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Review Article

Doxorubicin-Induced Cardiotoxicity: Molecular Mechanism and Protection by Conventional Drugs and Natural Products

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Abstract: Doxorubicin is useful anticancer drug because it's used in treatment of acute leukemia, Hodgkin's and non-Hodgkin's lymphomas, and many other malignant neoplasm. The mechanism of doxorubicin induce cardiotoxicity is multifactorial includes free radical stress, mitochondrial dysfunction and calcium overload these are the main causes of doxorubicin-induced cardiotoxicity. Doxorubicin therapy augments oxidative stress and disturbs cytosolic calcium homeostasis, increases intracellular calcium levels from the sarcoplasmic reticulum through activation of the ryanodine receptor and by blighting calcium clearance systems in cardiomyocytes**.** In this condition the researchers trying to develop cardio-protective strategy to decrease this cardio-toxic effect without decreasing its anticancer effect. Now day's oncologists and pharmacologist work to find out how to decrease the cardiovascular risk and prevent doxorubicin adverse cardiovascular effect**.** Therefore, the aim of this study was to illustrate the molecular mechanism and possible amelioration of doxorubicin induced-cardiotoxicity via conventional drugs and natural products.

Keywords: Doxorubicin, Cardiotoxicity, Natural Products

1. Introduction

Doxorubicin is one of the most worldwide used anticancer drugs, the discovery of doxorubicin was near to 1960s as powerful anticancer anthracycline antibiotics, it's one of essential chemotherapy that used to treat cancer. (Weiss 1992).

Doxorubicin is useful anticancer drug because it's used with other chemotherapeutic drug in treatment of acute leukemia, Hodgkin's and non-Hodgkin's lymphomas, bone and soft tissue sarcoma, Wilms cancer and many other malignant neoplasm (Lipshultz *et al*. 1991). Moreover, doxorubicin plus sirolimus is an effective combination in treating acute-positive lymphoma (Piguet *et al*. 2008 and AlKuraishy *et al*. 2015). Recently, the combination of doxorubicin with murine monoclonal antibody plays a role in the elimination of HIV-infected cells in mice; this combination gives a support for anti-retroviral therapy regimen (Baselga, *et al.* 1993). Additionally, doxorubicin inhibits plasmepsin II enzyme which is unique to malaria parasite thus, doxorubicin has an effective therapy for malarial parasitic infection (Friedman and Caflisch 2009).

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. The intercalation inhibits nucleotide replication and action of DNA and RNA polymerases (Tsuruo, Iida and Tsukagoshi 1982). The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generates highly reactive species including the hydroxyl free radical OH•. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin

have been shown to manifest the characteristic morphological changes associated with apoptosis or programmed cell death (Tewey 1984)(AlKuraishy *et al.* 2015). Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppressant, carcinogenic properties in rodents, and induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species, and atrophy to testes in rats and dogs (Kalyanaraman, *et al*. 2002). The exact mechanism of its cytotoxicity of a cancer cell is multifaceted such as inhibition of DNA replication, inhibition of RNA transcription; free radicals generation that ultimately leads to DNA damage, DNA cross-linking, alkylation, oxidation of membrane lipid causing membrane damage and finally inhibition of topoisomerase II (Jin 2011). The inhibition of topoisomerase causes block of resealing subsequent DNA, failure of super coiled DNA to relax blocks replication and transcription of DNA so; when DNA strand breaks may cause apoptosis of tumor cell (Tacar *et al.* 2013). As with all anti-cancer drug, doxorubicin administration is accompanied by adverse effect and drug reactions. Common adverse effects are bone marrow depression, gastrointestinal disturbances including moderate to severe nausea and vomiting esophagitis and stomatitis that may progressively to ulceration, alopecia may occur in majority of patients, hypersensitivity reactions. Therefore; doxorubicin is associated with dose- dependent cardiotoxicity which is the major limitation of its use (O'brien, *et al.* 2004)

Pharmacokinetic profile

Pharmacokinetic studies, determined in patients with a variety of kind of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphase disposition after intravenous injection. The preliminary distribution half-life of approximately 5 minutes proposes rapid tissue uptake of doxorubicin, whilst its slow removal from tissues is reflected by a terminal half-life of 20-48 hours. Steady-state distribution volume ranges from 809-1214 L/m2 due to extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74-76% (Alkuraishy *et al.* 2015).

Doxorubicin is excreted in the milk, with peak milk concentration at 24hours after treatment. Doxorubicin was noticeable in the milk equal to 72 hours after therapy with 70mg/m^2 of doxorubicin given (Egan, *et al.* 1985.) Doxorubicin does not cross the blood brain barrier, but the scientist trying to increase doxorubicin in the brain and increase its crossing of blood brain barrier by a peptide vector-mediated strategy (Rousselle, *et al.* 2000).

Doxorubicin metabolism is done via enzymatic reduction and cleavage of the daunosamine sugar yields aglycones, which are accompanied by free radical formation, the local production of which may donate to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol in patients is structure rate limited, with the terminal half-life of doxorubicinol being similar todoxorubicin. The relative exposure of doxorubicinol of doxorubicin, compared to doxorubicin ranges between 0.4-0.6 (Loveless, Arena and Felsted 1978).

Doxorubicin excretion is mainly by biliary excretion. Just about 40% of the dose appears in the bile in 5 days, while only 5-12% of the drug and its metabolites appear in the urine during the same time period. In urine, <3% of the dose was recovered as doxorubicinol over 7 days. Systemic clearance of doxorubicin is significantly abridged in obese women with ideal bodyweight greater than 130%. There was an important reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than115% ideal body weight (van Asperen 2000).

Moreover, administration of 10-75-mg/m^2 of doxorubicin to 60 children of 2 months to doxorubicin clearance averaged 1443 ±114 mL/min/m^2. However, clearance in infants younger than 2 years of age was decreased compared with older children and approached the range of clearance standards determined in adults. While the pharmacokinetics of elderly subjects has been evaluated, no dosage modification is suggested based on age (Cersosimo 1986).

1.1. Doxorubicin-Induced Cardiotoxicity

First reported of doxorubicin-induced cardiotoxicity was in 1967 with clinical presentation of heart failure in children treated with doxorubicin for leukemia, clinical studies showed persuasively that this cardiac irregularity could by directly augment with repeated doxorubicin administration from that time worries regarding chemotherapy starts (Alkuraishy *et al.* 2015). Aggressive and combination of chemotherapy has accomplished remission in most types of tumor. Furthermore, these studies established the cumulative of doxorubicin dose received positively associated with cardiotoxicity, so long-standing management of doxorubicin in childhood cancer is eight times more prone to have cardiovascular complications (Cabanillas, Burgess and Bodey 1983).

1.2. Presentation of Doxorubicin-Induced Cardiotoxicity

Doxorubicin-induces cardiotoxicity is typically divide into three types: acute, early onset chronic (within days or weeks) and chronic progressive cardiotoxicity (weeks to months after drug administration). Acute doxorubicin-induces cardiotoxicity may happens during doxorubicin administration and/or immediately later (Von Hoff, *et al.* 1979). It is typically involves temporary ECG abnormality such as ST-T changes decreased QRS voltage and QT prolongation, hypotension and vasodilatation. Other cardio-toxic changes may be rarely occurring such as Pericarditis-myocarditis syndrome (Loveless, Arena and Felsted 1978). Early-onset chronic cardiotoxicity in cardio-myopathy, which progresses to congestive heart failure, within one year after discontinuance of doxorubicin therapy. Congestive heart failure could occur when total cumulative dose of doxorubicin go beyond 550 mg/m^2 (Šimůnek, *et al.*

2009). Chronic cardiotoxicity reflects a progressive cardio-myocyte injury, with increasing the cumulative dose of doxorubicin that leads to thinning of ventricular wall and then systolic performance will be decreased, it is characterized by dilated cardiomyopathy and congestive heart failure. The histo-pathological changes are unique and consist of inflation of the sarcoplasmic reticulum of myocytes, swelling of mitochondria, cytoplasmic vacuolization swelling of mitochondria and myofibril disturbance and loss (Adams 2005). Finally, in late-onset chronic progressive type, doxorubicin -induced cardiotoxicity occurs at least one year after the achievement of therapy, the incidence of congestive heart failure can increase with the presence of other risk factors, such as age, family history, combination therapy and radiotherapy (Paridaens, *et al.* 2000).

All of previous types of doxorubicin -induced cardiotoxicity are subjected to inter-individual variations and there is no stander cumulative dose to cause this cardiotoxicity however there is strong association between increasing the cumulative dose and incidence of cardiovascular disease (Jones, *et al*. 2006).

Table 1. *The incidence of doxorubicin -induced cardiotoxicity in relation to the doxorubicin dose.*

Incidence of cardiovascular disease	cumulative doses
3-5%	400 mg
5-8%	450 mg
6-20%	500 mg

This table shows the incidence of doxorubicin -induced cardiotoxicity and the doxorubicin dose (Praga, *et al.* 1979).

1.3. Mechanisms of Doxorubicin Induced Cardiotoxicity

The mechanism of doxorubicin induce cardiotoxicity is multifactorial includes free radical stress, mitochondrial dysfunction and calcium overload these are the main causes of doxorubicin-induced cardiotoxicity. However, the change in gene expression and activation of ubiquitin-ligase – proteasome system and cell death all contribute to its cardiotoxicity. Moreover the level of oxidative stress induced by doxorubicin is up to 10 times more in the heart than in the its level in liver, kidney or spleen (Diamanti, *et al.* 2014).

1.4. Theories of Doxorubicin Induced Cardiotoxicity

1.4.1. Immunological Theory

Participation of an immunogenic reaction after oxidative stress is an alternative mechanism of doxorubicin -induced cardiotoxicity; doxorubicin could lead to a damaged plasma membrane of cardiac myocytes with consequent an enhanced immune response. A study in hypertensive rats showed an increase in antigen presenting dendritic cells after treatment with doxorubicin, indicating a stimulation of expression of antigens. Pre-treatment with dexrazoxane attenuated this increase, confirming the suggestion of the involvement of oxidative stress, followed by an immunogenic reaction (Attia, *et al.* 2016).

1.4.2. Metabolic Theory

Cancer patients often have unprompted exacerbation of lipid peroxidation and doxorubicin almost certainly inhibits this effect in a paradoxical manner. It is suggested that lipid peroxidation occurs when iron oxidizes incompletely to the ferric form. Doxorubicin and the formed hydrogen peroxide would slow down cardiac lipid peroxidation by affecting the Fe (II)–Fe (III) equilibrium of iron–oxygen complexes. This would mean that cardiac damage might involve parent doxorubicin or its metabolites other than the semiquinon. This hypothesis is reinforced by results of a study in which the formation of the metabolite doxorubicinol was demonstrated. This metabolite mediates iron release and negatively affects the function of protein as an iron regulatory protein (Yang, Teves and Kemp 2014).

1.4.3. Theory of Oxidative Stress Production

The mainly common assumption for the mechanism by which doxorubicin cause cardiotoxicity, includes the development of free radicals and superoxide, this theory is based chiefly on in vitro experiments but, several in vitro and in vivo models have been used to revise the cardio-toxic effects of doxorubicin evaluating a variety of endpoints. So, the response initiates with a one-electron reduction of doxorubicin to form a doxorubicin semiquinone radical by a reduced flavor-enzyme such as NADPH-cytochrome P450 reductase. The semiquinon radical forms a complex with iron lead to an anthracycline-iron (Fe2+) free radical complex. This complex reduces oxygen to produce superoxide and to regenerate doxorubicin. The superoxide is dismutated into hydrogen peroxide and oxygen (Saeed 2015). This causes an augmention in superoxide and reduces in nitric oxide formation. The consequential formation of peroxynitrite could also play a role in the cardiotoxicity thus; arrangement of superoxide, hydrogen peroxide and free iron, lipid peroxidation may be initiated. The exact vulnerability of the cardiac cells to the oxidative stress would be due to comparatively low levels of antioxidant enzymes in the heart. Certainly doxorubicin is able to cause additional decrease in the a priori low intensity of the antioxidant enzymes in rat hearts (Inoue 2014). Subsequent the oxidative stress theory, doxorubicin involves apoptosis. This programmed cell death process would be initiated by the development of oxidative free radicals. Apoptotic cell death was indeed found in rat cardiomyocytes and bovine aortic endothelial cells upon exposure to doxorubicin (Lushchak 2014).

1.4.4. Theory of Calcium Homeostasis Disequilibrium

Oxidative stress is able to provoke mitochondrial permeability transition with variations in mitochondrial calcium transport. Alterations in calcium carry can lead to tissue injury and cell killing and prejudiced cardiac contraction. In vitro experiments showed that doxorubicin treatment caused a permanent reduce in mitochondrial calcium filling capacity (Alkuraishy and Al-Gareeb, 2015). Indeed, doxorubicin encourage the discharge of calcium from sarcoplasmic reticulum vesicles so; calcium blocking agent verapamil have a protective effect against on

doxorubicin-induced cardiotoxicity, due to the calcium blocking of intracellular calcium overload and hence antagonizing the effect of doxorubicin on mitochondria whereas; others enclose an increase in cardiotoxicity when doxorubicin was given in combination with verapamil and dissimilar mechanisms for this effect are assumed (Callaghan and Luk 2014). Since; verapamil inhibit the function of P-glycoprotein thus; may boost intracellular cytotoxic drug concentrations. This may be practical in conquering resistance to chemotherapeutic drugs (Chen, *et al.* 2016). Therefore, the precise task of the altering capacities of doxorubicin on calcium regulation and its insinuation for cardiotoxicity leftovers to be elucidates.

1.5. Molecular Mechanism of Doxorubicin-Induced Cardiotoxicity

1.5.1. Extrinsic Pathway

Cardiac-targeted manifestation of soluble Fas (sFas), a competitive inhibitor of FasL, could alleviate doxorubicin -induced cardiotoxicity moderately by inhibiting cardiomyocyte apoptosis and reducing ROS and peroxynitrite formation in mice (Carvalho, et al. 2014). Doxorubicin treatment of rat cardiomyocytes increased mitochondrial ROS production, activated the calcium/calcineurin signaling pathway, and further activated nuclear factor-activated T cell-4 (NFAT4), leading to up-regulation of Fas/FasL since, NFAT5, a novel member of NFAT family, was degraded by proteolysis in cultured rat neonatal cardiomyocytes after doxorubicin exposure (Huang 2016). Transcription factor NF-κB was activated by ROS in doxorubicin -treated neonatal rat cardiomyocytes and myocardium that exerted a pro-apoptotic outcome through straight activation of apoptotic genes, including FasL, Fas, c-Myc and p53 (Dakic, *et al.* 2016). ROS down-regulated appearance of FLIP, a FLICE/caspase-8 inhibitory protein, and thus at slightest in part, sensitized Fas-mediated apoptosis. As well, an innate immune system has been implicated in the guideline of apoptotic pathway. Also; Toll likereceptor-2 (TLR-2) functions as a narrative "death receptor" that employs the apoptotic tackle such as FADD and caspase 8 without a conventional cytoplasmic death domain (Morris, *et al.* 2016). Moreover, fewer TUNEL-positive nuclei and less caspase-3 activity in myocardium were experiential in TLR-2-knockout mice than that in untamed type mice after doxorubicin treatment, that involve the reticence of NF-κB activation and lessening of pro-inflammatory cytokine in TLR-2-knockout mice (Dakic, *et al*. 2016).

1.5.2. Intrinsic Pathway

Doxorubicin therapy augments oxidative stress and disturbs cytosolic calcium homeostasis, ROS increases intracellular calcium levels through encourage liberate of calcium from the sarcoplasmic reticulum through opening of the ryanodine receptor and by blighting calcium clearance systems in cardiomyocytes (AlKuraishy; 2015). The increased intracellular calcium induces ROS production through calcium-sensitive ROS generating enzymes (AlKuraishy; 2015). Indeed, elevated oxidative stress, mitochondrial calcium level increases outside a threshold this activates mitochondrial permeability transition (MPT) causing liberates of cytochrome c and apoptosis inducing factor (AIF) from mitochondria then; doxorubicin -induced cardio-myocyte apoptosis is associated with increased expression and activation of p53 tumor suppressor protein (Callaghan and Luk 2014), thus; DNA lesions provoked by ROS or directly by doxorubicin activated ERK1/2, followed by amplified phosphorylation of p53, and up-regulated p53 downstream genes such as Bax (Morris, *et al.* 2016). Pifithrin-α, an inhibitor of p53, ameliorates and prevent the increased protein levels of Bax and efficiently inhibited doxorubicin -induced apoptosis in H9c2 cells (Morris, *et al.* 2016). P53 may also mediate doxorubicin-induced cardiotoxicity via other pathways independent of cardiomyocyte apoptosis like p53-mediated inhibition of rapamycin signaling that may contribute to cardiac dysfunction observed in acute doxorubicin-cardiotoxicity (Li, *et al.* 2015). Furthermore, transcriptional factor GATA-4 has been shown to be an essential endurance factor that regulates the apoptotic pathway via activating the anti-apoptotic gene Bcl-XL, therefore protecting mitochondrial utility and reliability. In addition, doxorubicin-induced cardiotoxicity leads to GATA-4 depletion, causing cardio-myocyte apoptosis, also doxorubicin-induced cardiotoxicity increased active GSK3β, a negative regulator of GATA-4 in the nucleus (Li, *et al.* 2015). Indeed, cardiac p300mRNA, a transcriptional coactivator required for the preservation of the differentiated phenotype of cardiac myocytes, was depleted in mouse hearts after doxorubicin therapy, but over-expression of p300 protein in cardiomyocytes might avert doxorubicin -induced cardiac dysfunction. It was believed to be due to the up-regulation of Bcl-2 and Mdm2 (Sin, *et al.* 2014). Moreover, doxorubicin activates p38 MAPK via hyperphosphorylation (Poizat, *et al.* 2005). Recently, doxorubicin activates ceramide generation which participates to cardiomyocyte apoptosis through mitochondrial fragmentation, mitochondrial outer membrane permeabilization, and cytochrome *c* release (Shamseddine, *et al*. 2015).

1.6. Endoplasmic/Sarcoplasmic Reticulum (ER/SR) Pathway

This pathway mediates cardiac apoptosis induced by doxorubicin, since Caspase-12, an essential caspase to commence SR-mediated apoptosis and is located in the SR, was activated by doxorubicin treated rat hearts, when heme oxygenase-1 expression was down modulated in H9c2 cells exposed to doxorubicin (Alyan and Barratt, 2016). Moreover, HO-1/Akt/Nrf2 pathway mediates cardiac mitochondrial biogenesis and down-regulation of HO-1 by doxorubicin which promotes intrinsic apoptosis (Mazevet, *et al.* 2013). Furthermore, deregulation of a phosphodiesterase 3A/inducible cAMP early repressor feedback loop, activation of the endo-cannabinoid system, activation of volume sensitive chloride channels and oxidative stress that induced up-regulation of lectin-like oxidized LDLreceptor-1 (LOX-1)

(Akaberi and Iranshahi 2016).

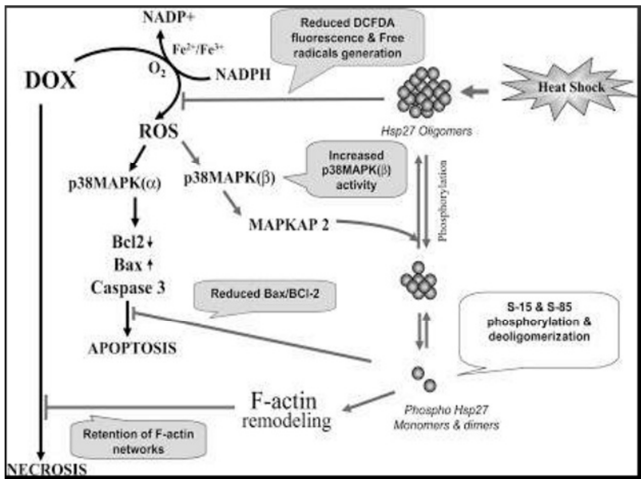

Figure 1. *Molecular mechanism of doxorubicin-induced cardiotoxicity.*

1.7. Biomarkers of Doxorubicin-Induced Cardiotoxicity

Scrutinizing of doxorubicin cardiotoxicity can be done by physical examination and electrocardiographic changes but these signs are not precise for identify doxorubicin induced-cardiotoxicity, though, decline in the voltage of the QRS wave (on ECG) is habitually investigative of necessitate to complete additional tests. Additionally, radionuclide angiography may be helpful in expecting the expand of cardio-myopathy (Salvatorelli and Menna 2015). On the other hand, the most susceptible indicator of cardio-myopathy is endo-myocardial biopsy but its use is restricted by histological skill. Consequently, uncomplicated methods for assessment of doxorubicin -induce cardiotoxicity, like plasma markers to recognize patients at risk. Some study uses other biomarker for assess the cardiotoxicity like Interleukin-17 (AlKuraishy *et al.* 2015). However now days the researcher work hard to find out other biomarker for cardiac function some study find that serum prolactin which give an idea about cardiac function and acute myocardial infarction and toxicity (Alkuraishy *et al.* 2016).

1.7.1. Biomarkers of Myocyte Injury

Myocyte damage results from relentless ischemia frequently, but in heart failure it is also a consequence of stresses on the myocardium such as inflammation, oxidative stress, and neuro-hormonal activation. The myofibrillar proteins, cardiac troponins T and I have appeared as susceptible and specific markers of myocyte injury. Cardiac troponin I was detectable (≥0.04 ng/ml) in about half of patients with complicated chronic heart failure without ischemia and after alteration it remained an self-sufficient predictor of death so; cardiac troponin T levels more than 0.02 ng/ml in patients with chronic heart failure were associated with a risk ratio for death (Herman, Lipshultz, *et al.* 1998). The serum levels of troponin T have been exposed to increase in the early stages of doxorubicin therapy and it was linked with diastolic dysfunction of the left ventricle (Herman, Zhang, et al. 1999). Most patients showed only transient positive troponin that normalized within 3 months. In patients with positive troponins cardiotoxicity incidence was observed in period from 1 to 8 months after the first detection of positive marker. At multivariate analysis positive troponin was the strongest independent predictor of cardiotoxicity with hazard ratio 17.6. In addition to predict cardiotoxicity, troponin I predicts lack of cardiac function recovery with positive predictive value 65% (lack of ejection fraction recovery in troponin positive patients) and negative predicting value 100% (ejection fraction recovery in patients with normal troponin I level). So, troponin is a standard marker for the assessment of cardiac risk during doxorubicin chemotherapy (Suzuki, *et al.* 1998). Moreover, brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP), are synthesized in the myocytes in reaction to high wall stress and pressure overload. The prognostic role of NT-pro-BNP in patients treated with high dose chemotherapy was evaluated, so persistent increase NT-pro-BNP developed significantly worsening of the left ventricular diastolic indexes from baseline (Sayed Ahmed, *et al.* 2001).

Creatine kinase MB fraction (CK-MB) which as well circulates in stable patients with ruthless heart failure and is an accurate predictor of death or hospitalization for heart failure, it detects damage of cardiomyocyte structure (Al-Kuraishy *et al.* 2016). But, N-terminal pro–brain natriuretic peptide is more specific in detection of cardiotoxicity with risk for development of heart failure after and during doxorubicin chemotherapy (Herman, Lipshultz, *et al.* 1998).

Troponins (I and T) are gradually more being used to stratify patients into higher and lower risk categories. This process iswell established in the cardiology literature and newly has been reported in oncology patients. In fact, an elevated troponin during doxorubicin chemotherapy appears to associate with increased risk for the progress of cardiac toxicity thus; cardiac troponins as a biological marker for myocardial damage can be used for checking in patients received doxorubicin, troponin I is a strong judge of left ventricular dysfunction and reduced cardiac outcome, mainly in patients presentation a persistent TnI increase (Herman, Zhang, *et al.* 1999).

C-reactive protein is an acute-phase protein produced by hepatocytes in reaction to the pro-inflammatory cytokine, augmented levels of C-reactive protein associated with the brutality of heart failure and is an independent predictor of poor outcomes in patients with acute or chronic heart failure thus; C-reactive protein has direct effects on the vascular endothelium by reducing nitric-oxide release and increasing endothelin-1 production (Sayed-Ahmed, *et al.* 2001). C-reactive protein is high-sensitivity test has been investigated of various malignances. In patients with dose-dense doxorubicin therapy the levels of C-reactive protein were augmented but did not associate with ejection fraction reduction (Ciocca, *et al*. 1993).

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine produced by the damaged myocardium, which is improved by stimulation of the sympathetic nervous system. Injured myocardium, as well as skeletal muscle, which are hypo-perfuse because of reduced cardiac output, activate

monocytes to produce the similar cytokines, which act on and extra impair myocardial function as a result of apoptosis and necrosis. Interleukin-6 induces a hypertrophic response in myocytes, whereas TNF-α causes left ventricular dilatation through activation of matrix metalloproteinases, Interleukin-6 and TNF-α levels could be used to expect the development of heart failure in asymptomatic elderly subjects, although blockade of TNF-α has not resulted in clinical benefit in patients with heart failure (Torre-Amione 2005). The augmented levels of soluble TNF-α were seen during doxorubicin chemotherapy (van der Veen, *et al*. 2000).

1.7.2. Biomarkers of Oxidative Stress

Augmented oxidative stress consequences from an inequity between reactive oxygen species and endogenous antioxidant defense mechanisms, seeing as it is intricate to determine reactive oxygen species directly in humans, indirect markers of oxidative stress-plasma-oxidized low density lipoproteins, malondialdehyde and myeloperoxidase have been required. In animal models administration of doxorubicin resulted in higher myeloperoxidase activity and lipid peroxidation, so in patients treated with doxorubicin the marker of lipid peroxidation (malondialdehyde), the amounts of the ratio of reduced to oxidized glutathione and the marker of free radical generating capacity of neutrophils (myeloperoxidase)(Kehrer 1993).

Heat shock proteins are present in cells in normal circumstances but are uttered at high levels in high temperature exposition or other stress. HSP27, 70, 90 and 110 boosts to become the dominantly expressed proteins after stress thus; heat shock proteins become over-expressed in cancer by multiple mechanisms. The levels of HSP in cancer patients are valuable in tumor diagnosis (Kehrer 1993). Additionally, it was recognized that some heat shock proteins have been amplified by doxorubicin treatment. In vivo rat model the levels of HSP90, known ErbB2 (epidermal growth factor receptor-2) protein stabilizer are increased by treatment with doxorubicin, with revealed binding of HSP90 to ErbB2. Registered in vivo increases in HSP90 and ErbB2 cardiac proteins occur even before cardiac dysfunction is noticed by echocardiography. Treatment with HSP90 inhibitor augments doxorubicin induced-cardiotoxicity, signifying the protective function of HSP90 during doxorubicin treatment (Ciocca and Calderwood 2005). Moreover, cyclosporine therapies induce HSP90 appearance in the heart and are related with modulation of protective endothelial nitric oxide synthase signaling so; HSP 70 guards the heart from hypoxia, thus; HSP70 dynamic during chemotherapy are limited probably due to the multitude of roles of HSP70s. Therefore, short term doxorubicin induced-cardiotoxicity causes numerous multipart reactions and depression of HSP 70 levels (Ciocca and Calderwood 2005).

Chromogranin A (polypeptide produced by the myocardium), galectin-3 (a protein produced by activated macrophages) and osteoprotegerin are other biomarkers that predict the cardiotoxicity and early detection of development of heart failure (Yanavitski and Givertz 2011).

1.8. Ameliorations of Doxorubicin Induced-Cardio-Toxicity

Controlled Delivery Systems

Development of controlled delivery systems with reduces or no toxicity is the focus of researchers in medical, pharmacological scientists, medicinal chemists and other health related person. The search for alternative medical treatment resembling drug delivery system carriers is necessary since most anti-cancer drugs especially doxorubicin, are considerably toxic to normal cells or lack specificity and selectivity, which prevent the use of high amounts in the treatment. Doxorubicin delivery systems achieve drug therapeutic index and enhance the efficacy of controlled drug release therefore may reduce doxorubicin induce cardiotoxicity (Allen 2013).

Most of doxorubicin family (anthracycline) is associated with cardiotoxicity. In this condition the researchers trying to develop cardio-protective strategy to decrease this cardio-toxic effect without decreasing its anticancer effect. Now day's oncologists and pharmacologist work to find out how to decrease the cardiovascular risk and prevent doxorubicin adverse cardiovascular effect (Ewer and Lippman 2005)(Al-Kuraishy, *et al.* 2016).

Dexrazoxane

Many drugs that are used in treatment of against doxorubicin cardiotoxicity via antioxidant mechanism or chelating agent decrease free radical, for example dexrazoxane one of most examined shields against doxorubicin induce-cardiotoxicity due to the intracellular conversion of dexrazoxane to an open-ring derivative ADR-925 which chelates iron, since one means of generating oxygen-free radicals can include intermolecular reduction of doxorubicin-iron conjugate and decrease its cardiotoxicity (Wouters, *et al.* 2005).

Iron cheaters have been developed to evade doxorubicin-induced cardiotoxicity, derxrazoxane bind to intracellular iron and eliminate the iron from the doxorubicin–iron complex and are applied aimed at preventing free radical formation. Dexrazoxane was found to be the major talented agent, after being tested in animals, several clinical trials demonstrated its capacities in reducing doxorubicin induced cardiotoxicity (Kaiserová, *et al.* 2007).

Furthermore, it is not known if dexrazoxane provides any protection against late cardiovascular effects, in a study in children treated with doxorubicin a cardio-protective effect of dexrazoxane was found. The FDA has approved dexrazoxane for use in adults if cumulative dosesof doxorubicin exceeds 300 mg/m^2. Doxorubicin pharmacokinetics seems to be unaffected upon dexrazoxane treatment. Dexrazoxane can be administered intravenously either as a slow injection or fast infusion before doxorubicin is initiated. The dosage to be given is usually a 10-fold of the doxorubicin dose and its dose limiting toxicity appears to be leucopenia.

Statins

Statins is a drug used in treatment of hyperlipidemia and dyslipidemia and have effect on cardio-metabolic Profile. (Al-Kuraishy and Al-Gareeb 2017), seem to be able to lower

the cardiotoxic effects of doxorubicin, at what time rats were concurrently treated with doxorubicin and the lipid lowering and antioxidant agent probucol, an increase in the antioxidant enzymes superoxide dismutase and glutathione peroxidase activities and a decrease in lipid peroxidation were found (Ahmed, Al-Gareeb and J 2014). According to the oxidative stress theory this improvement of antioxidant state of the heart could possibly lead to a well again myocardial structure and function. Moreover, lovastatin led to the anti-tumor activity and a cardioprotective effect in mice treated with doxorubicin (AlKuraishy and Al-Gareeb 2014).

Calcium Channel Blockers

Doxorubicin causes generation of free radicals through metabolism of its quinone structure, leads to induction of apoptotic and necrotic pathways with progress of irreversible cardiotoxicity. Felodipine was assessed against doxorubicin-induced cardiotoxicity since; felodipine not only improves cardiac marker enzymes but also prevents damage to myocardial tissue via inhibition of apoptotic pathways in myocardial caspase-3 activity following felodipine pretreatment. Felodipine pretreatment was able to maintain normal cardiac morphology and histo-architecture. Indeed, felodipine was not found to have any harmful effects on the myocardium or hemodynamic parameters of rats, this propose that pretreatment with felodipine prevents doxorubicin induced cardiotoxicity (Bachur and Gordon 1978). Calcium channel blocker also have protective effect by its antioxidant effect that act by direct scavenging effect, nicardipine and amlodipine has a potent antioxidant property, through direct scavenging activity, conservation of glutathione peroxidase enzymes activity, and inhibition of peroxidation (lipid peroxidation. In addition, calcium channel blocker reduces oxygen consumption and ischemic perfusion injury (Al-kuraishy and Al-Gareeb 2015).

B-Blockers

Carvedilol prevents doxorubicin-induced cardiotoxicity via reduction of myocardial strain without interfering with the therapeutic efficacy of doxorubicin. Additionally, metoprolol and labetalol illustrated significant cardioprotective effect during doxorubicin-induced cardiotoxicity. Therefore, β-blockers prevent ca overloading independently of the beta-adrenoceptors (Al-Kuraishy *et al.* 2011 and 2015).

Amifostine and Pentoxifylline

Amifostine is used in cancer chemotherapy and radiotherapy involving DNA-binding chemotherapeutic agents. It is marketed by Clinigen Group under the trade name Ethyol. Inside cells, amifostine detoxifies reactive metabolites of platinum and alkylating agents, as well as scavenges free radicals. Other possible effects include accelerated DNA repair, induction of cellular hypoxia, inhibition of apoptosis, and alteration of gene expression and modification of enzyme activity. A mifostine is believed to radio-protect normal tissue via Warburg-type effects. Amifostine is used therapeutically to reduce the incidence of neutropenia-related fever and infection induced by DNA-binding chemotherapeutic agents including alkylating agents (e.g. cyclophosphamide) and platinum-containing agents (e.g. cisplatin). It is also used to decrease the cumulative nephrotoxicity associated with platinum-containing agents. Amifostine is also indicated to reduce the incidence of xerostomia in patients undergoing radiotherapy for head and neck cancer (Büntzel, Fröhlich and Glatzel 1998). Amifostine was originally indicated to reduce the cumulative renal toxicity from cisplatin in non-small cell lung cancer. However, while nephro-protection was observed, the probability that amifostine could protect tumors could not be excluded. Additional data have shown that amifostine-mediated tumor protection, in any clinical scenario, is unlikely. Amifostine also widely studied for its effect in cardio protection, amifostine is a broad-spectrum cytoprotector which guards alongside variety of radio, and chemotherapy-related toxicities without decreasing their antitumor action. Amifostine provided a significant protection against doxorubicin -induced acute cardiotoxic effects in rats. This finding implies its potential to be a successful cardioprotector in patients treated with doxorubicin due to malignant diseases (Komaki, et al. 2004). Pentoxifylline is a xanthine derivative used as a drug to treat muscle pain in people with peripheral artery disease, Like other methylated xanthine derivatives, pentoxifylline is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, activates PKA, inhibits TNF and leukotriene synthesis, and reduces inflammation and innate immunity. In addition, pentoxifylline improves red blood cell deformability (known as a haemorrheologic effect), reduces blood viscosity and decreases the potential for platelet aggregation and thrombus formation. Pentoxifylline is also an antagonist at adenosine 2 receptors (Murray, *et al.* 2001). Indeed, pentoxifylline which possesses antioxidant and anti-inflammatory properties against cardiotoxicity induced by doxorubicin -induced acute cardiotoxic effects in rat's. thus; prophylactic management of rats with pentoxifylline diminished doxorubicin cardiotoxicity so; the clinical use of pentoxifylline as an adjuvant treatment to abrogate cardiotoxicity of doxorubicin and extend its clinical applications (Suravajhala, *et al.* 2014).

Trimetazidine

Is a cyto-protective anti-ischemic agent, which improves myocardial glucose utilization through inhibition of fatty acid metabolism (Alkuraish *et al*. 2016). Trimetazidine inhibits beta-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation. In an ischemic cell, energy obtained during glucose oxidation requires less oxygen consumption than in the beta-oxidation process. Potentiating of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischemia. By preserving energy metabolism in cells exposed to hypoxia or ischaemia, trimetazidine prevents a decrease in intracellular A. TP levels, thereby ensuring the proper functioning of ionic pumps and trans-membrane sodium-potassium flow whilst maintaining cellular homeostasis. Doxorubicin has a high affinity to tissues especially the heart. It causes hepatotoxicity and cardiotoxicity marked by a significant increase of aspartate aminotransaminase (AST) and alanine amino-transaminase

(ALT) levels and drop of the left ventricular ejection fraction (EF LV) by scintigraphy. Histological examination showed general alteration of myocardium structure. Concomitant administration of trimetazidine attenuates significantly the cardiotoxicity and hepatotoxity induced by doxorubicin. Thus, trimetazidine affords a protective effect on an animal model of doxorubicin-induced cardiotoxicity and hepatotoxicity (Al Kuraishy 2016)(Sentex, Sergiel and Lucien 1998).

Rennin-Angiotensin System (RAS)

RAS involvement in the pathophysiology of doxorubicin mediated cardiac dysfunction has raised the question as to whether the prophylactic use of RAS antagonists could potentially mitigate these cardiotoxic effects. Previous basic science studies have demonstrated that the prophylactic administration of angiotensin converting enzyme inhibition (ACEI), including Captopril, Enalapril, and Lisinopril, was partially cardio-protective in both acute and chronic animal models of doxorubicin-induced cardiomyopathy. In a rabbit model of doxorubicin mediated cardiomyopathy, oral Lisinopril for 10 weeks attenuated cardiomyocyteloss. Furthermore, intragastric administration of Captopril for 7 days resulted in a decline in lipid peroxidation, and enzymatic indicators of acute cardiac toxicity in a rat model of doxorubicin induced cardiomyopathy. Moreover, ACEI can prevent a decline in cardiac events in cancer patients receiving high dose doxorubicin also,, the prophylactic administration of ACEI or ARB in patients receiving doxorubicin based regimen was associated with a relative risk of 0.11 for the development of cardiotoxicity compared to placebo (AlKuraishy and Al-Gareeb; 2015).

Additionally, spironolactone administration used simultaneously with doxorubicin protects both myocardial systolic and diastolic functions so; spironolactone can be used to protect against anthracycline-induced cardiotoxicity. ACE inhibitors also have some cardio protective effect against doxorubicin induce-cardiotoxicity due to its anti-oxidant and decrease oxygen consumption (AlKuraishy and Al-Gareeb; 2015). Some studies found that inhibition of Carbonyl Reductase 1 can provide the promises by improving anticancer effect of doxorubicin in treatment of breast cancer this strategy well enabling the clinician to get rid of doxorubicin resistance and reduce the total cumulative dose to decrease doxorubicin -induce cardiotoxicity.

Cyclosporine

Cyclosporine is permitted by the FDA to avert and treat graft-versus-host disease in bone-marrow transplantation and to stop rejection of kidney, heart, and liver transplants. It is also standard in the US for the treatment of rheumatoid arthritis and psoriasis (AlKuraishy and Al-Gareeb; 2015). In cardiotoxicity induced by doxorubicin, there is significant injury of sacrolemmal inner and outer membrane, causing intracellular Ca^2 surplus that induce opening of mitochondrial permeability transition pore (MPTP) as well, this toxicity initiate complement stimulation, which make possible direct cardiac injure or throughout commencement of liberation of inflammatory and pro-inflammatory cytokines like interleukin -17, platelet activating factor (PAF) and histamine in addition; this cause an induction of superoxide assembly and oxidative stress injure that induce variation in membrane phospholipids, the entire of these effects initiating the inflammatory micro-vascular changes, and then cardiac damage (AlKuraishy and Al-Gareeb; 2015). In addition, the use of cyclosporine to prevent mitochondrial permeability transition pore opening at the onset of reperfusion will limiting myocardial infarction size (Iqbal, *et al*. 2008). Additionally, cardiotoxicity induced by doxorubicin lead to free radical production which will coalesce with membrane phospholipids and cause lipid peroxidation thus, increase in the MDA level causing cell damage and necrosis (Iqbal, *et al.* 2008).

The mitochondrial dysfunction due to fatty acid oxidation may increase the ischemic damage which leads to cell depletion from high-energy phosphate due to mitochondrial enzyme dysfunction and subsequently the mitochondrial membrane was depolarized and mitochondrial membrane transition pores will be opened and the mitochondrial reactive oxygen species will increase and exacerbates the oxidative stress (Al Kuraishy 2016). Thus, the utilizing of cyclosporine will protects the heart from oxidative stress and will restoring the pore to the original state which has protective effect to cardio-myocyte. It improves antioxidant capacity and cell membrane integrity.

Natural Products

The cardio-protective effect of various medicinal plants and plants products has been documented. (90). Sustainable agents from natural sources could serve as viable alternatives to currently available synthetic drugs in the management of cardiovascular-related disorders. This is especially important owing to the toxic side effects of most synthetic drugs and their high costs which make them not readily accessible to many patients. There are many plant have natural ability to protect against doxorubicin induce cardiotoxicity and other is under investigation like pomegranate (AlKuraishy and Al-Gareeb; 2012, 2016).

Parkiabiglobosa

Parkiabiglobosa, an extensive savanna tree was largely prescribed in traditional medicine for its multiplemedicinal virtues. Folk medicine has reported *Parkiabiglobosa* to be effective in the treatment of arterial hypertension, piles, amoebiasis, bronchitis, cough, burn, zoster, and abscess. The leaf extract may be capable of protecting against cardiotoxicity through its antioxidant principles or through synergistic interactions among the constituent phytochemicals. The cardio-protective occurs via diverse mechanism including antioxidant and anti-inflammatory and some plants or plant products could exert ramipril-like effect. The cardio-protective potential of *Parkiabiglobosa* might be due to its antioxidant and anti-hyperlipidemic activities (Rao, Palada and Becker 2004).

Vitexin

Vitexin may be an effective therapeutic agent against doxorubicin -induced cardiotoxicity. The mechanisms included attenuation of oxidative stress, reducing cardiac inflammatory cytokines, increased FOXO3a, and inhibition of caspase-3 activation. Thus; vitexin may be used as an effective

therapeutic agent to prevent doxorubicin-induced cardio-myopathy (Zhan *et al.* 2016).

Alginate Oligosaccharide

Alginate oligosaccharide is a non-immunogenic, non-toxic and biodegradable polymer, with anti-oxidative, anti-inflammatory and anti-endoplasmic reticulum stress properties. Alginate oligosaccharide prevents acute doxorubicin-cardiotoxicity in mice, at least in part, by suppression of oxidative stress and endoplasmic reticulum-mediated apoptosis. So; it may clinically serve as a novel preventive strategy against acute doxorubicin-cardiotoxicity (Tusi, et al. 2011.).

Ginkgo Biloba

In recent years, numerous research works have indicated that extracts of Ginkgo biloba leaves may be beneficial for preventing from the drug-induced toxicity on non-tumor tissues such as the liver, lung, kidney, and heart due to its various pharmacological properties, including anti-inflammatory effect, anti-tumor effect, anti-apoptotic effect, and antioxidant activity (Alkuraishy, I Algareeb, *et al.* 2014). Most recently, researchers have discovered that GB exerts modulator or protective functions by reducing oxidative stress and Aβ-induced dysfunction of mitochondrial oxidative phosphorylation of the neuronal cells and maintaining cellular energy demands. However, surveys on the effect of GB on doxorubicin-induced cardiotoxicity and the potential molecular mechanisms are limited and need an in-depth elucidation. When cardiomyocytes are subjected to oxidative stress or ischemia reperfusion, the p38MAPK and PI3K/Akt pathways can be altered inside the cells, leading to apoptotic cell death, which subsequently contribute to the deterioration of cardiac contractile function and left ventricular remodeling. Previous studies have suggested that Akt activation could protect heart function by inhibiting cell apoptosis and p38MAPK inhibition could attenuate cellular inflammatory reactions. Moreover, previous investigations indicated that the activation of PI3K/Akt signaling pathway promotes an essential cell survival signaling in cardiomyocytes (Brunet, Datta and Greenberg 2001). In previous studies on ischemia and ischemia-reperfusion induced cardiac arrhythmia, it was demonstrated that GB is able to exert anti-ischemia and cardio-protective effects by inhibiting the increase of the left ventricular end diastolic pressure, improving post ischemia-reperfusion cardiac pump function and protecting the ischemia myocardium from calcium overload reaction due to its negative effect on the intracellular calcium level. Herein, in conformity with the above studies, we equally discovered that GB could decrease the intracellular calcium level and protect from the myocardium damage induced by doxorubicin treatment. Moreover, GB could significantly improve the LVEF and LV mass, thus indicating the substantial effectiveness of GB pretreatment for the body (Llesuy, *et al.* 1985).

Melissa Officinalis

Is one of the most used medicinal plants in Europe and the Mediterranean region, Moreover, Melissa officinalis has been reported to show potent anti-tumor effects in a variety of human cancer cell lines and to induce apoptosis in colon carcinoma cells through formation of reactive oxygen species (ROS). Caffeic acid, protocatechuic acid, rosmarinic acid, ferulic acid, and syringic acid have been reported as the most abundant phenolic compounds in Melissa officinalis. The promising ameliorating effects of Melissa officinalis against doxorubicin-induced cardiotoxicity in rats through modulation of oxidative stress, diminution of inflammation and abrogation of apoptosis in rat heart. Identification of a mechanism for Melissa officinalis anticancer effect introduces the possibility that combining this plant with doxorubicin might enhance the therapeutic efficacy of doxorubicin in clinical oncology. Beneficial effect of the Melissa officinalis extract is likely due to the synergistic interactions of phenolic compounds and other triterpene acids of Melissa officinalis (Kim, et al. 2004).

Ginsenoside Rb1

Ginsenoside Rb1 attenuated doxorubicin -induced cardiomyocytes injury and apoptosis and reduced caspase-3 and caspase-8, but not caspase-9 activity in doxorubicin treated H9C2 cells. Meanwhile, pre-treatment with Ginsenoside Rb1 decreased the expression of caspase-3 and PARP in the protein levels, with no effects on cytochrome c, Bax, and Bcl-2 in doxorubicin -stimulated cells. Rb1 markedly decreased the CYP1A1 and CYP1A2 expression induced by doxorubicin. Furthermore, transfection with AhRsiRNA or pre-treatment with AhR antagonist CH-223191 significantly inhibited the ability of Ginsenoside Rb1 to decrease the induction of CYP1A, as well as caspase-3 protein levels following stimulation with doxorubicin. In conclusion, these findings indicate that AhR plays an important role in the protection of Ginsenoside Rb1 against doxorubicin-triggered apoptosis of H9C2 cells (Wang, *et al.* 2012).

Beet Root Juice

Doxorubicin is a broad-spectrum chemotherapeutic drug used to treat a variety of cancers, although its clinical use is restricted by irreversible cardiotoxicity. Earlier studies show that beet root juice (BRJ), a natural and safe herbal product with high levels of nitrate and antioxidants, is a potent chemo-preventive agent. Thus; lower concentrations of Beet root juice with doxorubicin represented the most effective combination of cardio-protection and chemoprevention. These findings provide insight into the possible cardio-protective ability of Beet root juice in cancer patients treated with anthracycline chemotherapeutic drugs (J Kapadia, *et al.* 2011).

Lactucaseniola

Reactive oxygen species (ROS) play an important role in the pathological process. Pretreatment with Lactucaseniola increased the viability of cardiomyocytes and could decrease lipid peroxidation. Also, Lactucaseriola inhibited the reduction of anti-apoptotic Bcl-2 protein and elevation of apoptotic Bax and caspase-3 proteins. So, Lactucaseniola exerts protective effect against oxidative stress-induced cardiomyocytes damage. Therefore, it has the potential to be used as cardio-protective agent by the patients with cardiovascular diseases (Hosseini and Mahdian 2016).

Paeoniflorin

Paeoniflorin, a mono-terpeneglucoside, is the major active ingredient of Paeonialactiflora Pall. It has been reported that Paeoniflorin exerts multiple pharmacological activities, such as inhibition of tumor invasion and metastasis, reduction of inflammatory factor production, prevention of insulin resistance, and neuro-protective effects. Moreover, Paeoniflorin inhibit doxorubicin-induced cardio-myocyte apoptosis by reducing the production of reactive oxygen species (ROS) and anti-oxidative activity. Furthermore, the inhibitory effect Paeoniflorin against doxorubicin -induced cardio-myocyte apoptosis may be associated with the down-regulation of miR-1 expression via a reduction in ROS production (Li, *et al*. 2015).

Naringenin

Naringenin, the bitter principle of grapefruit (Citrus paradisi), has a multitude of pharmacological effects including, antithrombotic, anti-inflammatory, anti-estrogenic, as well as chemo-preventive, actions. The concept that naringenin, like other flavonoids, possesses potential anti-radical effects. The possible cardio-protective effects of this flavonoid in male Swiss albino rats challenged with a single cumulative dose of doxorubicin. Recently, the flavonolquercetin and flavono-lignan could protect heart microsomes and mitochondria against the iron-dependent doxorubicin-mediated lipid peroxidation. Furthermore, flavonoid 7-mono-hydroxylrutoside was more powerful than catalase and SOD gene therapy as cardio-protector in doxorubicin-induced cardiac damage in neonatal rat cardiac myocytes. Naringenin exhibited an inhibitory effect on MDA production from ethyl arachidonate, as well as a scavenging property of hydroxyl free radicals in kidney tissue suggesting anti-oxidant role of the flavonoid. Naringenin significantly reduced the cardiac total NO when administered for 7 consecutive days prior to doxorubicin challenge. Manyflavonoids have been reported to diminish NO production following oxidant damage in different pathologic conditions such as infection and inflammation via regulating the induction of inducible nitric oxide synthase (NOs) (Wang, *et al*. 2012).

Oleanolic Acid

Oleanolic acid is triterpenoids complexes that exist extensively in food and herbs. It has diversity of biological effects such, as antioxidants, antifungal, anti-inflammatory, anti-hyperlipidemia, hepato-protective, tumor prevention, immunomodulatory, anti-HIV, anti-arrhythmic and cardio-tonic. It will offer an available and cheap traditional medicine resource for management of myocardial ischemia and doxorubicin-induced cardiotoxicity through inhibiting angiotensin-converting enzyme activity also; it modulates the immune-inflammatory reaction in mice with experimental autoimmune myocarditis and guard from cardiac injury (Liu 1995).

Trans-Tretinoic Acid

It plays an important role in numerous cardiac biological processes, but its protective effects on doxorubicin-induced cardiotoxicity stay unidentified. It protected cardiomyocytes against doxorubicin-induced toxicity, by activating the ERK2 pathway, devoid of compromising its anticancer efficacy; consequently, it is a promising candidate as a cardio-protective agent against doxorubicin-cardiotoxicity (Yang *et al*. 2016).

Thymol and Carvacrol

Administration of Thymol and Carvacrolfor 14 days before doxorubicin administration ameliorated the heart function and oxidative stress parameters. Thus, Thymol and Carvacrol had cardio-protective that might be attributed to antioxidant, anti-inflammatory, and anti-apoptotic activities (El-Sayed and Mansour 2016).

Sulforaphane

Previous study has revealed that oxidative stress caused by doxorubicin is one of the main mechanisms for its toxic effects on the heart. Since the re-dox-sensitive transcription factor, Nrf2, plays a major role in defending cells from the toxic metabolites produced during oxidative stress. Sulforaphane, a potent Nrf2-activating agent, protected H9c2 cells from doxorubicin-cytotoxicity, restored cardiac function and a significant reduction in doxorubicin-induced cardio-myopathy. Cardiac accumulation of 4-hydroxynonenal protein adducts, due to lipid peroxidation following doxorubicin-induced oxidative stress, was significantly attenuated by Sulforaphane treatment via elevating mitochondrial respiratory complex activities. Therefore, co-administration of Sulforaphane reversed the doxorubicin-associated reduction in nuclear Nrf2 binding activity and restored cardiac expression of Nrf2-regulated genes at both the RNA and protein levels (Fimognari, *et al*. 2007).

Coenzyme Q10

CoQ10 might give a number of protections against cardiotoxicity during cancer treatment based on the fact that significant differences in electrocardiographic measurements were identified between control and CoQ10 groups. However, using CoQ10 in clinical practice was not recommended, due to insufficient data (Heather *et al.* 2012).

Dihydromyricetin

Is a natural product extracted from ampelopsis grosse-dentat, exerted cardio-protective effect against doxorubicin-induced toxicity, it rescued loss of anti-apoptosis protein ARC provoked by doxorubicin was involved in the cardio-protection. Thus, Dihydromyricetinis a cardio-protective agent that protects myocardial cells from apoptosis and potentiating anticancer activities of doxorubicin (Zhu, *et al.* 2014).

2. Conclusions

Cardiac toxicity caused by doxorubicin therapy is of considerable importance nowadays as when was appeared 30 years ago. The number of the patients surviving cancer and chemotherapy is superior today and attendance of subclinical cardiac dysfunction is even more pronounced. Mechanisms of doxorubicin induce cardiotoxicity are multi-factorial and complex. In spite of multitude hypothesizes include free radical stress, mitochondrial dysfunction, calcium overload are the main causes of doxorubicin-induced cardiotoxicity. However, the change in gene expression and activation of

ubiquitin-ligase–proteasome system and cell death all contribute to its cardiotoxicity. Therefore, more researches clinical studies are needed to explain the mechanism and improve strategies in prevention, inhibition and cure of doxorubicin-induced cardiotoxicity.

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