Original article

Ginger extract attenuates labetalol induced apoptosis, DNA damage, histological and ultrastructural changes in the heart of rat fetuses

Hend T. El-Borm [a,*], Marwa S. Gobara [b], Gamal M. Badawy [b]

[a] Vertebrates, Comparative Anatomy and Embryology-Zoology Department-Faculty of Science-Menoufia University, Egypt
[b] Zoology Department-Faculty of Science-Menoufia University, Egypt

ABSTRACT

Labetalol is a medication used to treat maternal hypertension during pregnancy. However, it is often associated with many side effects. Recently, several studies have been focused on the protective effect of medicinal plant extracts, such as ginger, against drugs inducing toxicity. Therefore, it has been hypothesized that ginger aqueous extraction can ameliorate labetalol-induced histological, ultrastructural changes, DNA damage, and apoptosis in fetal heart tissue. To achieve the aim of this study, sixty pregnant female albino rats were divided into 4 groups (15 each). Group I (Control). Group II received ginger (200 mg/kg). Group III received labetalol (300 mg/kg). Group IV received labetalol first followed by ginger. All groups were orally injected daily during the organogenesis phase of gestation i.e., from the 6th to the 15th day, and sacrificed at the 20th day of gestation. Results showed that labetalol-induced marked histological and ultrastructural alterations. Also, there was severe DNA damage and an increase in the apoptotic rates determined by Annexin-V/PI dual staining assay. Injection of the ginger aqueous extract caused evident improvement in cardiac tissue, DNA damage, and apoptotic rates. In conclusion, the results suggest that ginger extract could be a potential candidate agent for reducing labetalol-induced cardiotoxicity in the fetal heart of albino rats.

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1. Introduction

Labetalol is one of the foremost broadly used antihypertensive drugs during pregnancy (Podymow and August 2011). The National Guideline Clearing House regarding the treatment of hypertensive disorders of pregnancy has recommended that the initial antihypertensive therapy should be started with nifedipine or labetalol to bring down the target blood pressure to 160 systolic and 110 diastolic (Magee et al., 2003). Numerous antihypertensive drugs, including labetalol, were classified as category "C", which states that human studies are missing, animal studies are either positive for fetal risk or are missing, and the drug should be given only if the potential benefits justify potential dangers to the fetus (Umans, 2007).

The value of medicinal plants in curing most diseases has been realized since ancient times. Ginger is a subtropical rhizome of the plant *Zingiber officinale* Roscoe, a member of the family *Zingiberaceae*. Ginger contains several compounds such as gingerol, shogaol, zingiberence, paradol, resin, starch, volatile oil, and vitamins C and A (Ali et al., 2008; Dhanik et al., 2017; Mao et al., 2019). It has a long history of medicinal use in traditional medicine for conditions such as headaches, toothache, colds, improvement of circulation of the limbs, and lowering blood cholesterol (Baliga et al., 2011; Zahedi et al., 2012; Haniadka et al., 2013) and also used as antioxidant, antimicrobial, antiviral, gastroprotective, antidiabetic, antihypertensive, cardioprotective, anticancer and immunomodulatory agent (Young et al., 2005; Ali et al., 2008; Baliga et al., 2011; Singh et al., 2018; Dissanayake et al., 2020). Many studies reported that ginger had no toxicity on mothers or embryos of rats (Abu Baker, 2013; Abd El-Aziz et al., 2018). Food and drug administration (FDA) have been listed *Zingiber offficinale* as "Generally Recognized as Safe" (Singh et al., 2018).

Ginger has reportedly been utilized in traditional medicine for the management and avoidance of hypertension and other

* Corresponding author.
E-mail addresses: hend.elbarm@science.menofia.edu.eg, Hendtarek98@yahoo.com (H.T. El-Borm).

cardiovascular diseases (Mao et al., 2019). Moreover, both *in vitro* and animal experiments reported that ginger possessed antioxidative characteristics so, it could scavenge superoxide anion and free radical damage that may excite the inflammatory response in the formation of atherosclerotic plaque, which is the precursor of most cardiovascular disease (Masuda et al., 2004; Wu et al., 2018). There is an association between oxidative stress due to heart failure after myocardial infarction and antioxidant level in rats, this revealed that high antioxidant may serve to support cardiac function whereas depressed cardiac function and heart failure may be due to antioxidant reserve reduction (D'Oria et al., 2020). Also, some studies revealed that ginger extract exhibited cardioprotective potential in treating myocardial injury induced by isoproterenol (Amran et al., 2015) and cisplatin in albino rats (Abas, 2017). Moreover, in stressed rat heart homogenates, ginger extract decreased the content of malondialdehyde, which was related to lipid peroxidation (Mao et al., 2019). Also, ginger has an amelioration effect on the age-related changes in the heart tissue of normal female rats (Kim et al., 2010). These results suggest that ginger exhibit a beneficial effect against myocardium damage. However, the effect of labetalol on internal fetal organs remains unexplored. Hence, the present study was designed firstly to investigate the possible cardiotoxicity of prenatal exposure to one of the antihypertensive drugs through maternal administration of labetalol during the organogenesis phase of embryonic development i.e. from the 6th to the 15th day of gestation. Secondly to examine the possible ameliorative role of ginger against the cardiotoxicity induced by labetalol administration in rat fetuses. For the sake of integrity, the planned aims included describing the histological, ultrastructural changes, genotoxicity, and cytotoxicity in the heart tissue of 20-day old rat fetuses.

2. Materials and methods

2.1. Animals and grouping:

Principles of animal care and use were carefully followed during conducting the present study according to the guide for the care and use of laboratory animals approved by faculty of science, Menoufia University, Egypt (Approval No. MNSE2220) and according to the National Institutes of Health guide for the care and use of laboratory animals (NIH publications No. 8023, received 1978). 90 healthy mature virgin females and fertile males of Wistar albino rats (*Rattus norvegicus*), with weights 160 ± 10 g and ages 17 ± 1 weeks, were purchased from Helwan Farm, Ministry of Health, Cairo, Egypt. They were kept in well-ventilated cages at room temperature and under controlled conditions of ambient temperature at the animal house, Faculty of Science, Menoufia University. They were kept in the laboratory for at least one week before initiation of the experiments for adaptation to laboratory conditions and free access to water and diet were supplied. Mating was induced overnight by housing females and males at a ratio of 2:1 respectively. The zero-day of pregnancy was detected when the vaginal copulatory plug was present. The selected pregnant females were divided equally into four groups (15 each) as follows:

1. Control group, administrated distilled water.
2. Ginger group was given an oral injection of ginger (200 mg/kg) (Abd El-Aty and Morgan, 2011).
3. Labetalol group given oral injection of labetalol (300 mg/kg) (Mahmoud et al., 1993).
4. Labetalol and ginger injected group, received an oral injection of labetalol first followed by ginger (200 mg/kg) one hour later.

Injection of both labetalol and/or ginger was carried out during the organogenesis phase of gestation i.e. from the 6th to the 15th day. The end of the experiment was determined at day 20 of gestation.

2.2. Labetalol administration:

Labipress tablets (each tablet contain labetalol hydrochloride 100 mg) were manufactured by DBK for pharmaceutical industries, Cairo, Egypt, and obtained from a pharmacy in Shebeen El-Koom, Menoufia. Tablets were ground and dissolved in distilled water and orally injected daily by ordinary syringe. The applied dose was 300 mg/kg body weight which is equivalent to the recommended human dose (Mahmoud et al., 1993).

2.3. Water extraction of ginger:

Fresh rhizomes of ginger (*Zingiber officinale*) was purchased from a local market at Shebeen El-Koom, Menoufia, Egypt. They were shade dried at room temperature and then crushed to powder. 125 g of powder was macerated in 1000 ml of distilled water for 12 h at room temperature and filtered through a 5 Mm filter paper to obtain the final aqueous extract. Accordingly, the concentration of the obtained extract was 24 mg/ml and equal to 120 mg/kg (Badawy et al., 2019). Ginger extract was orally given one hour after labetalol injection at a dose of 200 mg/kg body weight.

2.4. Investigated parameters:

2.4.1. Histological investigation:

Heart tissues were fixed in 10% neutral formalin for 24 h then washed under running tap water for 12 h. The specimens were transferred to 70% ethanol, dehydrated in an ascending series of ethanol, and cleared in xylene. Thereafter, the specimens were transferred to the oven with the temperature set at 60 °C to substitute xylene by pre-melted paraffin wax then blocked out in paraffin wax and sectioned using a rotary microtome (IHC World, China). Histological staining was performed with Ehrlich's hematoxylin and counterstained with aqueous eosin according to Suvarna et al. (2018). Histological sections were examined and photographed by the Olympus microscope (BX41, Japan).

2.4.2. Ultrastructural investigation:

For transmission electron microscope investigation, fetal heart specimens were separated and immediately fixed in 2.5% glutaraldehyde at room temperature. After rinsing in phosphate buffer, samples were postfixed in a buffered solution of 1% osmium tetra-oxide for 3 h at 4 °C. The specimens were then washed in phosphate buffer several times for 10 min. This was followed by dehydration in ascending grades of ethanol (30% up to absolute) and transferring to a solution of propylene oxide for clearing. The samples were then infiltrated and embedded in the epoxy resins using beam capsules and blocks were prepared. Semithin sections of 1 μm thickness were produced for light microscopical examination using LKB ultra-microtome equipped with a glass knife then ultra-thin (50 nm) sections were cut, mounted, and stained with uranyl acetate for 10 min. Sections were then stained with freshly prepared lead citrate for 10 min and washed with distilled water (Kuo, 2007). Examination of grids was done using the JEOL electron microscope (TEM-1400Plus, Japan), Electron Microscope Unit, Alexandria University. Selected sites were digitally photographed.

2.4.3. DNA fragmentation assay:

Nucleic acid extraction was done according to the method of El-Garawani and Hassab El-Nabi (2016). and described in detail in Sakr et al. (2014).

2.4.4. Flow cytometry Annexin-V/PI dual staining assay:

Fresh samples of the fetal heart were transported to the laboratory in isotonic saline and prepared according to Reichard and Asosingh (2018). The material was washed with isotone tris EDTA buffer, 3.029 gm of 0.1 M tris (hydroxymethyl aminomethane, 1.022 gm of 0.07 M sodium chloride (ADWIC) and 0.47 gm of 0.005 M EDTA. They were dissolved in 250 ml of distilled water and then adjust the PH at 7.5 by using 1 N HCl and centrifuged at 1800 rpm for 10 mins. One ml of cells suspensions in phosphate buffer was added onto a 5 ml tube and then resuspended in 2 ml 1x binding buffer (1 ml of 10x buffer + 99 ml dist·H2O) for a good mix. 100 μl of cells suspensions were taken in another 5 ml test tube then add 5 μl of annexin V (Cat. No.556547 BD pharmingen FITC apoptosis Kit) and directly 5 μl PI (PE label), the incubation time for at least 15 min. in dark at room temperature. After the incubation time resuspended the cells in 200 μl 1X binding buffer and immediately analyzed by the flow cytometer Accuri C6 (Becton Dickinson, Sunnyvale, CA, USA) equipped with a compact air cooked low power 15 mwat argon ion laser beam (488 nm). Four different populations of cells are easily distinguished which are viable cells (unlabeled), early apoptotic (bound to Annexin V only), necrotic (stained with PI), and late apoptotic/necrotic cells (both bound Annexin V and PI. The fluorescence distribution was displayed as a two-color dot plot analysis, and the fluorescent cells % in each quadrant was determined.

2.5. Data evaluation and statistical analysis:

All data sets were expressed as mean ± standard error of the mean (SEM). The data were analyzed statistically for normal distribution (student's T-test) and homogeneity of variances (Levene test) using a statistical package of social science (IBM SPSS) statistics software for windows. Version 22 (IBM Corp., Armonk, NY USA). Differences were considered insignificant whenever $P > 0.05$. The significances of the obtained data were classified into three categories, i.e. $P < 0.001$, $P < 0.01$, and $P < 0.05$ according to the obtained P values.

3. Results

3.1. Histological observation:

The heart of the control group showed normal cardiac muscle structure. The myocardium consisted of cross-striated muscle cells, cardiomyocytes, with one centrally placed nucleus. The intercalated discs were also seen between cardiac cells (Fig. 1A).

The heart of the fetuses maternally injected with ginger exhibited a normal structure similar to that of the control group. The myocardium consisted of branching and anastomosing longitudinal muscle fibers with oval vesicular central nuclei (Fig. 1B).

Examination of the fetal heart tissue of labetalol injected rats showed several histological alternations. These included many congested blood vessels, intracellular hemorrhage, and areas of pale homogenous acidophilic and vacuolated cytoplasm with either absence or presence of nuclei. Empty spaces and Pyknotic nuclei were also noticed. Besides, mononuclear cellular infiltration between the muscle fibers and fatty hydropic degeneration was also obvious in the myocardium of treated rat fetuses (Fig. 1C-G).

Sections were taken from rats which were injected with ginger and labetalol showed a near-normal structure of the myocardium with no lipid droplets. Slightly congestion of intramuscular blood vessels was noticed.

3.2. Ultrastructure investigation

Transmission electron microscopic examination of cardiac myocytes of the control group displayed no ultrastructural pathologic findings. Normal myofibrils structure with striations. The myofibrils were attached end to end by intercalated discs. They were also arranged in sarcomeres between Z- lines. Each cardiac myocyte contained a central oval euchromatic nucleus with a prominent nucleolus. The mitochondria were numerous and distributed in rows and were seen separating cardiac myofibrils. There were no abnormalities in both mitochondria and myofibrils (Fig. 2A&B).

The ginger group showed an almost normal appearance of the cardiomyocytes with apparently normal mitochondria in between muscle fibers, the normal architecture of myocardium with its nucleus and normal appearance of myofibril striations were seen (Fig. 2C).

Electron microscopy examination of the heart of the labetalol group confirmed the modifications observed with the optical microscope and provided more details on the effects of labetalol at the ultrastructural level. Severe damage in cardiac muscle was obvious. The myocardium revealed focal areas of fragmentation and extensive lysis of the myofibrils and disruption in the Z-line of fibrils. The nuclei of cardiac myocytes exhibited several degenerative changes where, some of them shrunken, pyknotic, and irregular outlines of the nucleus were also observed. Degeneration of mitochondria with loss of its cristae and vacuolation of the cytoplasm were observed. Degenerated intercalated discs and accumulation of collagen fiber bundles were seen in some myocytes (Fig. 2D-J).

The cardiac cells of rat fetuses in the group injected with labetalol followed by ginger showed a relative improvement. Most of the myocardial fibers restored their normal appearance, but few areas still degenerated. The mitochondria appeared relatively normal and the nuclei showed relatively normal distribution of chromatin and prominent nucleolus. Few vacuolations could be observed in the cytoplasm (Fig. 2K&L).

3.3. DNA fragmentation:

A significant ladder pattern of DNA fragmentation was observed in cardiac cells maternally treated with labetalol compared with control and ginger groups. On the other hand, the cardiac cells of the combined group displayed less DNA fragmentation compared with the ginger injected group (Fig. 3).

3.4. Detection of apoptosis by Annexin-V/PI dual staining:

The flow cytometry analysis, Annexin V/propidium iodide of cardiac cells showed that labetalol treatment caused cells to shift from viable to apoptotic. After treatment with labetalol, the early apoptotic rates were highly significantly increased by 16.71% compared with the control of 1.25%. Furthermore, the late apoptotic and necrosis rates were also increased to 22.73 & 18.61% respectively compared with control of 0.88 & 1.66%. Also, the percentage of viable cells showed a highly significant reduction of 41.95% compared with control of 96.21%. Otherwise, the injection of ginger after labetalol caused a noticeable increase in the percentage of the viable cells and a highly significant reduction in the apoptotic and necrosis rates compared with the labetalol group (Fig. 4 & Fig. 5).

4. Discussion

Taking into consideration the different types of antihypertensive drugs, clinicians have to be familiar with the potential side
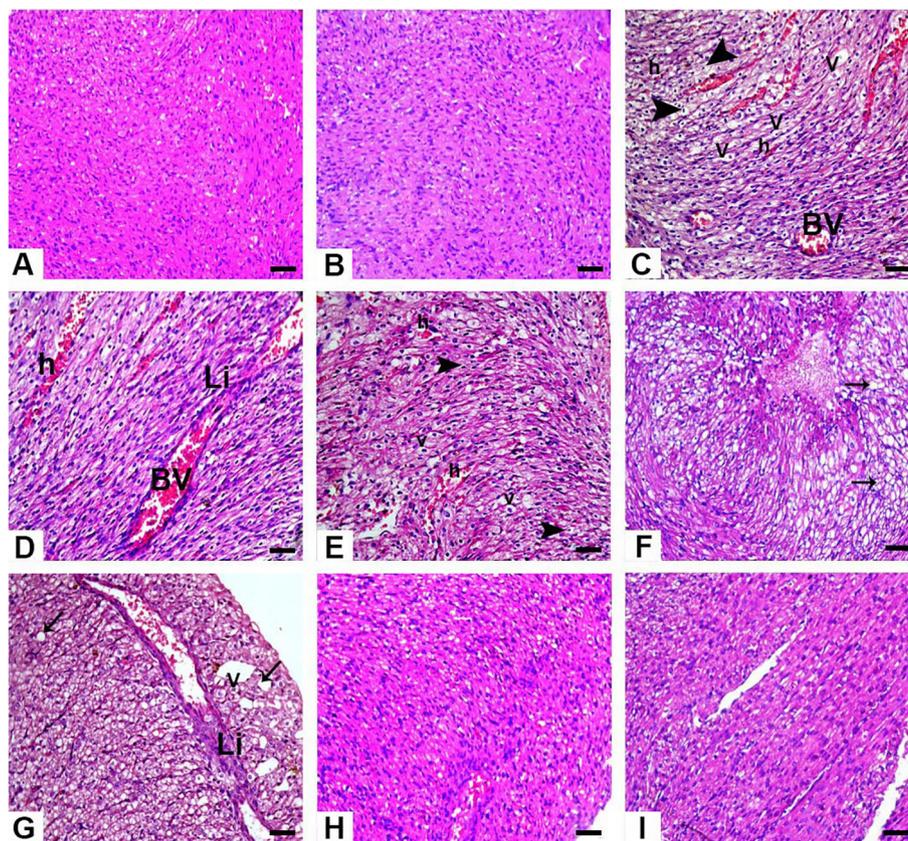
Fig. 1. Photomicrographs of sections in the cardiac muscle of 20-day old rat fetuses. (A) Control group. (B) Ginger group. (C-G) Labetalol group showing congested blood vessels (BV), pyknotic nuclei (Arrowhead), hemorrhage (h), vacuolated cytoplasm (V), leukocytic infiltration (Li), and fatty hydropic degeneration (Arrow). (H-I) Labetalol + ginger group. Scale bar = 0.015 mm.

impacts of these drugs. The perfect objective of antihypertensive therapy is not only to normalize the blood pressure level but also to prevent organ damage and the progression of cardiovascular disease. There are many contradictory opinions about the effect of antihypertensive drugs on the structure of the heart (Guerrero-García and Rubio-Guerra, 2018). Consequently, this study is an attempt to clarify the adverse histological ultrastructure and molecular effects of one of the popular antihypertensive drugs i.e. labetalol during pregnancy on the cardiac tissue of 20-day old rat fetuses.

It is well known that labetalol acts by blocking α and β adrenergic receptors to decrease peripheral vascular resistance without alteration of heart rate or cardiac output. It can reduce heart rate during exercise while maintaining cardiac output by an increase in stroke volume. It also relaxes vascular smooth muscle by a combination of partial β2-agonism and through α-blockade. Common side effects have been reported to labetalol like low blood pressure with standing, dizziness, feeling tired and nausea (Podymow and August 2011). As with all β blockers, labetalol has negative entropic effects and has the potential to cause acute left ventricular failure if given in sufficiently large enough closes to those patients who have impaired function of the left ventricle. Moreover, adverse cardiac effects related to β-adrenergic receptor blockade myocardial infarction and congestive heart failure (Rehsia and Dhalla, 2010).

The current study showed that histological examination of the cardiac tissue of rat fetuses maternally injected with labetalol has several pathological consequences. The cardiac tissue appeared with massive congestion in the blood vessels, hemorrhage, vacuolated cytoplasm with pyknotic nuclei, monocytes infiltration, and

fatty hydropic degeneration. The results obtained from this study are in agreement with Abed (2015) who showed that injection of chicken eggs with 10 or 15 mg/70 kg b.wt Metoprolol (β-adrenergic receptors) caused many pathological lesions in the heart tissue of the chick embryo. These changes including heart tissue damage, edema, vacuolation, blood vessel congestion, and hemorrhage. Sachdeva et al. (2014) showed that metoprolol did not reduce the incidence of the structural damage caused by isoproterenol injection in rats. Moreover, Momma and Taka (1989) reported that injection of 10 mg/kg nifedipine (calcium channel blockers) to the pregnant rats caused massive accumulation of pericardial fluid and ventricles dilatation in the mother and fetuses. On the contrary, some studies suggested that amlodipine and carvedilol have protective effects on doxorubicin-induced cardiotoxicity (Akshata and Shivalingegowda, 2020). Also, telmisartan which is an angiotensin II receptor blocker can prevent cardiac and perivascular fibrosis in renovascular hypertensive rats (Kawai et al., 2009; Abdel Kader et al., 2017).

In the present study, various ultrastructure alterations were observed in the heart of labetalol injected group, severe damage of cardiac muscle like extensive lysis of the myofibrils, disruption in Z-line, shrunken, pyknotic and irregular outlines of the nuclei, degeneration of mitochondria with loss of its cristae and vacuolation of the cytoplasm were observed. Degenerated intercalated discs and accumulation of collagen fiber bundles were seen in some myocytes. A previous study by Abdelmeguid et al. (2008) found that the ultrastructural effects of the antihypertensive captopril injection into mice were abnormal nuclei, marginated heterochromatin, abnormal condensed nucleoli, and degenerated mitochondria. On contrary, Abd-Ellah (2012) found that treatment
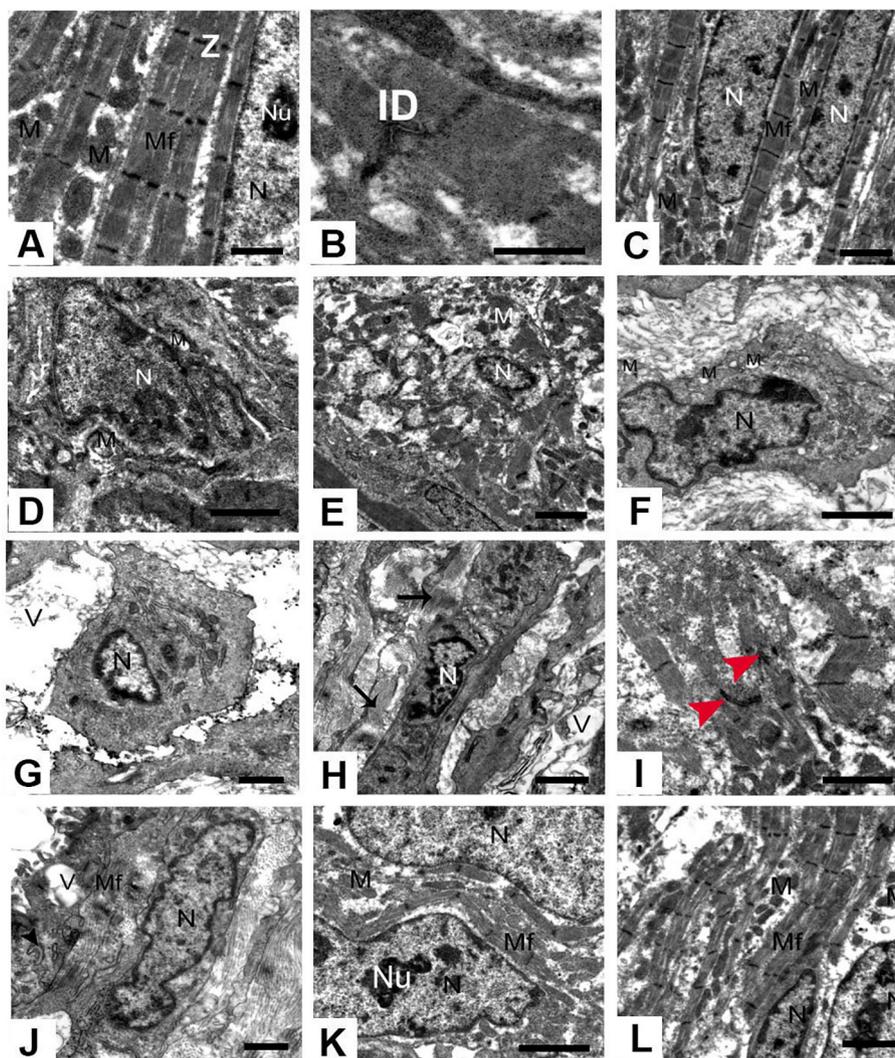
Fig. 2. Transmission electron micrographs of cardiac cells of rat fetuses. (A-B) Control group showing oval euchromatic nucleus (N) with a prominent nucleolus (Nu), normal myofibrils striations (Mf) with Z lines (Z), mitochondria in rows (M), and intercalated disc (ID). (C) Ginger group. (D-J) Labetalol group showing fragmented, pyknotic, and irregular nuclei (N), vacuolation (V), degenerated mitochondria (M), collagen fiber bundles (Arrow), fragmented, and lysis of myofibrils and degenerated intercalated discs (Red arrowhead). (K&L) Labetalol + ginger group. Scale bar = 2.0 µm for all except (A&B&G&J) = 1.0 µm.
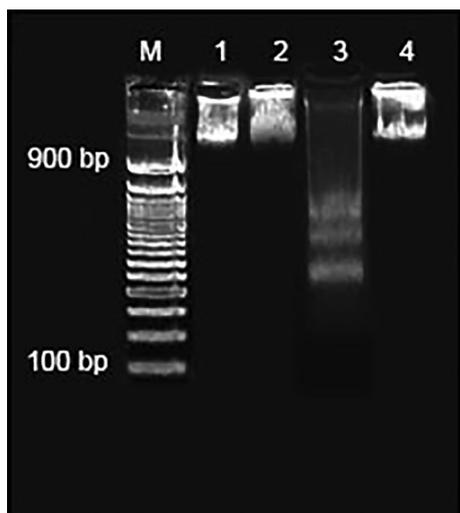

Fig. 3. DNA fragmentation of fetal cardiac cells using ethidium bromide-stained gel; marker (M), control (1), ginger (2), labetalol (3), and labetalol + ginger (4).

with captopril could mitigate the marked ultrastructure cardiotoxicity induced by 5- fluorouracil. Another study by Oliveira et al. (2004) showed that carvedilol and atenolol injection (adrenergic receptor antagonism) into rats have different effects against doxorubicin-induced cardiotoxicity. Atenolol had not no effect on doxorubicin-induced cardiac damage while carvedilol prevented most of the cardiac alternations caused by doxorubicin. Also, it has been found that perindopril (an angiotensin-converting enzyme inhibitor) and atenolol (β adrenergic receptor blocker) but not amlodipine (calcium channel blocker) have protective effects on alcohol-induced ultrastructure myocardial injury in rats (Sag et al., 2006).

According to the present study, labetalol was found to cause evident DNA damage and a noticeable increase in the apoptotic and necrosis rates of the cardiac cells of rat fetuses. It is well known that DNA strand breaks during apoptosis due to activation of endonucleases which can be determined by agarose gel electrophoretic analysis (Zhdanov et al., 2015). Annexin V/PI staining in flow cytometry analysis is based on the ability of the Annexin V protein to bind to phosphatidylserine (PS), which is translocated from the inner membrane in the viable cells to the outer cell
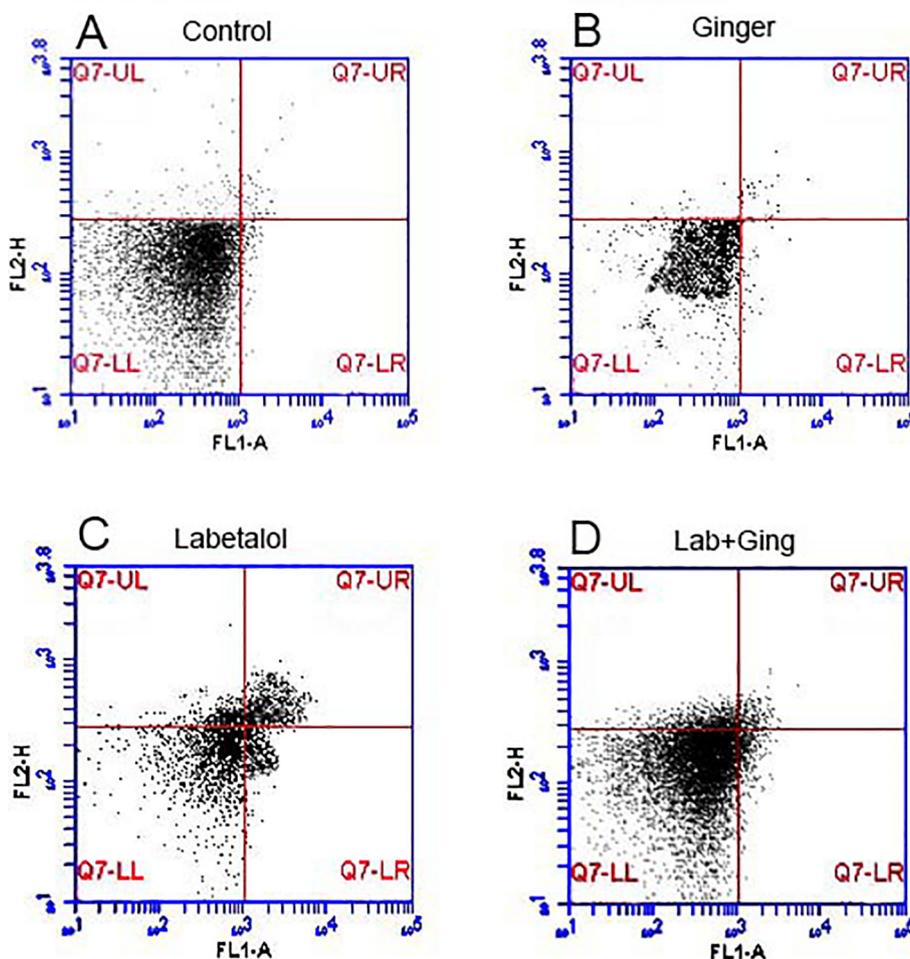
Fig. 4. Fluorocytograms of fetal cardiac cells of different experimental groups; (FL1-A) = Annexin V + ve cells and Y-axis (Fl2-H) = PI-labeled cells. The lower left portion (Q4-LL) of the fluorocytogram (-ve for both stains) shows viable cells, whereas the lower right portion (Q4-LR) (+ve for Annexin) shows early apoptotic cells, the upper right portion (Q4-UR) (+ve for both stains) shows late apoptotic cells and the upper left portion (Q4 UL) (+ve for PI) shows necrosis.
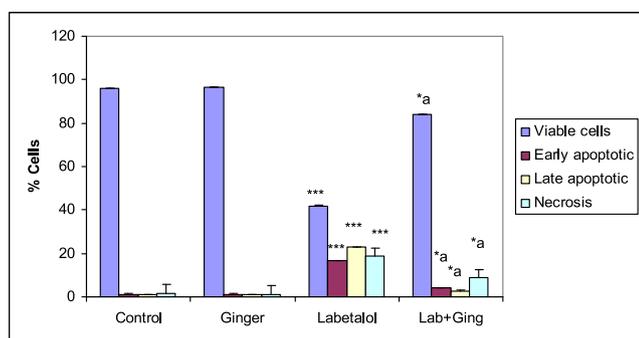

Fig. 5. Graph showing the percentage of viable, apoptotic, and necrotic populations in experimental groups. Data are represented as mean ± SEM. Asterisks (***$P > 0.001$, *$P > 0.05$) refer to the P-value compared with the control group. a = highly significant ($P > 0.001$) compared with labetalol group.

membrane upon induction of apoptosis so it becomes available for Annexin V binding. The addition of PI enabled viable, early apoptotic, late apoptotic, and necrotic cells to be distinguished (Baskic et al., 2006). A study by Claude et al. (2013) on the effect of antihypertensive drugs injection on genomic DNA revealed that Amlodipine induced DNA damage in somebody organs of mice. On the other hand, Tea et al. (1999) reported that apoptosis was highly increased after the administration of different antihypertensive drugs such as β-adrenergic blockade and renin-angiotensin in rats.

Medicinal plants have been utilized since ancient times for the treatment of numerous diseases. They have played a key role in world health. Although medicine in recent decades became more advanced, plants still make an important contribution to health care. The rhizome of ginger contains numerous bioactive constituents such as antioxidants (Nile and Park 2015) and anti-inflammatory (Zhang et al., 2016) which possesses health-promoting properties. Based on the scientific findings, ginger has the ability to treat many cardiovascular diseases (Wu et al., 2018), cardiac hypertrophy (Rohini et al., 2013), and hypertension (Ghayur et al., 2008).

The present study illustrated that ginger significantly ameliorated the pathological changes caused by labetalol in the fetal cardiac tissue. The cardiac tissue of the combined group showed near-normal structure without lipid droplets. Many studies confirmed the ameliorative role of ginger on heart tissue; Amran et al. (2015) reported that ginger extract with three doses (100, 200, and 400 mg/kg of b.wt) had a protective effect against myocardial infarction caused by isoproterenol in rats. Moreover, Abas (2017) has found that ginger extract at doses 200, 400, and 600 mg/kg b.wt. protect against cisplatin-induced cardiotoxicity in male albino rats. Similarly, a study by Ajibade et al. (2013) indicated that ginger extract at doses 1 or 2 g/kg/day can protect against Monosodium Glutamate induced cardiotoxicity in Wistar rats. Also, ginger

has an amelioration effect on the age-related changes in heart tissue in normal female rats (Kim et al., 2010).

Treatment with ginger after labetalol revealed marked amelioration in the ultrastructure of cardiomyocytes compared to those of the labetalol group. Most of the myocardial fibers restored their normal appearance, but few areas still degenerated. This is in agreement with Shalaby et al. (2019) who found that ginger extract (200 mg/kg/day orally) prevented the adverse ultrastructure changes in cardiomyocytes caused by cyclophosphamide injection in rats. Furthermore, another study investigated the protective properties of the ginger ethanolic extract against myocardial damage caused by alcohol administration. The transmission electron microscopic examination revealed that ginger injection at a dose of 200 mg/Kg b.wt. reducing the architectural damage, recovery of the intercalating disk, nuclei, and regenerate the myofibrils (Subbaiah, 2017). Also, Elhawwary and Omar (2019) reported that ginger extract has a good influence on the ultrastructure changes of the cardiac cells caused by cisplatin in rats.

According to the present study, ginger had ameliorative effects on DNA fragmentation and the apoptotic and necrotic rates as it increases the percentage of viable cells and decreased the apoptotic and necrotic percentages. The data matched with Lu et al. (2003) who reported that ginger oil significantly reduced DNA damage caused by H_2O_2 *in vitro* so, it can be used as an antioxidant due to its ability in scavenging oxygen radicals. Also, it has been found that the active component of ginger i.e. [6]-gingerol can effectively protect against OH-induced DNA damage (Lin et al., 2014). Besides, the ginger aqueous extract had a protective effect against Benzo(a)pyrene-induced DNA damage in human peripheral blood lymphocytes (Nirmala et al., 2007). Moreover, Hassab El Nabi et al. (2019) found that ginger oil significantly improved DNA damage caused by etoposide in albino rats. Recently, Makpo et al. (2020) reported that aqueous ginger extract at a dose of 200 mg/kg daily prevented DNA damage in rats. Also, [6]-gingerol has been observed to prevent genotoxicity and reduce oxidative cell death induced by toxicants (Lee et al., 2011; Yang et al., 2011). Also, Mohammad et al. (2018) reported that ethanolic ginger extract (200 mg/kg) could inhibit testicular cell apoptosis in chronic diabetic rats. Furthermore, ginger at a dose of 100 mg/kg could decrease apoptosis caused by gentamicin in male rats (Zahedi et al., 2012). Sakr and Badawy (2011) reported that ginger reduced the numbers of apoptotic cells in metiram treated mice. Generally, ginger may show a defensive impact against labetalol induced cardiotoxicity due to its anti-apoptotic, anti-oxidant, and anti-inflammatory properties.

In conclusion, this study provided evidence that labetalol injection during rat organogenesis is associated with the induction of fetal cardiotoxicity. Histopathological, ultrastructural, and molecular evaluations showed that co-administration of ginger protected most of the damage caused by labetalol in the cardiac tissue structure, DNA, and apoptotic rats. Therefore, ginger might be a potential candidate agent against labetalol induced cardiotoxicity.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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