MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.12.792.797

OPEN ACCESS

Key Words
Doxorubicin, cardiotoxicity, oxidative stress, apoptosis, AMPK, cardioprotection

Corresponding Author
Ramalingam Kothai,
Department of Pharmacology, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be University), Salem - 636008, Tamilnadu, India
kothair@vmpha.edu.in

Received: 11th October 2024
Accepted: 20th November 2024
Published: 31st December 2024

Citation: Smitha Sarah Thambi, Balasubramanian Arul and Ramalingam Kotha, 2024. A Systematic Review on Doxorubicin-induced Cardiotoxicity. Res. J. Med. Sci., 18: 792-797, doi: 10.36478/makrjms.2024.12.792.797

A Systematic Review on Doxorubicin-induced Cardiotoxicity

[1]Smitha Sarah Thambi, [2]Balasubramanian Arul and [3]Ramalingam Kothai

[1]Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamilnadu, India
[2,3]Department of Pharmacology, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be University), Salem - 636008, Tamilnadu, India

Abstract
Doxorubicin (DOX) is an effective chemotherapeutic agent used to treat colorful cancers but is limited by its cure-dependent cardiotoxicity. This review discusses the crucial mechanisms involved in DOX- convinced cardiac damage, including oxidative stress, intracellular calcium dysregulation, mitochondrial dysfunction, AMPK signaling inhibition, apoptosis, and bloodied autophagy. Clinical instantiations range from subclinical changes to heart failure, with early signs similar as reduced left ventricular ejection bit and increased cardiac biomarkers. Several pharmacological and natural agents including dexrazoxane, metformin, statins, sildenafil, vitamin E, and curcumin have shown cardioprotective goods by targeting these pathways. Understanding these mechanisms and treatments is essential to reduce cardiovascular pitfalls and ameliorate patient issues during DOX- grounded chemotherapy.

INTRODUCTION

Doxorubicin (Dox) is a member of the anthracyclines family and is a secondary metabolite of a mutant strain of Streptomyces peucetius var. caesius. For a variety of cancer types, Dox is an efficient antineoplastic agent. However, its widespread use in cancer treatment is limited by a number of systemic side effects. It is a well-known and often used antineoplastic medication for the treatment of several diseases, including as breast cancer, leukemia, and pediatric cancer. Dox damages DNA by acting as an inhibitor of the DNA topoisomerase II enzyme[1]. Doxorubicin is commonly used as chemotherapy to treat hematogenous malignancies and solid tumors[2]. However, because many cancer survivors experience congestive heart failure (CHF) while undergoing this medication, its use is restricted[3]. If anthracyclines are taken in excess of the 400–700 mg/m2 dosing range, they can produce dose-dependent cardiac toxicity. Nine percent of individuals receiving anthracycline treatment for a year have an altered left ventricular ejection fraction[4].

Dox-induced cardiomyopathy is thought to be primarily caused by oxidative stress and apoptosis-mediated cardiomyocyte loss. One of the early phase events in Dox-induced cardiomyopathy is the depletion of sarcoplasmic reticulum calcium. Changes in Ca2+ and calmodulin-dependent kinase II levels are closely linked to cardiac cell death and heart failure[5]. Furthermore, it is believed that Dox-mediated cardiotoxicity is caused by reduction of mitochondrial biogenesis, mostly through the activation of cell death pathways through inhibition of topoisomerase 2ß[6]. Furthermore, a number of other mechanisms, including mitochondrial dysfunction, a disruption in iron regulatory protein, nitric oxide release, inflammatory mediators, calcium dysregulation, autophagy, and cell death, have been shown to play important roles in Dox-induced cardiotoxicity, in addition to the crucial role played by reactive oxygen species (ROS)[1]. Numerous medications are used to treat Dox-induced cardiotoxicity, such as dexrazoxane, which binds at topoisomerase 2ß and lessens heart failure and cardiotoxicity in people with sensitive hearts. Numerous strategies, such as phytochemicals, ß-blockers, and angiotensin inhibitors, exhibit protective effect against Dox-induced cardiotoxicity and stop cardiovascular dysfunction[6].

A reduction in left ventricular ejection fraction (LVEF) from baseline is an early sign to DOX-induced cardiotoxicity[7]. Clinical cardiotoxicity is defined by the European Society of Cardiology (ESC) as a drop in LVEF of 10 percentage (%) points from baseline to a value less than 50%[8]. According to the European Association of Cardiovascular Imaging and the American Society of Echocardiography, subclinical cardiotoxicity is defined as preserved LVEF with a 15% decrease in Global Longitudinal Strain (GLS) and/or an increase in serum biomarkers for cardiac injury, such as troponin, and clinical cardiotoxicity as a 10% point drop in LVEF from baseline to a value below 53%[9]. It is crucial to remember, nonetheless, that the majority of research investigations have defined cardiotoxicity according to their own standards. Acute, early, and late onset or chronic cardiotoxicity are the three categories of cardiotoxicity, which can happen at any point during or after therapy[8]. Acute cardiotoxicity happens during treatment and frequently manifests as left ventricular failure, electrocardiogram (ECG) abnormalities, and supraventricular arrhythmias[8]. Although these symptoms typically go away, they can also develop into early or late cardiotoxicity[10]. Both are linked to the development of CHF, while early cardiotoxicity happens within the first year of medication and late cardiotoxicity happens years later[11]. In order to identify early myocardial damage, it is advised to monitor left ventricular systolic function using imaging modalities and cardiovascular biomarkers both before and after anthracycline-based treatment is finished. Thus, the purpose of this review is to go over the specific processes that lead to Dox-induced cardiotoxicity. Additionally, some of the significant phytochemical and pharmacological substances that describe positive effects against cardiotoxicity caused by Dox.

MATERIALS AND METHODS

Mechanisms of doxorubicin-induced cardiotoxicity: Numerous theories have been put out to explain Dox-induced heart failure or cardiotoxicity. Elevated oxidative stress in cardiac tissue is directly linked to Dox cardiac complications. Because there are less antioxidants and sulfhydryl groups present, increased oxidative stress results in the production of ROS, which damages the heart muscle. Moreover, Dox-induced cardiotoxicity also results in apoptosis due to changed Ca2+ ion levels. Caspases are activated to cause apoptosis in endothelial cells and cardiomyocytes[12]. We found a comprehensive list of the molecular pathways underlying Dox-induced cardiotoxicity here.

Intracellular Calcium Dysregulation: While Ca2+ chelators prevent the production of ROS and apoptosis in cardiac muscle cells, Dox increases dysregulation of calcium levels, which raises intracellular calcium, produces ROS, and causes apoptosis in cardiomyocytes[13]. The hazardous metabolite DOXOL, which blocks the sodium-calcium exchanger channel, is produced during the metabolism of Dox[14,15]. Through the sarcoplasmic reticulum calcium pump, the sodium-calcium exchanger channel regulates cardiac contractility and raises L-type calcium channel activity[16]. Additionally, Dox-induced

cardiomyopathy is caused by a change in the calcium exchange regulating gene, which impacts the calcium storage gene, phospholamban, ryanodine receptor (RyR), and Sarco/endoplasmic reticulum ATPase (SERCA2a). This impairs the heart's systolic and diastolic functions. Furthermore, compared to Dox, the study found that Dox metabolites are more harder to eliminate. Heart muscle is impacted by this metabolite, which is maintained on the cell and results in severe calcium dysregulation[17].In addition, there is another mechanism linking the increase in intracellular calcium to the activation of calcium-dependent proteases called calpains. Oxidative stress was found to increase the quantity of calcium stored in the cardiac muscles' sarcoplasmic reticulum, which results in calcium ion leakage that activates the capillaries. These calpains cause cardiac cells to undergo apoptosis by cleaving the apoptotic factor caspase-12; a similar process was found when Dox was administered[18].

AMPK (AMP-activated protein kinase) signaling in Dox induced cardiotoxicity: Three subunits make up the macromolecule protein complex known as AMPK, including the catalytic site a and the two regulatory sites ß and γ. There are two subunits of α found in the heart, including α 1 in the endothelium cells and α 2 in the cells of the heart muscle. Following Dox treatment, the AMPK pathway is inhibited, and the heart's ACC (acetyl-coA carboxylase) enzyme activity is decreased. Through genotoxic stress and oxidative stress, which cause DNA damage, Dox-induced AMPK signaling suppression activates other pathways like Akt and MAP kinase. Additionally, increased energy stress and cardiac tissue hypertrophy are caused by AMPK inhibition[19].

Autophagy: Eukaryotic cells use autophagy, a conserved mechanism, to preserve cellular homeostasis and ensure survival in both stressful and normal conditions. It is thought to be a preventive mechanism because it entails eliminating long-lived and damaged organelles in both healthy and pathological settings. Crucially, the autophagy process in the heart is dysregulated in response to stress, which can result in heart failure and cardiac dysfunction[20,21]. Cardiotoxicity is the outcome of Dox's aberrant overexpression and downregulation of autophagy-related genes. The down-regulation of the Bcl-2 protein caused by the p53-mediated inhibition of GATA-4 is likely how Dox therapy triggers the start of autophagy. Furthermore, Dox starts the autophagy process by making Bcl-2 more phosphorylated, which prevents Bcl-2/Beclin1 from interacting[22,23].

Involvement of Creatine Kinase: A protein called creatine kinase is found in many bodily tissues and serves as a store of energy. However, only the CK-MB isoenzyme of creatine kinase is expressed in cardiac tissues. When ferrous iron is present, dox-induced oxidative stress destroys the creatine isoenzyme, resulting in the production of the free radical peroxynitrite. By converting creatine to phosphocreatine, which uses ATP as a substrate, this enzyme helps to preserve energy[24].

Dox and Apoptosis: Dox promotes apoptosis via both extrinsic and intrinsic mechanisms[25]. Because of an imbalance between oxidants and anti-oxidants, these pathways cause cardiac muscle cells to undergo apoptosis. Increased oxidative stress from Dox administration triggers the activation of HSF-1 (heat shock factor 1), which in turn triggers the production of HSP-25 (heat shock protein). This stabilizes the p53 protein, which is in charge of producing proapoptotic factors like FasL, Fas, c-Myc, and p53 that result in the death of cardiac muscle cells[26]. Additionally, Dox treatment raised the amount of HSP-70 in the blood and its expression in mice's heart tissue, which results in fibrosis and inflammation[27]. HSP-27, HSP-10, HSP-20, HSP-22, and HSP-60, on the other hand, are likewise protective, guard against apoptosis, and preserve cardiac function[28]. According to a recent study by Lan *et al*., by preventing TLR-4/NLRP3 activation, the overexpression of HSP-22 in cardiac tissue may lessen the heart damage caused by Dox administration[29].

RESULTS AND DISCUSSIONS

Symptoms of Cardiotoxicity: Heart failure (HF), structural damage, and hypertension are among the documented side effects of several conservative chemotherapy drugs that can cause defects in the heart muscle. The incidence of Ejection-fraction reductions of = 5% to < 55% indicate the presence of HF symptoms, while ejection-fraction reductions of = 10% to < 55% indicate the absence of symptoms. Additional cardiac injury can be divided into acute, chronic, irreversible, and reversible categories. Type 1 refers to irreversible cardiac damage, while type 2 refers to reversible damage. In contrast to type 2 damage, which is dose-independent and unrelated to aggregate dose, type 1 (direct damage) is typically caused by an aggregate dose. Additionally, dizziness, fluid retention in the legs, heart palpitations, chest pain, shortness of breath, and stomach distention are clinical signs of cardiotoxicity[30].

Treatment Options:

Role of Dexrazoxane: It swiftly passes across the plasma membrane and is a cyclic derivative of EDTA [31]. It is an adjuvant that scavenges free radicals and has chelator activity on lipid peroxidation and iron-mediated oxygen-free radical activation. The cardioprotective effect of this chelate reaction is demonstrated by the decrease in iron-free radical levels[32].

Metformin: Type 2 diabetes mellitus is commonly treated with metformin, a medication that is part of the biguanide class and has antihyperglycemic properties[33]. In rats given Dox, metformin exhibits cardioprotective effects on rat heart myocytes. Dox reduces the expression of the platelet-derived growth factor receptor (PDGFR) and deactivates the AMPK signaling pathway. On the other hand, metformin therapy increases PDGFR expression, which in turn activates the AMPK signaling pathway[34].

Effect of Statins: The enzyme HMG CoA reductase, which limits the rate of cholesterol manufacture, is inhibited by statins. Statins are used as antihyperlipidemic medications and aid in decreasing cholesterol levels. Atherosclerosis and coronary heart disease are two cardiovascular conditions for which statins are frequently prescribed[35]. According to reports, statins also have cardioprotective effects and stimulate cardiac muscle's AMPK signaling. Ras-related C3 botulinum toxin substrate 1 (Rac1) and the RNS (reactive nitrogen species) are prerequisites for this signaling pathway[36]. Pitavastatin inhibits Rac1, as demonstrated in a mouse model of Dox cardiotoxicity, and protects the heart by lowering cardiac muscle apoptosis and controlling constriction. Other statins, such as rosuvastatin and lovastatin, also exhibit cardioprotection[37].

Sildenafil: By preventing cardiac muscle apoptosis, maintaining mitochondrial membrane potential, controlling myofibrillar integrity, preventing ventricular dysfunction, and shielding against ST-interval prolongation in a mouse model treated with Dox, medications that block phosphodiesterase-5 (PDE-5) exhibit a positive response in cardiac protection. Likewise, via regulating the NO/cyclic GMP, mitochondrial K+ATP channel, and oxidative stress, the PDE-5 inhibitor sildenafil showed a protective effect in Dox-induced cardiotoxicity[38].

Phenylephrine: This agonist belongs to the class of sympathomimetic drugs that specifically activate a adrenergic receptors. Cardioprotection against Dox-induced cardiotoxicity is demonstrated by cardiac a1-adrenergic receptors. Phenylephrine and other a1-adrenergic receptor agonists are beneficial because they lessen the heart muscle dysfunction, interstitial fibrosis, and apoptosis brought on by Dox. This protective role preserves mitochondrial function and is achieved by the production of the anti-apoptotic proteins Bcl2[39].

Role of Vitamin E: Vitamin E, which is fat-soluble, is made up of four tocopherols and four tocotrienols. Because of its antioxidant qualities, vitamin E shields cell membranes from reactive oxygen species. A study demonstrates how vitamin E protects against the cardiotoxicity caused by dox. When Dox causes acute cardiotoxicity, vitamin E helps. Other antioxidants, such as vitamin C, the selenium-organic complex PZ51, reduced glutathione, ambroxol, ursolic acid, and oleanolic acid, have few advantages over cardiotoxicity[40].

Role of Curcumin: One of turmeric's main active ingredients is curcumin, a biphenolic molecule. In addition to its widespread use as a food additive and coloring, curcumin has shown some potential medical benefits[41]. Curcumin exhibits preventive properties against cardiac damage brought on by Dox. Dox lowers antioxidant levels, induces pyroptosis, raises ROS levels, and causes lipid peroxidation. Additionally, Dox inhibits the PI3K/Akt/mTOR pathway, resulting in cardiotoxicity. Following Dox therapy, the antiapoptotic factor Bcl2 is inhibited and BAX expression is increased, leading to mitochondrial cell death. Curcumin, a naturally occurring substance with anti-inflammatory properties, is extracted from the plant Curcuma longa. Following curcumin therapy, Bax levels are lowered and mitochondrial cell death is avoided. Additionally, curcumin suppresses the inflammasome and modifies pro-pyroptosis indicators such as NLRP3, caspase1, and IL-18 to prevent pyroptosis. Curcumin also lowers CK, LDH, and AST levels in heart damage brought on by dox[42].

CONCLUSION

Doxorubicin (DOX), an anthracycline anticancer medication, is frequently recommended to treat malignant tumors in both adults and children, including those of the breast, ovary, leukemia, lymphoma, and other organs. However, the administration of Dox causes cardiac toxicity, which raises the risk of mortality and restricts its broad clinical use in cancer patients. Dox-induced cardiotoxicity involves a number of pathways, such as deregulation of Ca2+ homeostasis with compromised apoptosis, oxidative stress, altered mitochondrial function, and changes in iron regulatory protein. As a result, addressing these changes with new phytochemicals such as allicin, metformin, enalapril, adiponectin, visnagin, and schisandrin B has demonstrated protective effects against Dox-induced cardiotoxicity and may lower the death rate among cancer patients.

REFERENCES

1. K. Renu, Abilash V.G., PB TP, Arunachalam S. Molecular mechanism of doxorubicin-induced cardiomyopathy: An update. European journal of pharmacology. 2018 5: 241-253.
2. M.A. Frias, Lang .U, Gerber-Wicht .C, James .R.W. Native and reconstituted HDL protect cardiomyocytes from doxorubicin-induced apoptosis. Cardiovascular research. 2010 85: 118-126.

3. S.M. Swain, Whaley .F.S, Ewer .M.S. Congestive Heart Failure in Patients Treated with Doxorubicin: A Retrospective Analysis of Three Trials. Cancer: Interdiscip. Int. J. Am. Cancer Soc. 2003 97: 2869-2879.
4. C.G. Nebigil, Désaubry L. Updates in anthracycline-mediated Cardiotoxicity. Front Pharmacol. 2018, 9: 1262.
5. N. Zhao, Li Q, Sui H, Zhang H. Role of oxidation-dependent CaMKII activation in the genesis of abnormal action potentials in atrial cardiomyocytes: A simulation study. BioMed Res. Int. 2020 1: 1597012.
6. P.A. Henriksen. Anthracycline Cardiotoxicity: An Update on Mechanisms, Monitoring and Prevention. Heart. 2018 104:971-977.
7. A. Pardo Sanz, Zamorano JL. 'Cardiotoxicity': Time to define new targets?. Eur. Heart J. 2020 41: 1730-1732.
8. J.L. Zamorano, P. Lancellotti, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). European heart journal. 2016., 37: 2768-2801.
9. J.C. Plana, Galderisi .M, Barac .A, Ewer .M.S, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal–Cardiovascular Imaging. 2014, 15:1063-1093.
10. Wojtacki J, Lewicka-Nowak E, Lesniewski-Kmak K. Anthracycline-induced cardiotoxicity: clinical course, risk factors, pathogenesis, detection and prevention-review of the literature. Med. Sci. Monit., 2000 6: 411-420.
11. R.E. Scully, Lipshultz .S.E. Anthracycline cardiotoxicity in long-term survivors of childhood cancer. Cardiovascular toxicology. 2007 7:122-128.
12. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J. mol. cell. cardiol., 2012 52:1213-1225.
13. S.V. Kalivendi, Konorev .E.A, Cunningham .S, Vanamala .S.K, Kaji .E.H, Joseph .J, Kalyanaraman B. Doxorubicin activates nuclear factor of activated T-lymphocytes and Fas ligand transcription: role of mitochondrial reactive oxygen species and calcium. Biochem. J., 2005, 389: 527-539.
14. L.X. Fu, Waagstein .F, Hjalmarson Å. A new insight into adriamycin-induced cardiotoxicity. Int. J. cardiol.. 1990, 29: 15-20.
15. Dos Santos Goldenberg RC. Doxorubicin-induced cardiotoxicity: from mechanisms to development of efficient therapy. Cardiotoxicity. 2018 Nov 14:1.
16. Keung EC, Toll L, Ellis M, Jensen RA. L-type cardiac calcium channels in doxorubicin cardiomyopathy in rats morphological, biochemical, and functional correlations. The Journal of clinical investigation. 1991 87: 2108-2113.
17. P. Menna, Salvatorelli E, Gianni L, Minotti G. Anthracycline cardiotoxicity. Anthracycline Chemistry and Biology II: Mode of action, clinical aspects and new drugs. 2008:21-44.
18. Jang YM, Kendaiah S, Drew B, Phillips T, Selman C, Julian D, Leeuwenburgh C. Doxorubicin treatment in vivo activates caspase-12 mediated cardiac apoptosis in both male and female rats. FEBS letters. 2004 577: 483-490.
19. Timm KN, Tyler DJ. The role of AMPK activation for cardioprotection in doxorubicin-induced cardiotoxicity. Cardiovascular drugs and therapy. 2020, 34:255-269.
20. Li Z, Song Y, Liu L, Hou N, An X, Zhan D, Li Y, Zhou L, Li P, Yu L, Xia J. miR-199a impairs autophagy and induces cardiac hypertrophy through mTOR activation. Cell Death & Differentiation. 2017 24:1205-1213.
21. Lekli I, Haines DD, Balla G, Tosaki A. Autophagy: an adaptive physiological countermeasure to cellular senescence and ischaemia/reperfusion-associated cardiac arrhythmias. Journal of Cellular and Molecular Medicine. 2017, 21:1058-1072.
22. S. Kobayashi, Volden P, Timm D, Mao K, Xu X, Liang Q. Transcription factor GATA4 inhibits doxorubicin-induced autophagy and cardiomyocyte death. Journal of Biological Chemistry. 2010 285:793-804.
23. J.M. Velez, Miriyala .S, Nithipongvanitch .R, Noel T, Plabplueng CD, Oberley T, Jungsuwadee P, Van Remmen H, Vore M, St. Clair DK. p53 Regulates oxidative stress-mediated retrograde signaling: a novel mechanism for chemotherapy-induced cardiac injury. PloS one. 2011 6: e18005.
24. D.S. dos Santos, R.C. dos Santos Goldenberg, Doxorubicin-Induced Cardiotoxicity: From Mechanisms to Development of Efficient Therapy, Cardiotoxicity, IntechOpen, 2018.
25. Liu B, Bai QX, Chen XQ, Gao GX, Gu HT. Effect of curcumin on expression of survivin, Bcl-2 and Bax in human multiple myeloma cell line. Zhongguo shi yan xue ye xue za zhi. 2007 15: 762-766.
26. K. Vedam, Nishijima .Y, Druhan .L.J, Khan M, Moldovan NI, Zweier JL, Ilangovan G. Role of heat shock factor-1 activation in the doxorubicin-induced heart failure in mice. American Journal of Physiology-Heart and Circulatory Physiology. 2010, 298:H1832-41..

27. Liu P, Bao HY, Jin CC, Zhou JC, Hua F, Li K, Lv XX, Cui B, Hu ZW, Zhang XW. Targeting extracellular heat shock protein 70 ameliorates doxorubicin-induced heart failure through resolution of toll-like receptor 2–mediated myocardial inflammation. Journal of the American Heart Association. 2019, 8: e012338.
28. Shan YX, Liu TJ, Su HF, Samsamshariat A, Mestril R, Wang PH. Hsp10 and Hsp60 modulate Bcl-2 family and mitochondria apoptosis signaling induced by doxorubicin in cardiac muscle cells. Journal of molecular and cellular cardiology. 2003, 35: 1135-1143.
29. Y. Lan, Wang .Y, Huang .K, Zeng .Q. Heat shock protein 22 attenuates doxorubicin-induced cardiotoxicity via regulating inflammation and apoptosis. Frontiers in pharmacology. 2020 11: 257.
30. M. Csapo, Lazar L. Chemotherapy-induced cardiotoxicity: pathophysiology and prevention. Clujul medical. 2014, 87:135.
31. J.T. Mack, Dexrazoxane. xPharm: The Comprehensive Pharmacology Reference, Elsevier, 2007, pp. 1–7.
32. P.E. Schroeder, Hasinoff BB. Metabolism of the one-ring open metabolites of the cardioprotective drug dexrazoxane to its active metal-chelating form in the rat. Drug metabolism and disposition. 2005, 33:1367-1372.
33. H. Ren, Shao .Y, Wu .C, Ma .X, Lv .C, Wang .Q. Metformin alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway. Molecular and cellular endocrinology. 2020, 500:110628.
34. L.C. Kobashigawa, Xu .Y.C, Padbury JF, Tseng YT, Yano N. Metformin protects cardiomyocyte from doxorubicin induced cytotoxicity through an AMP-activated protein kinase dependent signaling pathway: an in vitro study. PloS one. 2014 9: e104888.
35. Alenghat FJ, Davis AM. Management of blood cholesterol. Jama. 2019, 321:800-801.
36. W. Sun, Lee .T.S, Zhu M, Gu C, Wang Y, Zhu Y, Shyy JY. Statins activate AMP-activated protein kinase in vitro and in vivo. Circulation. 2006, 114:2655-2662.
37. K.N. Timm, Tyler .D.J. The role of AMPK activation for cardioprotection in doxorubicin-induced cardiotoxicity. Cardiovascular drugs and therapy. 2020, 34: 255-269.
38. A. Das, Durrant .D, Mitchell C, Mayton E, Hoke NN, Salloum FN, Park MA, Qureshi I, Lee R, Dent P, Kukreja RC. Sildenafil increases chemotherapeutic efficacy of doxorubicin in prostate cancer and ameliorates cardiac dysfunction. Proceedings of the national academy of sciences. 2010, 107:18202-18207.
39. Aries A, Paradis P, Lefebvre C, Schwartz RJ, Nemer M. Essential role of GATA-4 in cell survival and drug-induced cardiotoxicity. Proceedings of the National Academy of Sciences. 2004, 101:6975-6980.
40. El-Demerdash E, Ali AA, Sayed-Ahmed MM, Osman AM. New aspects in probucol cardioprotection against doxorubicin-induced cardiotoxicity. Cancer chemotherapy and pharmacology. 2003, 52: 411-416.
41. M.L. Lestari, Indrayanto G. Curcumin. Profiles of drug substances, excipients and related methodology. 2014, 39: 113-204.
42. S.M. Man, Karki .R, Briard .B, Burton .A, Gingras .S, Pelletier .S, Kanneganti .T.D. Differential roles of caspase-1 and caspase-11 in infection and inflammation. Scientific reports. 2017,7: 45126.