

The Potential Role of Thioctic Acid in the Attenuation of Doxorubicin Induced-Cardiotoxicity



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Introduction

During 1950s in Italy a soil sample was isolated and found new strains of *Streptomyces peucetius* bacteria from which a new antibiotic was extracted with potent effect against murine tumors, this antibiotic named daunorubicin [1]. In 1960s, a clinical trial was done on the drug and result a successful in treating acute leukemia and lymphoma, and finally a new antibiotic was discovered which named adriamycin which change to doxorubicin. Doxorubicin has a potent antitumor activity more than daunorubicin with a higher therapeutic index [2]. In 1967 the cardiotoxicity due to danurubicin was approved, the greatest risk of doxorubicin-induced toxicity is cardiotoxicity, so administration of doxorubicin should be dose-limited [3]. Doxorubicin changes the structure and function of cardiomyocytes, the genes that cause this are the brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) which are highly expressed in doxorubicin- induce cardiotoxicity, so; these two genes are responsible for cardiac hypertrophy [4]. The molecular mechanism behind this event involves formation of oxygen free radicals and iron oxidation. Since doxorubicin known to affect multiple biomarkers, the assessment of troponins and specific natriuretic peptides (pro BNP and DNP) is believed to predict doxorubicin-induced cardiotoxicity in early stages [5].

Mechanism of Doxorubicin-Induced Cardiotoxicity

Oxidative Stress: Doxorubicin-induced acute cardiotoxicity is result from oxidative stress and free radical production which induced by high dose of doxorubicin that initiating oxidative myocardial injury due to conversion of doxorubicin by intracellular enzymes into semiquinone free radical [6]. The heart is most susceptible organ to damage by free radicals due to low activities of antioxidant enzyme such as (superoxide dismutase, glutathione, and catalase enzymes) as a result, the accumulation of free radicals

that lead to lipid peroxidation, mitochondrial membrane damage, injury of nucleic acid, and destruction of myocardium endoplasmic reticulum [7].

Mitochondrial Damage: Mitochondria considered as the most progressively and extensively injured in doxorubicin induced cardiotoxicity because of the cationic drug doxorubicin which accumulated in the inner layer of the mitochondrial that forming a nearly-irreversible compound with cardiolipin [8]. The protein that needs cardiolipin coupled to work correctly, and since doxorubicin disrupt the cardiolipin protein interface and forming more superoxide [9]. Moreover, transport carnitine is extremely affected by doxorubicin that contributes to the mitochondrial dysfunction [10]. It is quite acceptable that these actions will disrupt mitochondrial metabolism, since mitochondria responsible for production of 90% of the Adenosine triphosphate (ATP) utilized by cardiomyocytes so, many ultrastructural pathologic changes will take place such as mitochondrial swelling and myelin figures within the mitochondria [11].

Doxorubicin-Iron Complex: Doxorubicin iron complex had been recognized that doxorubicin has a strong affinity to iron and this complex increase the lipid peroxidation through its interactions. In the presence of unbound iron atom, doxorubicin will encourage to form a cycle of free radical production, also doxorubicin metabolite form doxorubicinol which have the ability to interact with thiol groups of cell membrane proteins [12].

Apoptosis: The oxidative stress that evoked by doxorubicin can initiates the apoptotic signal leading to cardiomyocyte apoptosis also; the extrinsic and intrinsic apoptotic-pathways will be involved. Noticeably, doxorubicin induces apoptosis indirectly via production of free radicals [13].

Intracellular Calcium Dysregulation: Doxorubicin-induced cardiotoxicity can be augmented by increase the level of intracellular calcium and the dysregulation of intracellular calcium that generate free radicals [14]. The redox oxygen species and H_2O_2 generated also change the homeostasis of calcium in a multiple muscle cell types by disturbance of normal sarcoplasmic reticulum function. This is accomplished by inhibiting the Ca^{2+} ATPase pump [15]. Doxorubicin increases the release of calcium from the sarcoplasmic reticulum by increasing the chance of its channel's open state. Additionally, doxorubicin inhibits the sodium calcium exchanger channel inside sarcolemma that enhances the activity of the L-type calcium channel [16].

Neutrophils Activation: Myocardial damage also caused by neutrophils activation which releases myeloperoxidase and IL-17 so; these mediators regarded as potent indicators of cardiotoxicity [17]. Thioctic acid also named lipoic acid is a fatty acid compound that contains sulfur in its structure. Lipoic acid acts as an antioxidant and co-enzyme in the body so it called universal antioxidant because of the ability to modulate different kind of free radicals. Several studies showed that thioctic acid improves several conditions in the body that caused by free radicals, for example heart disease, cancer and other disorders which related with inflammation and aging [18]. The oxidized thioctic acid and reduced thioctic acid forms a potent redox couple that has a potent reduction potential so they consider as a potent antioxidants [19]. Truly, both thioctic acid and reduced thioctic acid scavenge different type of free radical such as hydroxyl radicals and hypochlorous acid, but the thioctic acid only cans scavenge singlet oxygen [20]. Furthermore, thioctic acid stimulates other endogenous antioxidants (e.g. vitamins C and E) and neutralizing many oxygen species [21]. Moreover, thioctic acid chelate redox-active metals *in vitro* and *in vivo*. The oxidizing form and reducing form bind with a number of metal ions, but in different properties according to the metal types [22]. Thioctic acid enters in recycle and stimulates many transcription factors, such these transcription factors that responsible for the production of GSH which is Nrf2. Under stress when the amount of free radical increase Nrf2 amount will decrease, at this moment lipoic acid will protect Nrf2 from influence by oxidative stress by its action as anti-oxidant [23]. Thioctic acid has been reported to attenuate and prevent myocardial damage during ischemic-reperfusion injury and anthracycline induced cardiotoxicity [24].

Thioctic acid has the ability to decrease serum BNP and cardiac hypertrophy by attenuation of mRNA and protein levels of C/EBP β which is responsible for cardiomyocyte hypertrophy. Also, thioctic acid decrease BNP serum levels through acting directly on scavenging free radicals, increasing the activity of natural antioxidant, reduction of oxidative stress and inflammation [25]. Moreover, thioctic acid decreases the level of caspase-3 due to antioxidant, anti-inflammatory and anti-apoptotic properties against doxorubicin toxicity in rats [26]. Additionally thioctic acid causes significant increases in serum glutathione peroxidase level

due to its potent antioxidant activity [27]. As well, thioctic acid illustrated a significant decrease in cardiac troponin I serum levels due to its antioxidant properties which modulate the oxidative stress and enhancement of endogenous glutathione [28]. In addition, thioctic acid has a significant effect in reduction of lipid peroxidase due to significant anti-oxidative and anti-inflammatory properties [29]. Over and above, thioctic acid led to a significant decrease in serum malondialdehyde serum levels as in many experimental contemporary studies that showed a significant effect of thioctic acid on the reduction of MDA serum levels during acute doxorubicin induced-cardiotoxicity in rat due to the potential antioxidant activity [30].

Furthermore, many experimental studies illustrated a significant decrease in TNF- α serum levels in rats that pre treated with thioctic acid due to reduction of LPS-stimulated release of inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukin (IL-1), (IL-1 β) and IL-6 [31]. Therefore, thioctic acid produced significant cardio-protection due to different mechanisms. Thioctic acid is a potent co-factor for mitochondrial dehydrogenase so; it preserves mitochondrial function during cardiac injury through reduction of ATP hydrolysis, augmentation of ATP production and normalization of cardiomyocyte PH [32]. Thioctic acid also prevents myocardial necrosis and apoptosis via inhibition of ischemic-reperfusion damage which triggered by oxidative stress [33]. The molecular mechanism of thioctic acid in attenuation of doxorubicin-induced cardiotoxicity is so complicated. During cardiotoxicity, proapoptotic gene is activated that trigger protein kinase MAP, nuclear factor-kB and TNF- α thereby apoptosis will be induced. The extra-cellular signals of protein kinase are p38 α/β kinase, regulated kinase ERK1/2 and terminal kinase c-Jun-NH2 [34]. Regulated kinase ERK1/2 is concerned with cell survival while terminal kinase c-Jun-NH2 is involved in induction of apoptosis thus; ERK1/2 antagonist led to significant apoptosis since; ERK1/2 has anti-apoptotic property. Therefore, the molecular effect of thioctic acid during doxorubicin-induced cardiotoxicity is activation of anti apoptotic pathway and inhibition of apoptotic pathway [35].

Conclusion

Thioctic acid illustrated a significant cardio-protection during doxorubicin induced-cardiotoxicity through modulation of oxidative stress and anti-oxidant potential.

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