

A Novel Insight into the Cardio toxicity of Antineoplastic Drug Doxorubicin

Abstract

Doxorubicin is a generally used antineoplastic agent in the treatment of numerous types of cancer. Little is known about the relations of doxorubicin with cardiac biomolecules. Serious cardio toxicity including dilated cardiomyopathy frequently performing in a fatal congestive heart failure may do as a consequence of chemotherapy with doxorubicin. The purpose of this study was to determine the effect of exposure to doxorubicin on the changes in major amino acids in towel of cardiac muscle (praline, turbine, glutamic acid, arginine, aspartic acid, leucine, glycine, valine, alanine, isoleucine, threonine, lysine and serine). An *in vitro* commerce study was performed as a comparison of amino acid biographies in heart towel ahead and after operation of doxorubicin.

Keywords: Myocardium • Cardiomyopathy • Commerce • Amide bond • Spectrophotometry • Ion- exchange liquid chromatography

Introduction

Doxorubicin, an anthracycline antibiotic, is extensively used to treat a number of cancers, including as bone and lung cancers. The first anthracyclines were insulated from the color-producing *Streptomyces paucities* var. *caesius* in the 1960s and named doxorubicin (DOX) and daunorubicin (DNR). They still remain one of the most effective chemotherapeutic antitumor agents, which effect is grounded on intercalation into DNA helix. In addition, they inhibit the exertion of enzyme topoisomerase II that prevents DNA repairing. Doxorubicin (DOX) also acts by stabilizing a response, in which DNA beaches are cut and covalently connected to the tyrosine remainders of topoisomerase II, ultimately impeding DNA resealing. Topoisomerase II-convincing DNA damage is followed by a growth arrest in the G1 and G2 phases and apoptosis [1]. Anthracyclines ply their cytotoxic effect also by generating reactive oxygen species (ROS), similar as H₂O₂ and superoxide anion revolutionary. These pro-oxidant parcels of DOX have a eventuality to induce cell death through an oxidative damage of mitochondria. On the other hand, doxorubicin may beget several side goods, which are substantially substantiated by serious downfalls of the cardiac muscle including dilated cardiomyopathy, congestive heart failure, arrhythmias and also myelo toxicity. All these goods significantly limit clinical use of DOX. Despite the expansive studies of the cardio toxicity of DOX at cellular, biochemical, molecular, and inheritable situations, it has not satisfactorily been illustrated yet. Most probably, it's a multifactorial process where differences in cellular structure, conformation of ROS that attack then on-target structures, and induction of apoptosis play the important places. Thus, new strategies for dwindling the cardio toxicity of DOX are looking for [2].

The purpose of the study was to probe the influence of DOX on major amino acids present in myocardium. Proline, taurine, glutamic acid, arginine, aspartic acid, leucine, glycine, valine, alanine, isoleucine, threonine, lysine and serine in the downcast trend were determined as the

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Received: 01-Aug-2022, Manuscript
No. JPRCP-22-71834; Editor
assigned: 04-Aug-2022, **PreQC No.**
JPRCP-22-71834 (PQ); **Reviewed:** 18-
Aug-2022, QC No. JPRCP-22-71834;
Revised: 22-Aug-2022, Manuscript
No. JPRCP-22-71834 (R); **Published:**
29-Aug-2022, DOI: 10.37532/
jprcp.2022.5(4).67-70

most common amino acids in the amino acid profile attained by IELC. Their attention ranged from $1 \mu\text{mol mL}^{-1}$ for serine to $14 \mu\text{mol mL}^{-1}$ for proline, where values of attention were attained as the pars from ten independent measures. These values ranged in quantities analogous to values of some amino acids that were determined in mortal heart in the study by Wetzel. All these amino acids were latterly used for covering possible relations with DOX [3]. Originally, IELC was used to determine AA content in myocardium before and after DOX operation. An ion-exchange liquid chromatography (Model AAA- 400, Ingo's, and Prague, Czech Republic) with post column derivatization by ninhydrin and an absorbance sensor in the visible light range (VIS) was used. A glass column with inner periphery of 3.7 mm and 350 mm length was filled manually with strong action exchanger in the sodium cycle LG ANB with roughly $12 \mu\text{m}$ patches and eight porosity [4]. The column was tempered on the 60°C . The double channel VIS sensor with an inner cell of $5 \mu\text{L}$ volume was set to two wavelengths 440 and 570 nm. Result of ninhydrin was prepared in 75 v/v methylcelosolve (Ingos, Prague, Czech Republic) and in 2 v/v 4 M acetic buffer (pH 5.5). Drum chloride (SnCl_2) was used as a reducing agent. Prepared result of ninhydrin was stored under inert atmosphere (N_2) in dark at 4°C . Elution of amino acid was done by a buffer containing 10.0 g of citric acid, 56 g of sodium citrate, and 8.36 g of NaCl per liter of result and pH was 3.0. Flow rate was 0.25 mL min^{-1} [5]. Reactor temperature was set on 120°C . For dilution of samples, a dilution buffer was used (composition thiodiglycol 5 mL L^{-1} , citric acid 14 g L^{-1} , sodium chloride 11.5 g mL^{-1}). For monitoring of AA- DOX relations the same parameters of analysis were used rather of the time of analysis, which depended on amino acid determined [6].

Conclusions

In our study, we determined that doxorubicin induces conformation of complexes with amino acids in myocardium. This fact supports the well-known knowledge about the cardio toxicity of doxorubicin. Despite the fact that some suppositions about the medium of the anthracycline- convinced cardio toxicity have been established, it has not yet been sufficiently explained [7]. An effect of doxorubicin on amino acids may be an important factor involved in this multifactorial and veritably complicated process. Possible conformations of complexes

may play important part in the adverse goods of doxorubicin; still, this miracle must be further delved. We also carried out comparison of the quantitative representation of amino acids in myocardium before and after operation of doxorubicin. We observed significant reduction of situations of all amino acids in myocardium after exposure to doxorubicin [8]. These findings lead us to knowledge that amino acids play an important part in the cardio toxicity of doxorubicin in a cure-dependent manner. Original amino acid composition of heart may hypothetically play an essential part in resistance of heart to doxorubicin. Nonetheless, sensitive BCAAs are veritably important demanded form TOR managed protein synthesis [9]. The result might be set up in nutrition supplements furnishing fanned chain amino acids, and therefore guarding the proper function of protein conflation, but their effectiveness would have to be tested. Therefore, the current study was designed to analyze the organ protecting impact of a methanolic extract of the seeds of *S. cumini* through histopathological Associate in nursing organic chemistry studies alongside an examination of its supposed symptom action. For the analysis of the antidiabetic drug potential of plants, except streptozotocin, alloxan-induced symptom in rats is taken into account to be an efficient preliminary screening model and is wide used [10]. Alloxan could be a beta-cell toxin that has been extensively accustomed induces DM in an exceedingly wide selection of animals. It effectively destroys the beta-cells within the islets of Langerhans within the duct gland, inflicting a discount of endogenous hypoglycemic agent secretion that paves the method for the diminished utilization of glucose by tissues. Therefore, it ends up in the elevation of glucose levels, reduces macromolecule content and elevates total cholesterol, cholesterol and triglycerides [11].

Single dose (i.p.) treatment of rats with alloxan hydrate (150 mg/kg) considerably ($P < 0.05$) enhanced glucose. Treatment with methanolic extract of *S. cumini* seeds and gliclazide were found to cut back the elevated aldohexose levels markedly in alloxan-induced polygenic disease check animals. The *S. cumini* extract could act on island functions by increasing the amount of duct gland islets. Hypertriglyceridemia and hypercholesteremia square measure the foremost common lipid abnormalities in polygenic disease. Daily administration of the methanolic extract of *S. cumini* seeds for fourteen days

considerably ($P < 0.01$) diminished cholesterol, lipid and total cholesterol, whereas the cholesterol level was enhanced [12].

Flavonoids found in *S. cumini* square measure expected to account for this activity, since it's been established that this category of compounds will increase the expression of cAMP-dependent phosphokinase, the accelerator chargeable for 3-hydroxy-3-methyl-glutaryl-coenzyme A enzyme inhibition. However, such reduced lipid levels may also flow from to reduce viscous absorption of cholesterol still as enhanced free carboxylic acid and triacylglycerol clearances following hypoglycemic agent action improvement. Histopathological studies of organ tissues (heart, liver, pancreas, urinary organ and spleen) didn't indicate any noxious effects of the extract. The methanolic extract of *S. cumini* seeds didn't show any protecting or recovery effects on the urinary organ or spleen as compared to the diabetic management animals. However, the histopathological study on the guts and liver of the methanolic extract of *S. cumini* seeds-treated teams shows terribly promising results.

The histopathological observations on the guts show that the internal organ tissue from the diabetic cluster displays marked morphological changes like delicate lump within the heart muscle fiber and infiltration by mixed inflammatory cells. This square measure in stark distinction to the tissue sections of the conventional management animals. The internal organ tissue of methanolic extract of *S. cumini* seeds extract-treated (200 mg/kg) cluster shows traditional morphological options compared to each the diabetic management and therefore the gliclazide (25 mg/kg) treated animals, that clearly reveals that the extract has protecting and recovery ability on internal organ tissue. this is often because of its ability to cut back heart muscle sphacelus biomarkers, specifically aspartate transferase, amino acid transferase, uric acid, amino acid phosphokinase, and wet-nurse dehydrogenase as seen our study and additionally reportable by Mastan et al. [13]. Myricetin, quercetin, rutin, ellagic acid and acid are reportable to act on distinct pathways of cardio-metabolic disorders, that the presence of those compounds within the *S. cumini* seed extract may be the explanation for the cardio-protective ability of the extract. On the opposite hand, the histopathological study on liver tissues reveals that the diabetic management cluster has marked morphological changes as well as sphacelus within the viscus muscle fibre and infiltration by mixed

inflammatory cells, whereas the methanolic extract of *S. cumini* seeds extract (200 mg/kg) treated cluster shows vital recovery from harm as compared to the diabetic management and gliclazide (25 mg/kg) teams. This correlates with ability of the extract to cut back blood serum AST, ALT, total macromolecule and animal pigment levels. Moreover, the liver protecting activity of the extract could also be attributed to saponins, tannins and flavonoids gift within the seeds of the plant. Our results indicate a big positive impact of the methanolic extract of *S. cumini* seeds on diabetic heart and liver [14-15].

Acknowledgement

None

Conflict of Interest

No conflict of interest

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