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# Research Article
# Effects of Adenosine Triphosphate on Vandetanib-Induced Heart Damage in Rats

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## Abstract

**Background and Objective:** Vandetanib is a drug with anticancer activity that belongs to the tyrosine kinase inhibitor group. Cardiotoxicity is one of the serious side effects induced by vandetanib. Vascular endothelial growth factor (VEGF) inhibition is the main responsible mechanism for this side effect. VEGF increases intracellular adenosine triphosphate (ATP) levels and reduces the production of Reactive Oxygen Species (ROS), protecting the cell from oxidative stress. The study aims to investigate the protective effect of exogenous ATP against possible vandetanib-induced heart damage in rats. **Materials and Methods:** The animals were divided into three groups; vandetanib (VDB), vandetanib+ATP (VAT) and Healthy Groups (HG). Total Oxidant Status (TOS) and Total Antioxidant Status (TAS) levels and Oxidative Stress Index (OSI) were analyzed from the heart tissue. Troponin I (TP I), creatine kinase-MB (CK-MB) levels were analyzed from the blood sample. The cardiac histopathological examination was also performed. **Results:** Results shows that the OSI and TOS levels of VDB group animals increased significantly, TAS levels were found to be significantly lower compared to VAT and HG. Both TP I and CK-MB levels were significantly higher in the VDB group. However, the ATP administration to VAT group animals brought these values closer to HG. In histopathological examination, substantial myocardial damage was observed due to vandetanib exposure. However, ATP administration ameliorated structural damage signs induced by vandetanib. **Conclusion:** Vandetanib exposure substantially induced oxidative stress-related damage in rat heart tissue. Exogenous ATP replacement was able to ameliorate the toxic consequences of vandetanib, biochemically and histopathologically probably due to reduction of the ROS products.

Key words: Vandetanib, adenosine triphosphate, cardiotoxicity, rat

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Vandetanib is a widely used anticancer drug that belongs to the tyrosine kinase inhibitor group. Vandetanib has been reported to interrupt Vascular Endothelial Growth Factor (VEGF) and epidermal growth factor receptor signaling[1]. VEGF is a multifunctional protein that essentially induces angiogenesis by consecutive complex processes such as Endothelial Cell (EC) proliferation and migration. VEGF inhibition by vandetanib constitutes an important therapeutic target by reducing angiogenesis, which plays a key role in tumor persistence and growth[2]. However, VEGF inhibition has been held responsible for adverse effects in many tissues, including the cardiovascular system. VEGF signaling is important for proper EC functions and vascular structure integrity. VEGF inhibition may cause serious cardiac adverse effects such as hypertension, arterial thromboembolism, cardiac ischemia and contractile impairment[3].

The mechanism of side effects is explained as impaired nitric oxide synthesis and excessive pressure load due to abruption of angiogenesis[4,5]. VEGF has demonstrated a protective effect from oxidative stress by increasing adenosine triphosphate (ATP) levels and reducing Reactive Oxygen Species (ROS) production. Gua *et al.*[6] showed that the underlying mechanism of VEGF action was by enhancing the mitochondrial functions. ATP is a molecule mostly formed through mitochondrial oxidative phosphorylation and provides a vital energy source for myocytes[7].

As is known, mitochondria play an important role in developing oxidative stress during the electron-transforming process. Depending on internal and external factors, ROS overproduction may damage mitochondrial and cytosolic membranes, protein complexes and deoxyribonucleic acid[8]. A recent study showed that ATP deficiency triggers lipid peroxidation in rats, causing tissue damage[9]. Since the heart requires large amounts of ATP, mitochondrial dysfunction induced by VEGF inhibition is expected to result in excessive ROS formation[7].

Oxidative stress has been shown to play an important role in the pathophysiology of cardiac damage[10]. In light of this data, vandetanib may lead to oxidative heart damage by inhibition of mitochondrial functions. Current study aims to investigate the protective effects of exogenous ATP against possible vandetanib-induced heart damage in rats.

## MATERIALS AND METHODS

This study was conducted in Erzurum Ataturk University Animal Research Laboratory for a month in June, 2020. The research duration took approximately 3 months after the experiment was completed.

**Animals:** Eighteen male albino Wistar rats weighing between 285-298 g used in the experiment. The animals obtained from Erzurum Ataturk University were housed at average room temperature (22°C) for one week to adapt to the environment. Animals were fed ad libitum during the experiment and performed alternating 12 hrs light/dark cycles. Animal experiments were performed in accordance with the National Guidelines for the Use and Care of Laboratory Animals. All phases of our study have been approved by the animal experiments local ethics committee (Date: 03/03/2020, Meeting no: 77040475-010.03-E.2000072885).

**Chemicals:** Thiopental sodium from IE Ulagay (Turkey), vandetanib from Sanofi-Aventis (Ireland) and ATP from Zdorove Narodu (Ukraine) obtained for the experiment.

**Experiment groups:** The animals were divided into three groups; vandetanib (VDB), vandetanib+ATP (VAT) and Healthy Groups (HG).

**Experimental procedure:** ATP was injected intraperitoneally to VAT (n-6) group animals at a 25 mg $kg^{-1}$ dose per day for a month. During this time, HG (n-6) and VDB (n-6) group animals received an equal volume of isotonic saline (0,9 % NaCl) as a solvent in the same way. One hour after applying ATP and isotonic saline, vandetanib was administered to the VDB and VAT groups at the dose of 25 mg $kg^{-1}$ with a catheter directly to the stomach. This procedure was repeated once a day for 30 days. At the end of this period, all animals were sacrificed with 50 mg $kg^{-1}$ thiopental sodium and their hearts were removed. Troponin I (TP I) and creatine kinase-MB (CK-MB) levels were determined from blood samples taken from tail veins before the anesthesia procedure. The removed heart tissues were examined biochemically and histopathologically. All results obtained from the experiment compared with each other.

**Biochemical analysis of heart tissue:** Supernatant portions of homogenates prepared from heart tissues were used for biochemical analysis. Total Oxidant Status (TOS) and

Total Antioxidant Status (TAS) levels and Oxidative Stress Index (OSI) analyzed from the heart tissue using appropriate methods.

**Total oxidant status and total antioxidant status in tissue:** TOS and TAS levels of tissue homogenates were determined using a novel automated measurement method and commercially available kits (Rel Assay Diagnostics, Turkey), both developed by Erel[11,12]. In the TOS method, the oxidants present in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction was enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion produced a colored complex with xylenol orange in an acidic medium. The color intensity, which could be measured at 530 nm spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The results were expressed as μmol hydrogen peroxide ($H_2O_2$) equivalent/L. The TAS method is based on the bleaching of characteristic color of a more stable ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) radical cation by antioxidants and measurements were performed at 660 nm. The results were expressed as mmol Trolox equivalent/L. The ratio of TOS to TAS was called OSI. OSI was calculated as TOS divided by TAS[13].

**Biochemical analysis of blood samples**

**Troponin I assay:** TP I levels were measured in the VIDAS Troponin I Ultra kit by utilizing the ELFA (Enzyme-Linked Fluorescent Assay) technique. All steps of the test were done automatically on the VIDAS device using the test reagents available in the kit. The sample transferred to anti-cardiac TP I antibodies which were marked with alkaline phosphatase (conjugate). TP I conjugated after the mixture was released into the solid phase supplier. Composed conjugate bound to the inner wall of the antigen. Unbound content washed and removed. The conjugate enzyme catalyzes 4-methylumbelliferyl phosphate and the generated product (4-methylumbelliferone) measured at a wavelength of 450 nm. The intensity of fluorescence is proportional to the concentration of antigen present in the sample. The results are expressed as ng $L^{-1}$.

**Creatine kinase-MB assay:** CK-MB, which was obtained from rats plasma, measured by Roche/Hitachi Cobas c 701. All steps of the test were performed by immunological UV test following the procedure and using ready-made test reagents. CK-MB isoenzyme has two active sites called CK-M and CK-B. The catalytic activity of the CK-M subunits inhibited to 99.6% in the sample with the help of the CK-M specific antibodies without affecting the CK-B subunits. The remainder of the CK-B activity, which corresponds to half of the CK-MB activity, was determined by the total CK method. The results are expressed as U $L^{-1}$.

**Histopathological examination:** Removed cardiac tissues were fixed in 10% formalin solution for 24 hrs. Samples were then treated with a conventional grade of alcohol (70, 80, 90 and 100%) to remove the water within tissues. Tissues were then passed through xylol and embedded in paraffin. After routine tissue treatment, 5 micron thick sections were obtained from the paraffin blocks and stained with Hematoxylin and Eosin. All sections were evaluated under a light microscope (Olympus BX 52, Tokyo, Japan) by pathologists who were blind to treatment protocols. Histopathological data (Polymorphonuclear leukocyte (PNL) infiltration, hemorrhage and necrotic/degenerative changes in myocytes) were analyzed by the pathologist and ratings to between 0 and 3 (none-0, mild-1, moderate-2 and severe-3).

**Statistical analysis:** Normal distribution of the data was tested using the one-sample Kolmogorov-Smirnov test. Continuous variables were presented as mean±SD. An analysis of variance was utilized to compare multiple group means. The following post hoc evaluation was made by LSD (least significant differences) method. The $p<0.05$ values were considered to be statistically significant. Statistical analyses were performed using SPSS 20.0 software for Windows (SPSS Inc, Chicago, IL).

## RESULTS

**Biochemical results of heart tissue:** TOS and TAS levels were analyzed from the heart tissue. Results showed that the OSI and TOS levels of the VDB group significantly increases compared to VAT and HG ($p<0.001$). The difference in TOS levels and OSI between HG and VAT was statistically insignificant ($p>0.05$). In contrast to TOS, TAS levels were significantly lower in the VDB group than VAT and HG ($p<0.001$). There was no significant difference between the HG and VAT groups in terms of TAS levels ($p>0.05$) (Fig. 1).

**Biochemical results of blood samples:** Both TP I and CK-MB levels were significantly higher in the VDB group compared to the VAT and HG ($p<0.001$). TP I and CK-MB levels were found to be similar between HG and VAT groups. This difference was statistically insignificant ($p>0.05$) (Fig. 2).

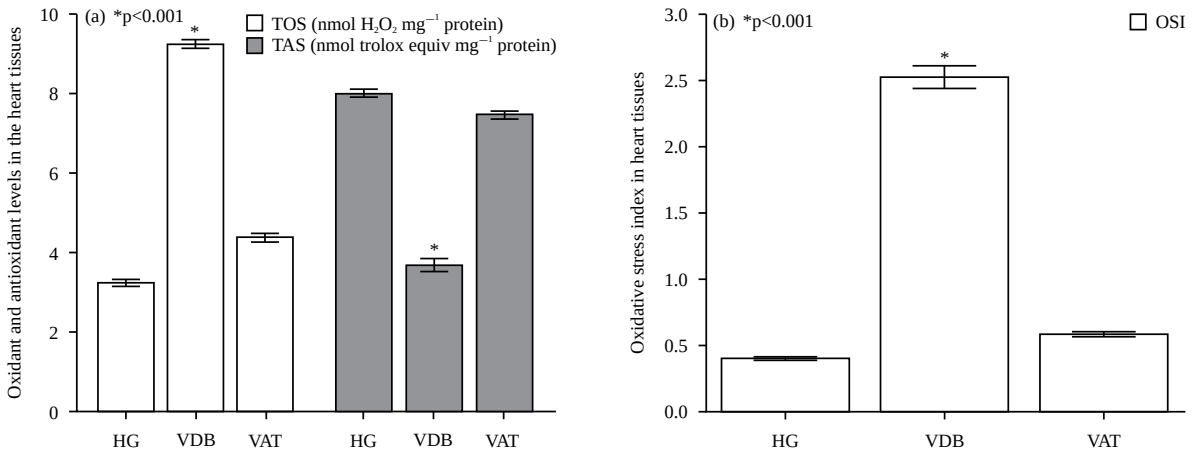


Fig. 1(a-b): (a) TOS/TAS levels and (b) OSI in the heart tissue of VDB group
*p<0.001 according to VAT and HG (by GraphPad)

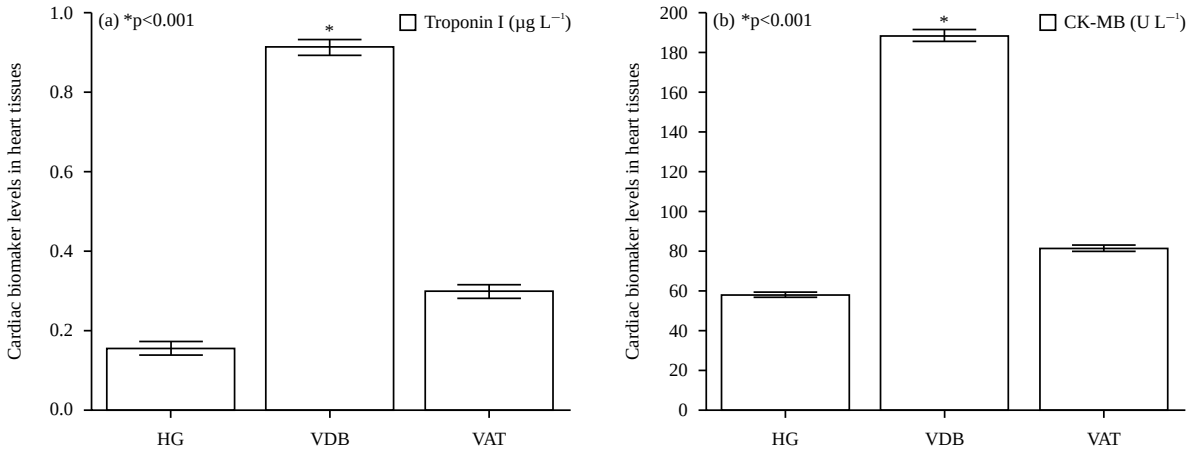


Fig. 2(a-b): (a) Tp I and (b) CK-MB levels in the heart tissue of VDB group
*p<0.001 according to VAT and HG (by GraphPad)

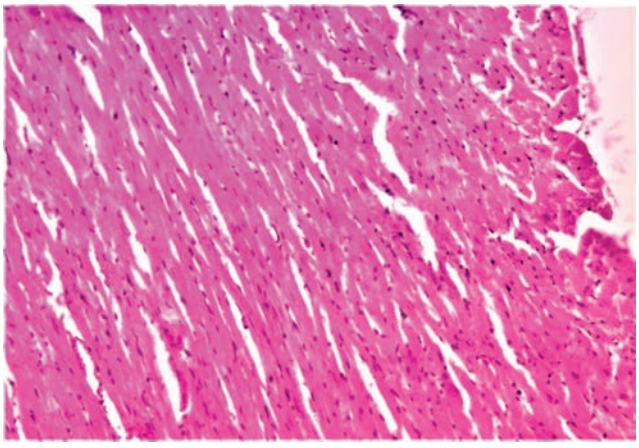

Fig. 3: Normal histological structures of the HG heart (H and E×200)

**Histopathological results:** Statistically significant differences were detected among groups in terms of histopathological findings (Table 1). Under microscopic examination, normal histological structures of the endocardium, myocardium and epicardium layers were observed in HG heart tissue (Fig. 3). Heart tissues of VDB group rats had severe hemorrhage compared to VAT and HG, respectively ($p<0.05$, $p<0.001$) (Fig. 4a). It was determined that VAT group animals' histopathological findings were close to HG (Fig. 4b). Besides, severe PNL infiltration and necrotic/degenerative changes in myocytes were observed in VDB group animals compared to VAT and HG, respectively ($p<0.05$, $p<0.001$) (Fig. 4c). Similar histopathological findings were observed in VAT group rats compared to HG, except for mild degenerative changes and mild PNL infiltration (Fig. 4d).

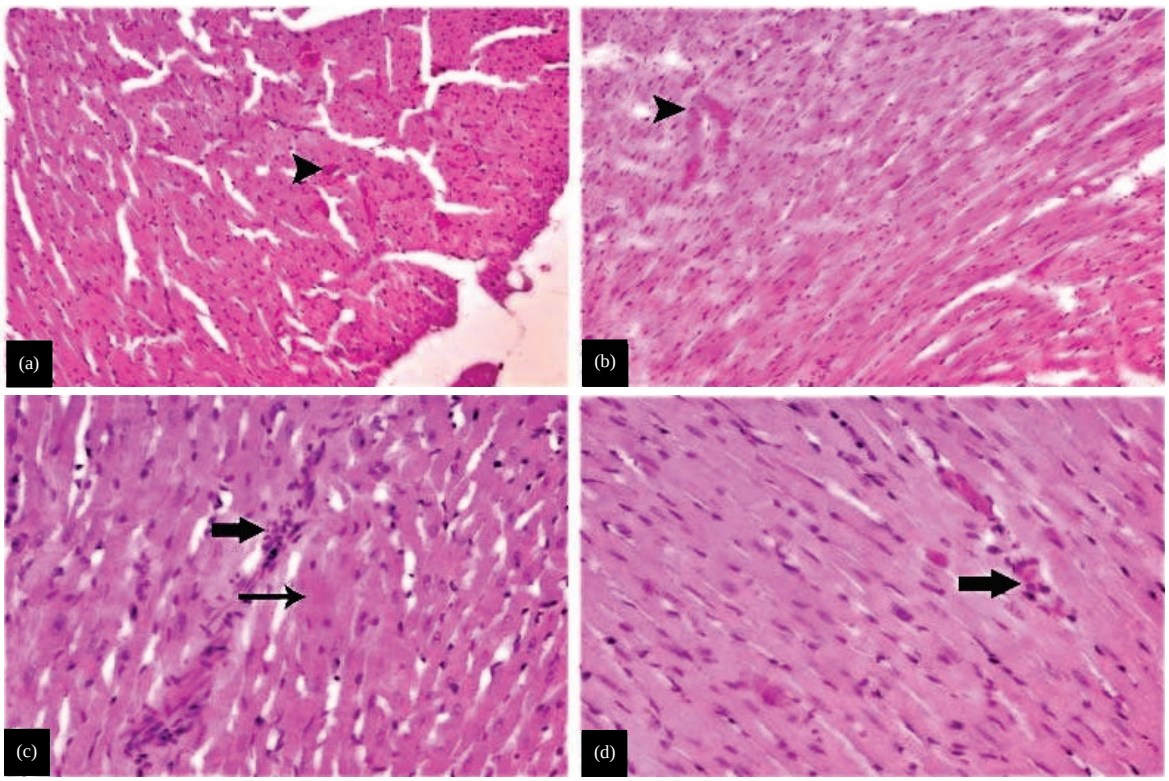


Fig. 4(a-d): (a) VDB group specimen with severe hemorrhage signs, (b) VAT group specimen with mild hemorrhage signs, (c) VDB group specimen with severe PNL infiltration (thick arrow) and necrotic/degenerative changes (thin arrow) and (d) VAT group specimen with mild PNL infiltration (H and E×400)

Table 1: Heart tissues of VDB group rats had severe hemorrhage, PNL infiltration and degeneration compared to VAT and HG. Histopathological findings of VAT group animals found to be close to HG

| Parameters | HG (n:6) (Mean±SD) | VDB (n:6) (Mean±SD) | VAT (n:6) (Mean±SD) | p-value* | p-value# |
|---|---|---|---|---|---|
| Hemorrhage | 0.16±0.40 | 2.83±0.40 | 1.83±0.40 | <0.001 | <0.05 |
| PNL infiltration | 0.33±0.40 | 2.66± 0.51 | 1.16±0.40 | <0.001 | <0.05 |
| Necrotic/degenerative changes | 0.00±0.00 | 2.16± 0.40 | 1.16±0.40 | <0.001 | <0.05 |

*According to HG and VAT groups, #According to VDB and VAT groups

## DISCUSSION

Many studies have so far been conducted to prevent cardiotoxicity due to antineoplastic drugs[14]. This study focuses on the prevention of vandetanib-induced oxidative heart damage by exogenous ATP administration. To the best of our knowledge, this is the first study investigating the effects of ATP treatment on long-term vandetanib-induced heart damage in rats. Experimentally we tried to reverse vandetanib-induced oxidative damage by applying exogenous ATP. The results showed that the vandetanib treatment significantly increases oxidative stress and cardiac injury parameters. However, pretreatment with exogenous ATP brought these parameters close to healthy animal levels. As well as biochemical evidence of vandetanib-induced oxidative tissue damage, the present study demonstrated histopathologically significant heart tissue damage signs.

Vandetanib reveals anticancer property mainly by inhibiting VEGF activity[1]. However, beneficial effects of this drug may be limited by adverse effects on many tissues and cardiotoxicity is one of the most important side effects[15]. VEGF inhibition disrupts angiogenesis, ultimately triggering ROS overproduction and oxidative tissue damage[16]. Studies revealed evidence that VEGF exerts cardioprotective effects by reducing oxidative damage[17]. VEGF has been shown to increase Fatty Acid Transport Proteins, provide an energy source for cells and have a key role in preventing mitochondrial dysfunction during oxidative stress[18]. Another

study supporting the above-mentioned mechanism showed that VEGF plays an important role in regulating mitochondrial functions by stimulating the expression of some nuclear-encoded mitochondrial genes[19]. The factors inducing ATP deficiency may accelerate mitochondrial protein complexes dysfunction, subsequently resulting in ROS overproduction[20]. Previous studies demonstrated the preventive effect of exogenous ATP on oxidative damage in different tissues[21,22].

Oxidative stress intensity raises TOS levels, conversely lowers TAS levels[23]. The current study shows that in the VDB group animals, high OSI and TOS levels and low TAS levels indicate ATP deficiency and subsequent oxidative damage induced by VEGF inhibition. However, TOS and TAS levels of the VAT group found to be close to HG, indicating the protective effect of exogenous ATP on oxidative damage. Vandetanib therapy likely disrupted mitochondrial functions, altering the oxidant/antioxidant balance in favor of oxidants. The recently published study showed that exposure to tyrosine kinase inhibitor increases oxidative stress by impairing mitochondrial function[24].

Cell membrane lipids are potential targets for ROS products that initiate cell damage[25]. CK-MB and TP I are sensitive indicators for myocardial injury and are widely used for myocardial infarction confirmation[26]. Although the mechanism of myocardial damage in oxidative stress is not fully understood, studies have shown that excessive ROS formation causes myocardial membrane damage, resulting in membrane leakage and subsequent release of cardiac biomarkers into the circulation[27,28]. The present study has also demonstrated that vandetanib exposure increased TP I and CK-MB levels in rats' blood serum; whereas, parenteral ATP administration has prevented excessive elevation of TP I and CK-MB levels. Myocardial cells are highly susceptible to ATP deficiency due to extreme demand for energy sources. ROS induce myocardial remodeling and may play an important role in the pathophysiology of functional and structural heart damage[29]. Moreover, ROS mediates apoptosis of myocytes and can directly impair contractile function[20]. Bagheri-Yarmand *et al.*[30] have shown that tyrosine kinase inhibitor promotes oxidative stress-induced apoptosis in medullary thyroid cancer. In addition Hasinoff and Patel[32] have shown that kinase inhibitor with anticancer activity causes myocyte damage and elevated serum cardiac biomarkers in vitro conditions.

A recently published study showed a correlation between TP I leakage into blood serum and the degree of histopathological damage[33]. Our study histopathologic damage signs were well correlated with biochemical results. Severe destruction signs such as PNL infiltration, bleeding and necrotic/degenerative changes were observed in animals exposed to Vandetanib. Furthermore, in animals pretreated with ATP, histopathologic changes were close to the HG except for mild PNL infiltration and slightly congested vessels. The present study histopathological examination findings suggested that ATP parenteral administration could prevent destruction signs induced by vandetanib in heart layers and vessels. Our results coincide with the Aldemir *et al.*[31] study demonstrating the protective effect of parenteral ATP administration on sunitinib-induced oxidative heart damage. Although ATP could be considered to possess the therapeutic potential, it is not clear if exogenous ATP pretreatment will reduce the anticancer activity of vandetanib. Furthermore, functional studies might be carried out to confirm whether biochemical and histopathological changes correlate with cardiac function alterations.

## CONCLUSION

Vandetanib exposure substantially induced oxidative stress-related damage in rat heart tissue. Oxidative parameters and cardiac biomarkers might be favorable indicators in the identification of vandetanib-induced cardiotoxicity. Replacement of diminishing ATP was able to ameliorate the toxic consequences of vandetanib biochemically and histopathologically, probably reducing the ROS production

## SIGNIFICANCE STATEMENT

Today, vandetanib plays an important role in treating many cancers-however, the side effects associated with vandetanib concern many patients. Our study purpose is to examine the cardiotoxic effects of vandetanib in rats and protection by administering exogenous ATP. ATP is the primary energy source for cell viability. Myocardial cells are highly susceptible to ATP deficiency due to extreme demand for energy sources. In this study, data are presented demonstrating the development of cardiac oxidative stress, the release of markers of cardiac toxicity and morphology of cardiac injury after administration of vandetanib and protection by ATP administration. Biochemical oxidative damage parameters and histopathological signs revealed that exogenous ATP replacement may prevent vandetanib-induced cardiotoxicity in rats.

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