A Review on Cardio Deleterious Effect of Doxorubicin Therapy with Possible Strategies that may Counteract Cardiotoxicity

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ABSTRACT
Doxorubicin is an anthracyclines that was first isolated from Streptomyces peucetius strain and revealed activity to counter tumor of murine with trade name Adriamycin. Doxorubicin revealed important efficacious therapeutic role in different cancer types, however it have a deleterious toxicity on the heart. This cardiotoxicity could attributed to free radical generation, disturbance of myocyte oxidative stress, lipid peroxidation, programmed cell death and disoriented autophagy. Its usefulness has been restricted due to acute (dose- dependent) and chronic (cumulative) cardiotoxicity with prolonged QT wave interval in ECG. Accumulation of doxorubicin within mitochondria lead to disruption of the electron transport chain and an elevation of ROS hydrogen peroxide H_2O_2 and superoxide O_2• - production, in addition to enhancing OH• formation by forming a complex with Fe^{3+} that enter a redox cycle and initiating lipid peroxidation and DNA destruction. Doxorubicin can form ternary complex via binding with topoisomerase 2 isozymes and DNA that prevents replication of DNA and arrest cell cycle causing its apoptosis. Myocytes mediated mitophagy of damaged mitochondria may interrupted by doxorubicin inducing accumulation of injured mitochondria and eventually autophagy. An extra mechanism of doxorubicin-induced cardiotoxicity have been reported thereby affecting cardiac progenitor cells growth and functional characteristics. The main cells have been suggested to mediate cardiotoxic effects of doxorubicin are cardiac fibroblasts which stimulate apoptosis of cardiomyocytes. Antioxidants can neutralize the clinical appearance of cardiotoxicities of anthracyclines doxorubicin for example dietary supplements like vitamin E, vitamin C, vitamin A, omega-3 fatty acids, coenzyme Q and flavonoids recognized to prevent oxidative injury.

مراجعة للتأثير الضار للقلب من علاج دوكسوروبيسين مع الاستراتيجيات الممكنة التي قد تقلل من السمية القلبية

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الكلمات المفتاحية: دوكسوروبيسين. السمية القلبية. الاكسدة؛ بوليميريز الحمض النووي مضادات الأكسدة.

الخلاصة
دوكسوروبيسين هو أنثراسيكلين تم عزله لأول مرة من سلالة Streptomyces peucetius و كشف عن نشاط لمواجهة ورم الفئران بالاسم التجاري أدريامايسين. أظهر دوكسوروبيسين دورًا علاجيًا مهمًا وفعالًا في أنواع مختلفة من السرطان ، إلا أن له سمية ضارة على القلب. يمكن أن تُعزى هذه السمية القلبية إلى توليد الجذور الحرة (free radicals)، واضطراب الإجهاد التأكسدي للخلايا العضلية ، وبيروكسيد الدهون ، وموت الخلايا المبرمج ، والالتهام الذاتي المشوش. تم تقييد فائدة هذا الدواء بسبب السمية القلبية الحادة (المعتمدة على الجرعة) والمزمنة (التراكمية) مع فترة موجة QT المطولة في تخطيط القلب. يؤدي تراكم دوكسوروبيسين داخل الميتوكوندريا إلى حدوث اضطراب في سلسلة نقل الإلكترون وزيادة إنتاج بيروكسيد الهيدروجين ، أنواع الاكسجين التفاعلية ROS

، H_2O_2 وفوق أكسيد (superoxide O_2• -) ، بالإضافة إلى تعزيز تشكيل OH بتكوين مركب مع Fe^{3+} يدخل دورة الأكسدة والاختزال ويبدأ بيروكسيد الدهون وتدمير الحمض النووي. يمكن أن يشكل دوكسوروبيسين معقدًا ثلاثيًا عن طريق الارتباط بإيزوزيمات توبويزوميراز 2 والحمض النووي الذي يمنع تكرار الحمض النووي ودورة الخلية التي تسبب موت الخلايا المبرمج. قد تتعطل الخلايا العضلية الوسيطة من الميتوكوندريا التالفة عن طريق الدوكسوروبيسين الذي يتسبب في تراكم الميتوكوندريا المصابة وفي النهاية الالتهام الذاتي. تم الإبلاغ عن آلية إضافية للتسمم القلبي الناجم عن دوكسوروبيسين مما يؤثر على نمو الخلايا البادرة للقلب والتشخيص الوظيفي. تم اقتراح أن الخلايا الرئيسية للتوسط في التأثيرات السامة للقلب للدوكسوروبيسين هي الخلايا الليفية القلبية التي تحفز موت الخلايا المبرمج في عضلات القلب. يمكن لمضادات الأكسدة تحييد المظهر السريري للسمية القلبية لأنثراسيكلين دوكسوروبيسين على سبيل المثال المكملات الغذائية مثل فيتامين هـ وفيتامين ج وفيتامين أ وأحماض أوميغا 3 الدهنية والإنزيم المساعد Q والفلافونويدات المعترف بها لمنع الإصابة التأكسدية.

INTRODUCTION

Doxorubicin, the first anthracyclines (Fig. 1) that was discovered after isolation from *Streptomyces peucetius* strain and revealed activity to counter tumor of murine. Clinical trials shown approved effectiveness against lymphoma and acute leukemia in 1960s[1]. Adriamycin is a trade name for doxorubicin revealed important efficacious therapeutic role in different cancer types, although it became one of the most important chemotherapeutic approaches it have a deleterious toxicity outlines especially on the heart[2]. The suggested mechanism of doxorubicin cytotoxicity on the tumor cells is formation of free radicals[3]. Although doxorubicin has significant effectiveness against different type of hematologic and solid tumors this efficiency has been restricted because of the deleterious cardio toxic effect of doxorubicin. Generation of free radicals, disturbance of myocyte oxidative stress, lipid peroxidation, programmed cell death as well as disoriented autophagy are the main cellular mechanism associated with doxorubicin cardio toxic adverse events[4]. The new strategy to reduce the deleterious effect of doxorubicin and ensure precise delivery to tumor cells is using drug delivery nano-system. In the passive targeting the small size of drug-nanoparticles permit them to access tumor site without the body biological attack, while the active targeting allow specialized binding between the receptors and targeting groups loaded on the surface of nanoparticles[5].

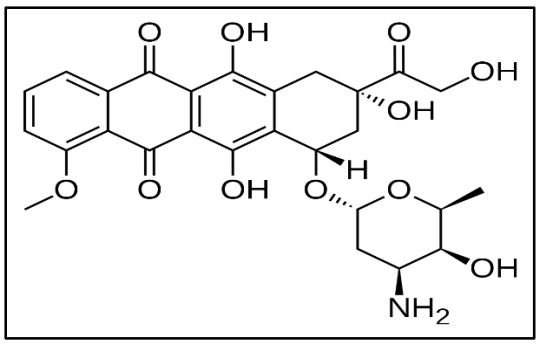

Fig. 1: Chemical structure of doxorubicin[6]

Efficiency versus cardiotoxicity of doxorubicin:

Doxorubicin show effectiveness against broad ranges of solid tumors, hematological malignancies and carcinomas. However, its usefulness has been restricted due to acute (dose- dependent) and chronic (cumulative) cardiotoxicity[7]. Acute cardiotoxicity occurs after 2-3 days after administration a high dose of doxorubicin and presented by prolongation of QT wave interval of electrocardiogram (ECG) which is more frequent in elderly and children below 5 years. This cute onset toxicity can be clinically

controlled and frustrated, while chronic cardiotoxicity induced after 10-15 years from doxorubicin termination therapy and recognized by left ventricular failure which cannot controlled or changed[8]. Cardiotoxicity of doxorubicin may be resulted from accumulation of doxorubicin within the cardiomyocyte which is the characteristic pharmacokinetic of doxorubicin as well as the depressed concentration of antioxidant enzymes in myocardium. There are different possible mechanisms of doxorubicin induced cardiotoxicity[9]:

1- Increments of oxidative stress within cardiomyocytes:

Increased level of oxidative stress within myocardium is the first mechanism of doxorubicin induced toxicity, a robust of reactive oxygen species (ROS) generation and ensuing membrane depolarization of mitochondria which has essential role by releasing cytochrome C (Cyt c) are the causative factors of oxidative stress elevation.[10] Accumulation of doxorubicin within mitochondria lead to disruption of the electron transport chain and an elevation of ROS production. Hydrogen peroxide (H2O2) and Superoxide radicals (O2• -) formed by reduction of doxorubicin to semiquinone radical by NADH- dependent enzymes. The extremely reactive hydroxyl radical (OH•) then formed due to conversion of O2• - accompanied by ferrous iron (Fe2+) action through Fenton reaction which can be inhibited by chelators like desferrioxamine via disturbing hydroxyl radical formation (equation 1)[11]. Besides that, Doxorubicin has been proposed to react with Fe3+ producing a complex that enter a redox cycle thereby enhancing OH• formation that react with cellular molecules like lipids, proteins and DNA initiating lipid peroxidation and DNA destruction which can be scavengered by antioxidant endogenous defense mechanism that involve enzymatic and non-enzymatic antioxidants such as glutathione (GSH), glutathione peroxidase, catalase and superoxide dismutase[12], (as shown in Fig. 2).

$$Fe^{2+} + H2O2 \rightarrow Fe^{3+} + HO\bullet + OH^- \quad \textbf{(Equation 1)}$$

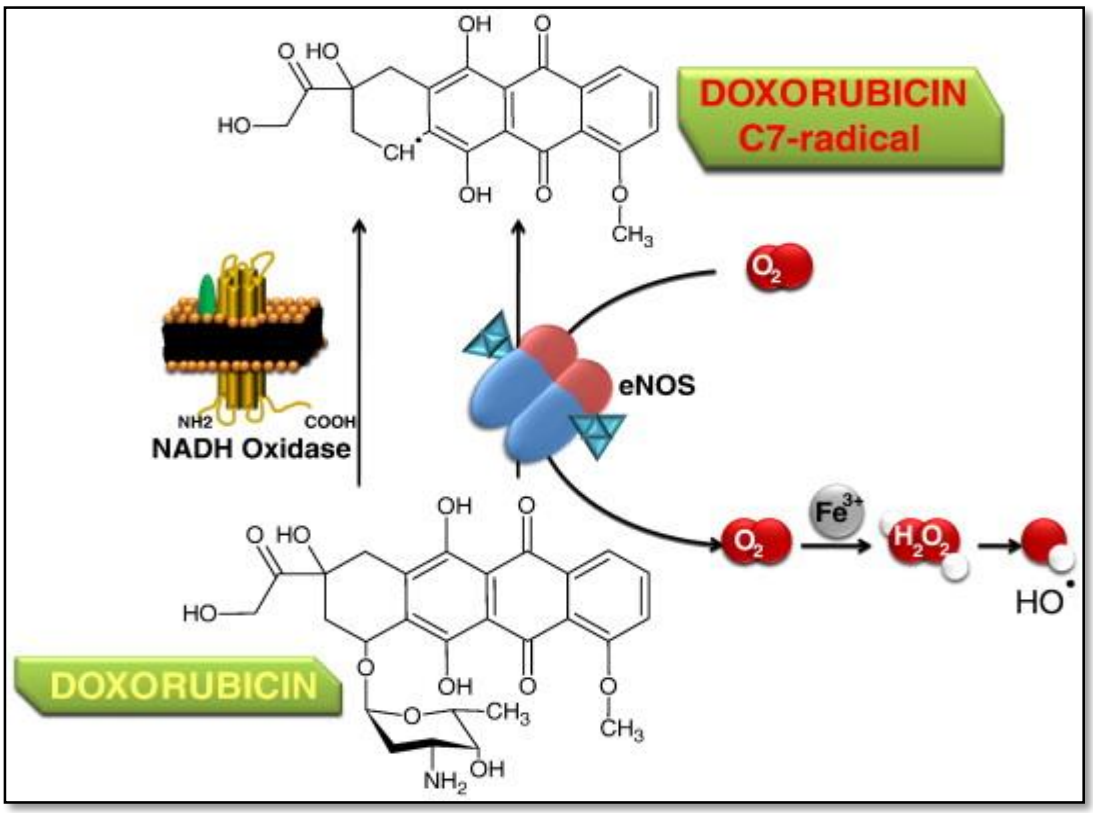

Fig. 2 Molecular transformations of doxorubicin[13].

2- Binding to topoisomerase 2 β:

Topoisomerase II is a vital enzyme that is prerequisite for virtually every process that involves movement of DNA within the nucleus or the opening of the double helix.

Topoisomerases encourage transeint single or double strands breaks of DNA to control changes through chromatin remodelling, DNA transcripition, replication and recombination. Top2α isozyme mostly expressed during proliferation of cells (malignant and non-malignant) while Top2β is more prevalent in quisent cells like cardiac myocytes of mammalian adults and its expression not changed during cell cycle. DNA double strand cleavage initiated by Topoisomerase II through the nucleophilic attack of the active site tyrosine on the phosphate of the nucleic acid backbone[14] (Fig. 3).

Doxorubicin forming ternary complex through binding with topoisomerase 2 isozymes and DNA exerting a cytotoxic effect. Apoptosis induced when doxurubicin bound with Top2α the resulting complex prevents replication of DNA and arrest cell cycle (as shown in Fig. 4). While binding with Top2β causing oxidative metabolism via mitochondrial dysfunction which prompted by inhibiting peroxisome proliferator – activated receptor[15].

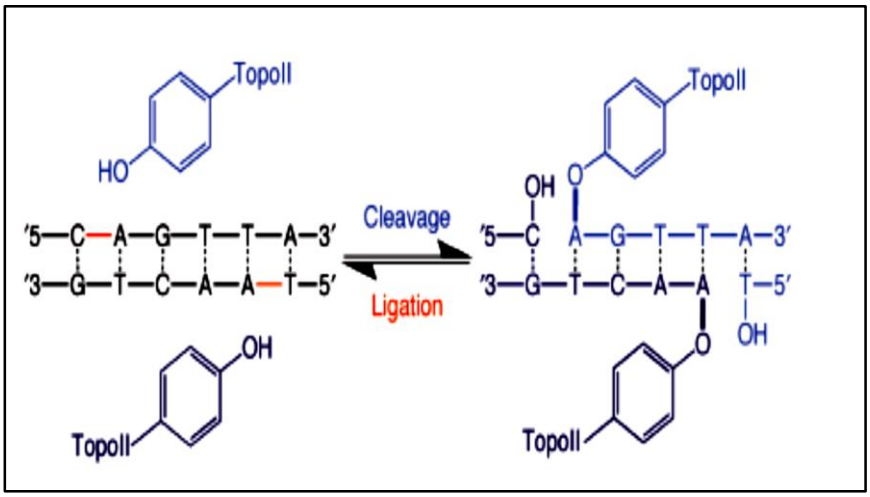

Fig. 3: Double-stranded DNA cleavage mediated by topoisomeraseII [14].

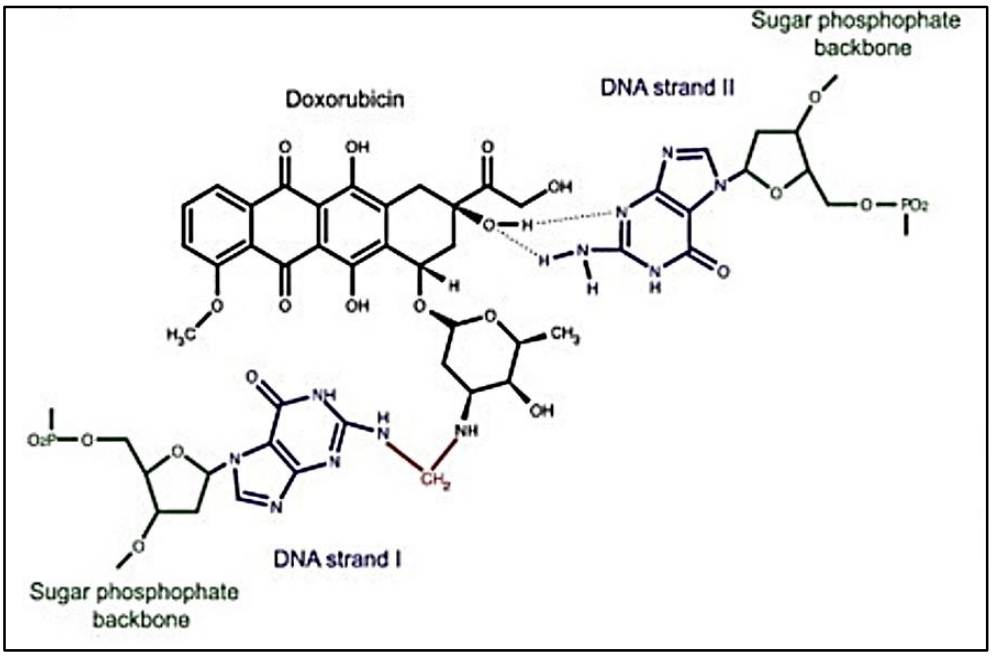

Fig. 4: Doxorubicin binding with topoisomerase[16].

3- Doxorubicin induces autophagy:

Releasing of apoptotic protiens after reactive oxygen species overload togethor with prevented clearance of injured mitochondria. Myocytes gaurantee lysosomal clearance of damaged mitochondria by a process called mitophagy, which is affected by doxorubicin[17].

This type of autophagy is essential in cells that abandant in mitochonria, like cardiomyocytes. Despite the importance of mitochonria as a supplier of ATP, they are ammunition of ROS, therfore accumulation of injured mitochondria can defeat cardiomyocytes antioxidant abilities.

Additional DNA damage caused bu overwhelmed myocytes by extreme ROS producing more mitochondrial dysfunction and additional ROS formation.

Depletion of cardiomycytes mitochondrial ATP makes the heart function insufficient as well as metabolically inflexible. Doxorubicin diminishes mitophage in cardiac myocytes via Parkin mediated p53 inhibition compromising lysosomal clearance of damaged mitochondria[18].

Additionaly, doxorubicin augment expression of 4-hydroxynonenal (4-HNE) in cardiac myocytes produced from lipid peroxidation and elevates the action of mitochondrial aldehyde dehydrogenase 2 (ALDH2) decreasing 4-HNE and ROS formation in doxorubicin treated cardiac myocytes[19].

4- Regeneration of cardiomyocytes:

Cardiac regeneration have a maximum capability to auto- regeneration during fetal and neonatal lifes while have a limited ability in the adult mammalian hearts. Inspite of the presense of amplifiying cells within the endoogenous compartment of the adult heart has been frequently confirmed. The cardiac proginator cells are the mostly extensive specialized empryionic cells in the myocardium, this togethor with multipotent cells c-kit- positive that involved in tissue repair/ homeostasis which occur in several diseases induced in rodents and humans models. An extra mechanism of doxorubicin induced cardiotoxicity have been reported thereby affecting cardiac proginator cells growth and functional charectaristics[20, 21].

The exhaustion of cardiac progenitor cells reservior resrticted the mechanims that control the structural and functional renovation safety of the failing heart. A greater number of cardiac progenitor cells marked with the histone in its phosphorylated forms founded in myocardium of doxorubicin treated patients, representing the buildup of cellulare senescense and oxidative DNA damage[22].

Functional insufficiency of cardiac progenitor cells may be accountable for a greater vulnerability of the myocardium to damage.

Actually, following exposure to doxorubicin, human cardiac progenitor cells could not prompt any functional and structural improvement, approving the unsuccessfulness of doxorubicin-exposed cardiac progenitor cells in performing their functional effeciency in the cardiomyopathy[23].

Pretreatment with resveratrol which is activator of sirtuin-1 with actual antioxidative characteristics could inhibit senescence and growing arrest of cardiac progenitor cells by declining of ROS buildup intracellularly and augmenting oxidative stress defense[24].

5- Cardiac fibroblasts:

Cardiac fibroblasts have important role in preseving normal cardiac function and taking essential measure in cardiac remodelling during pathological situations.

Doxorubicin-induce cardiomyopathy lead to fibrosis of myocardial cells which is a common characteristic of a wide diversity of cardiovascular pathogenesis[25].

Fibrogenic response initiation and maintenance are controlled by a multipart interaction of cytokines and growth factors. Speciefically that interstitial fibroblasts activation and transformation to myofibroblasts triggered by transformance of growth factor-β (TGF-β) and effectors belong to it, hence encouraging extracellular matrix constituents formation like collagen type I[26].

ROS are supposed to elaborate the amplifiction of pathways related to TGF-β which stimulate differentiation of fibroblast through NADPH oxidase.

Myocardial inflammation and fibrosis that encourages the making of several mediators like TGF- β and tumor necrosis factor α (TNFα), inaddition to IL6 and 8 as a result of senescence during cardiovascular pathologies. Following doxorubicin exposure TNF α receptor upregulated and prefer myocardial cells apoptosis. The main cells have been suggested to mediate cardiotoxic effects of doxorubicin are cardiac fibroblasts which stimulate apoptosis of cardiomyocytes[27].

Antioxidants as a cardioprotective stratiegies:

As a major suggestion regarding the oxidative pathway as a vital occasion in doxorubicin pathophysiological induction of cardiomyopathy, pre or coadministration of substances have antioxidant nature prior or with chemotherapeutic agent has been discovered to neutralize the clinical appearance of cardiotoxicities.

Addition of an antioxidant agents to anthracycline schedules has been shown *in vitro* and *in vivo* in animal models to assess this addition thus shrink the oxadative destruction of cardiac cells[28].

Dietry supplements like vitamin E, vitamin C, vitamin A, omega-3 fatty acids, coenzyme Q and flavonoids recognized to prevent oxidative injury. Even with hopeful results evident on preclinical revisions, only a few amount of these antioxidant agents has passed to clinical trials as well as fewer has revealed a confident impact on cardiac function and structure[29].

In vitro studies revealed that majority of these antioxidants have a neutral activity that weaken antineoplastic efficacy, counteracting the essential basis for a safe and effective

use of adjuvants that must not interfere with the cytotoxicity of chemotherapeutic agents in a variety of tumor cells, authorizing surveillance, which antitumor mechanisms used in cancer cell might be different from touching non-cancer cells[30]. Several clinical trial evident that direction of antioxidants adjuvant to chemotherapeutic agents has a cardioprotection event, despite information on the rate of the tumor response were mostly lost.

Intracellular glutathion synthesis promoted by N-acetylcysteine was presented to shrink oxidants. Nevertheless, a controlled non Biased trial assessing retardance of doxorubicin induce cardiomyopathy plus N-acetylcysteine stated no benefitial effect because heart failure rate was same among groups[31].

Intracellular antioxidant Coenzyme Q10 is guards the proteins and membrane phospholipids from oxidative injury caused by free radical induction. Outcomes of small trial registering pediatric patients with cancer presented valuable influence on cardiac function within a group getting coenzyme Q10 by oral throughout chemotherapy. Conversely, those initial outcomes not confirmed in greater clinical trials[32].

Dexrazoxane, intracellular iron chelating agent, which establish efficiently a cardioprotection contrary to cardiotoxicity induced by anthracycline in some children and adults from random trials. While it is solitary cardioprotective therapy agreed in chemotherapy guidelines, apprehensions about probable interference with anthracyclines efficacy as antitumor, or hazardous occur of rebound malignancy may be possible in pediatric patients restricted for its use[33].

Top2-β inhibition prevents cell death and DNA double strand breaks appears mostly qualified pathway, established with investigational outcomes suffering diminished cardioprotection when using dexrazoxane derivatives missing Top2-β activity. Carvedilol and nebivolol are β-adrenergic blockers that stated to recover the function of heart in patients received doxorubicin[34, 35] .

Carvedilol shown significant elevation in systole performance and the level of troponin-I reduced in clinical trials conducted in acute lymphoblastic leukemia children using doxorubicin pre-treated with carvedilol. While, the outcomes of small clinical trials include prophylactic administration of carvedilol to patients taking anthracyclin chemotherapy revealed reduced frequency of systolic and diastolic dysfunction[35].

Nebivolol had a cardioprotective effect when compared with placebo, in patients with breast cancer treated with doxorubicin. According to experimental data, there is agreement that the cardioprotectivity of such drugs depends on mechanism differ from that attributed as β-blockers, which able to retard the exhaustion of endogenous scavengers and lipid peroxidation. Additionally, the vasodilation ability dependent on nitric oxide donation and the accumulation of peroxynitrite is inhibited this ascribe the successful of the treatment with nebivolol. Remarkably, the cardiotoxicity presented by a decrease in ejection fraction induced by anthracycline can be counteracted by the combination of a β-blocker, carvedilol, plus ACE-inhibitor, enalapril, when either pre-dispensed, with no signs referring to dysfunction in systole, or administered on time after detection of diminishing of ejection fraction[36, 37].

Statins have pleiotropic effects, which contribute to cardiotoxicity inducted by anthracycline that utilized for its anti-inflammation plus antioxidation efficacy. Particularly, statins improved antioxidant defense and alleviated cardiac inflammation subsequent doxorubicin therapy. Clinically, statins use in cancer patients receiving chemotherapy is linked with a safeguarding of cardiac function and a lessen danger of heart failure or related mortality[38].

The antioxidants revisions in cardiovascular illnesses require study in living organisms, high level of reactive oxygen species provoke cellular injury, while at lower levels they act as signaling molecules modifying numerous responses of cells. Certainly, although the strong basis of therapeutic aiming in anthracycline redox actions to induce cardiomyopathy, the treatment with antioxidant has unsuccessfulness to aid cardiac protection. Another feature that magnify the importance of these outcomes is that, the antioxidants (themselves) could display a dual action by acting concomitantly as antiradicals in addition to pro-oxidants[39]. Actually, while antioxidants usage is growing, this type of supplement is not beneficial at all. Dietary supplements advertised for cardiovascular illnesses retardation are not accurately studied for their efficacy in diverse physiological and pathological situations of cardiovascular system. The knowledge of redox pathways managing the diverse metabolites of reactive oxygen in cardiovascular pathophysiology might permit to design novel studies in utilizing antioxidants for management of cardiac diseases[40, 41].

Consequently, subcellular compartment of reactive oxygen species and reactive oxygen species-mediated signaling can be of dynamic prominence for both cardiovascular physiology and reaction to stressors should impact the development of novel intervention policies. In this case, the directing antioxidants to exact compartments, so that hinder with definite signaling of subcellular pathology, might favor the estimated activities than the location-unspecific and feasibly unwanted antioxidant activity tried earlier[42].

CONCLUSION

Doxorubicin can cause remarkable cardiotoxicity through oxidative stress generation from injured mitochondria that exceed the capacity of physiological antioxidant pathway, which eventually induce cardiac myocytes autophagy and fibrosis. Such toxicity can be diminished or reduced by co-administration of antioxidants as prophylactic approach for the expected cardiotoxicity of the anthracycline doxorubicin, or alternatively by modifying doxorubicin formulation into nanoparticle system with high targeting toward tumor site.

CONFLICTS OF INTEREST

No conflicts reported by authors.

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