *et al.* (1999) who reported that, chronic chlorpromazine administration in schizophrenic patients can lead to cardiomyopathy. They attributed cardiomyopathy to blocking of alpha adrenoceptor. They concluded association of cardiomyopathy with chlorpromazine. These results coincide with previous findings of Saito *et al.* (1985) who observed myocardial degeneration, atrophic muscle fibers and myocardial fibrosis in chlorpromazine treated rats.

In the present study, examination of the myocardial sections of chlorpromazine treated rats showed some cardiac muscle fibers with vacuoles. The cardiac muscle fibers showed haphazard orientation. Most of them showed disorientation with large sized vacuoles in between. Degeneration of muscle fibers with vacuolation could be explained due to cellular injury that occurs in variety of conditions such as infectious disease, especially those associated with high fever, intoxications from chemical and metallic poisons, extensive burn and anoxaemia (Scotti and Hackel, 1985). These findings suggest the occurrence of cardiomyopathy in chlorpromazine intoxicated animal group. This in agreement with Kumar *et al.* (2010) who diagnosed cardiomyopathy histopathologically by hypertrophy and haphazard orientation of cardiac muscle fibers and enlargement of their nuclei.

Also, some of the cardiac muscle fibers in the present work were separated from each other by wide intercellular space with large areas of cell loss (myocytolysis). The myocytes autolysis (myocytolysis) could be explained as a result of liberation of

hydrolytic enzymes from lysosomes in the dead or dying cells and so the cytoplasm became homogenous and intensely acidophilic (Bentley *et al.*, 2002).

In the present study, the nuclei of myocytes of chlorpromazine treated rats were variable in shape. Some nuclei appeared with peripherally marginated chromatin. Small and deeply stained (pyknotic) nuclei were observed. Others were fading out. These nuclear changes might be due to necrosis which might be due to a decrease or cut in its blood supply. Rutschow *et al.*, 2006 demonstrated that Myocyte necrosis and apoptosis can be linked to elevated proinflammatory cytokine levels, such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interferon- γ .

Also, Gupta *et al.*, 2010 reported that, during the progression of cardiac hypertrophy to heart failure, the nuclear shape of the myocytes became bizarre with an irregular nuclear envelope.

In the current study, examination of the myocardial sections of chlorpromazine treated rats revealed extravasated red blood cells and congested blood vessels. Focal areas of cellular infiltration, as well as fibroblast cells were observed. Extravasation may be explained by changes in capillary permeability. Fahmy, (2008) postulated that extravasation of blood might occur because of microvascular injury as a result of ischemic state caused by interference of normal oxidative metabolism. One other possibility is a direct toxic effect on the heart that attracts an inflammatory infiltrate (Elias *et al.*, 1999).

In the present study, there was reduction in the PAS positive material (most probably glycogen) in the cardiac muscles. The depletion of glycogen content in the cardiac muscle might be due to either impaired glycogen synthesis as a result of cardiac muscle degeneration and inability of the affected cardiac muscle to store it or increased glycogenolysis as increased demands for glucose under these conditions of energy deficit that increased the strain on the myocytes (Fitzl *et al.*, 2000).

Microscopic examination of myocardial sections of chlorpromazine treated rats stained with Masson trichrome (MT) revealed increase of collagen fibers among cardiac muscle fibers and around blood vessels in comparison with the control. This run in harmony with Saito *et al.*, (1985) who observed an increase in the connective tissue of myocardial fibers in rat model treated with chlorpromazine for long time. Similar findings were detected by Kissane, 1985 who referred occurrence of myocardial fibrosis to vascular insufficiency. This myocardial fibrosis could interfere with the cardiomyocyte nutrition and function and lead to more deterioration.

On the other hand, Fibroblasts may respond to both mechanical loading Wang *et al.*, (2003) and transforming growth factor- β 1 stimulation Petrov *et al.*, (2002) by a switch to a myofibroblastic phenotype

that is accompanied by stimulation of collagen production. Accumulation of collagen in the cardiac interstitium or reactive interstitial fibrosis is accompanied by loss of matrix cross-link integrity **Sabbah et al., (1995)** and by a change in the ratio of collagens I and III (**Pauschinger et al., 1999**). This may contribute to increased myocardial stiffness with impaired systolic and diastolic functions (**Sabbah et al., 1995 and Pauschinger et al., 1999**).

The cadherins are a super-family of transmembrane glycoproteins that mediate Ca²⁺-dependent cell–cell adhesion, recognition and vital during tissue differentiation. E-cadherin was located at the intercalated disc of the myocytes in co-localization with connexin 43. E-cadherin is expressed in cytoplasmic region of cell as the cytoplasmic region regulate the cell-cell binding function of the extracellular domain of E-cadherin, possibly through interaction with the cytoskeleton (Craig et al., 2010).

In the current study, examination of myocardium from chlorpromazine treated rats that were stained immunohistochemically with E- cadherin revealed negative immunoreaction in cytoplasm of cardiac cardiomyocytes. This negative immunoreactivity indicate malfunction of cardiac muscle and this agreed with (**Ferreira-Cornwell et al., 2002**) who found that misexpression of E-cadherin in the adult myocardium led to severe cardiomyopathy in transgenic mice due to defects in the intercalated discs.

These results postulate a light on the dangerous of chlorpromazine cardio toxicity that may lead to sudden arrhythmias & sudden death as mentioned in previous studies as reported in drug information; Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature (**Wu et al., 2005**)

Cardiac arrhythmias and apparent sudden death have been associated with therapeutic doses of chlorpromazine (**Fowler et al., 2006**)

Nasser & Michell (2006) ported that, there is a risk of sudden death and the risk related to anti-psychotic is thought to increase in people with pre-existing cardiac disease. Those taking antipsychotic at high dose for long periods.

Killian et al., (1999) on their study on clozapine which is a diabetodiazepine antipsychotic found a high incidence of fatal and on fatal myocarditis in the first month of treatment of about 500 (five hundred) young adult patients with schizophrenia.

In the current study, examination of the myocardiums of the rats in group IV, which received chlorpromazine along with curcumin, revealed that the myocardium had an almost normal architecture with the exception of many congested blood capillaries and a few distorted myocytes. This indicate that curcumin

contributes to the attenuation of the inflammatory & apoptotic pathway in the myocardium and protect against myocardial toxicity in rat this in agreement with **Venkatesan (1998)** who demonstrate that, curcumin treatment protect against acute adriamycin cardiotoxicity The cardioprotective effects of curcumin on myocardial injury rat model could include anti-inflammation activities and inhibition of apoptosis that occurred in the cardiomyocytes (**Kim et al., 2008**)

Administration of curcumin improved the antioxidant status and thereby preventing the damage to the heart, mainly because of the antioxidant sparing action of curcumin. The antioxidant mechanism of curcumin may include one or more of the following interactions. Scavenging or neutralizing of free radicals (**Ruby et al., 1995**), inhibition of oxidative enzymes like cytochrome P₄₅₀, (**Appiah et al., 2007**) oxygen quenching and making it less available for oxidative reaction, interacting with oxidative cascade and preventing its outcome (**Sandur et al., 2007**) and disarming oxidative properties of metal ions such as iron. (**Miriyala et al., 2007**).

Curcumin inhibited the oxidative stress, cytokines and hypoxic injury. So, curcumin reduced the fibrosis and apoptosis in the injured and ischemic rat heart tissue (**Kim et al., 2008**)

Recently, **Duan et al., (2012)** suggested that Curcumin can attenuate myocardial ischemia and reperfusion injury through the activation of the Janus kinase 2 and signal transducer and activator 3 of transcription JAK2/STAT3 signaling pathway, which transmits a survival signal to the myocardium.

Moreover, **Izem-Meziene et al., 2012** explained the cardio-protective effect of curcumin through prevention of mitochondrial damage and Mitochondrial morphology and permeability transition pore (mPTP) opening.

Thus, in this work, curcumin may effectively prevented tissue damage by decreasing the oxidative stress and restoring the antioxidant status.

Conclusion:

Chlorpromazin causes myocardial damage in experimental rats. Curcumin could be used as protective agents against long term use of chlorpromazine to ameliorate damaging effects on myocardial muscles as it has positive contribution as a dietary supplement for the prevention of myocardial injury and heart disease

Corresponding authors

Manar A.Bashandy

Anatomy Department, Faculty of Medicine-Menoufyia University.Egypt

E-mail: maalbash@yahoo.com

Safa abdel Zaher

Forensic and clinical toxicology Department, Faculty of Medicine-Menoufyia University.Egypt

E-mai: sfamin2007@yahoo.com.

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