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Review Article:

Doxorubicin Cardiotoxicity: An Update Regarding the Mechanism of Toxicity and Mitigation Strategies of Bee Propolis

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Abstract

Introduction: Doxorubicin (Dox.) is a very effective antineoplastic agent for treating various tumours. It produces an anti-cancer mechanism through the intercalation of DNA and reducing topoisomerase II enzyme activity in fast-proliferating cancers. However, Dox. is associated with limited-use adverse effects specifically accumulative and dose-dependent heart toxicity which is the underlying cause for increasing the risk of mortality in cancer patients that use this kind of anticancer. **Results**: Many related mechanisms have been suggested for Dox.-induced cardiac toxicity such as oxidative stress and deteriorated mitochondrial function, a disturbance in iron regulatory protein [(IRP)-1], the release of nitric oxide, autophagy and dysregulation of Ca^{2+} level. Unfortunately, there is no clinically approved protective agent against Dox.-induced cardiotoxicity has been discovered yet. **Aim**: The current review attempts to focus on collecting information related to the mechanism of stimulating heart disease resulting from the use of Dox. and trying to understand it at the molecular level and addressing the most important compounds, especially the natural ones, and their proposed mechanism of action against Dox.-induced heart toxicity. **Conclusion**: Dox. still one of the most effective anticancer medications. Due to its undesirable cardiotoxicity and the lack of effective preventative methods, Dox. uses could increase the risk of death and restrict its potential clinical applications. Many mechanisms have been implicated in Dox.-induced cardiac toxicity. Therefore, targeting this alteration using bee propolis has shown strong protective effects against the cardiotoxicity of Dox. and the decrease the death rate among patients suffering from cancer.

1. Introduction

Doxorubicin (Dox.) is a secondary metabolic product of a mutated strain of *Streptomyces peucetius* and known as anthracycline antibiotic using as antitumor agent (1). Dox. is effective in a verity of tumours, including solid and haematological tumours such as breast cancer and paediatric leukaemia respectively (2). Dox. is pharmacodynamically working by restraining topoisomerase II enzyme and blocking DNA and RNA creation and production of reactive oxidative stress (O.S.) (3). The acute adverse effects of Dox. appear within 2-3 days of drug administration including nausea, vomiting, alopecia, neutropenia and arrhythmias. However, the use limiting factor is the occurrence of acute cardiotoxicity in approximately 11% of patients (4). However, cardiotoxicity is a major risk of Dox. in all patients using it, specifically in childhood cancer with a high threat of emerging characteristic cardiac toxicity symptoms at an early stage, and this risk remnant high within thirty years following treatment (5). The cardiac events may encompass many effects such as cardiac dysfunction, myocardial ischemia or infection, pericardial disease, hypertension, arrhythmias and heart failure (6). Reactive oxygen species, disruption of (IRP)-1, inflammatory mediators, the release of nitric oxide, calcium dysregulation, autophagy, and cell death are the key underlying mechanisms of cardiotoxicity caused by Dox. that have been identified via numerous studies (7). The administration of propolis to the animals before Dox. therapy significantly altered the heart's oxidative damage. Propolis is a resinous combination that bees collect from sap flows, tree buds, or other plants. It is used as a sealant for unnecessary open pores in the hive (8). The composition and effectiveness of propolis varies widely depending on its source, location, environment, and age. It includes around 150 polyphenol substances, including their esters, including flavonoids and phenolic acid. These flavonoids' exact mode

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of action, however, is unclear. Moreover, it includes trace elements, vitamin B complexes, vitamin E and C, as well as a number of vital minerals like Ca, Zn, Mg, Cu, Mn, Fe, and Ni. As a result, it displays a variety of biological activities such as actions that are cytotoxic, antioxidant, free radical scavenging, and antimicrobial (9). There have also been reports of its anti-inflammatory, antiviral, and immunomodulatory properties, as well as potential use for the coronavirus 2019 (COVID-19) (5). This review focuses on the latest updates on the mechanism of cardiotoxicity of Dox. and the way to reduce this toxicity using natural compound called bee propolis.

1.1 Incidence of cardiotoxicity

Dox. cardiotoxicity can be acute or chronic. The acute cardiotoxicity incidence is about 11% and it could occur within 48-72 h of administration (4). However, chronic Dox. cardiotoxicity incidence is lower than acute one with an occurrence rate of about 1.7 % (5). It is mostly apparent within thirty days of using the last dose of the drug, but it could appear after six to ten years following its administration (10). The occurrence of cardiotoxic effects of Dox. is dose-dependent. The incidence will be 4%, 18%, or 36% when the dose of Dox. is 500-550 mg/m^2, 551-600 mg/m^2 or more than 600 mg/m^2 respectively (11). Combination therapy of Dox. with other anticancer could be another risk factor to increase the incidence of Dox.-induced cardiotoxicity (4). Age is another risk factor for developing Dox. cardiotoxicity. Very young and very old patients are more susceptible to developing this toxicity (4). The presence of some concomitant cardiac diseases such as hypertension is considered a risk factor for an increasing incidence of Dox. cardiotoxicity induced by Dox. (4).

1.2 Morphological and histological changes observed with doxorubicin-induced cardiotoxicity

All four cardiac cavities could be dilated. However, the dilatation of cardiac chambers is less severe compared to the dilatation that occurs in ischemic and non-ischemic cardiac diseases. Also, the contractile function and ventricular ejection fraction declined, with concurrent diastolic dysfunction(4,10). Histological changes commonly featured in the Dox. cardiotoxic incidence are including areas of patchy myocardial interstitial fibrosis and scattered vacuolated cardiomyocytes. Adria cells are recognised adjacent to areas of fibrosis. Partial or total loss of myofibrils and myocyte vacuolar degeneration are essential features of Dox. cardiotoxicity. The T-tubules and sarcoplasmic reticulum are distended. The disorganization of nucleus-chromatin and substitution of chromatin by pale filaments are also characteristics of Dox. cardiotoxicity (4,12).

1.3 Underlying molecular mechanisms of Dox. cardiotoxicity

Several theories have been put up to explain how Dox. can cause cardiotoxicity or heart failure. Increased O.S. in cardiac tissue is directly related to the cardiac complications of Dox. When there are less antioxidants and sulfhydryl groups present, increased O.S. induces the formation of reactive oxygen species (ROS), which harms the heart muscle. Furthermore, changed Ca^{2+} ion levels, which result in apoptosis, are a component of Dox.-induced cardiotoxicity. Cardiomyocytes and endothelial cells undergo apoptosis when caspases are activated (13). We have assembled comprehensive molecular mechanisms for Dox.-induced cardiotoxicity here (**Figure 1**).

1.3.1 Oxidative stress

The biggest concern that leads to cardiac muscle cell damage following Dox. treatment is the production of free radicals (14). Elevated ROS generation and lipid peroxidation in heart tissues are two mechanisms through which Dox.-induced cardiotoxicity manifests (14,15). ROS are promoted by aglycones and the iron complexes they have with anthracyclines (14). Several molecular pathways have been proposed during the past 30 years for the production of ROS and its detrimental effects on cardiac tissue. These processes have demonstrated the participation of several enzymes, including NADPH (nicotinamide adenine dinucleotide phosphate) oxidase (NOX), mitochondrial-dependent ROS generation, NOS (nitric oxide synthase), and others, that act to promote O.S. (13). Here, we've covered all of these molecular mechanisms. Dox. causes the creation of the Dox. semiquinone radical, which then converts free O_2 into the superoxide (O^{-}_2) free radical by binding to the endothelial nitric oxide synthase (eNOS) reductase enzyme. Superoxide free radicals and nitric oxide levels are out of equilibrium when the medication binds to the eNOS reductase enzyme. Cardiotoxicity results from a drop in nitric oxide levels and an increase in superoxide levels (16). According to a research, Dox. treatment produces an increase in eNOS mRNA and protein levels in the aortic endothelial cell of bovine, which triggers redox stimulation and results in apoptosis (14,17). An intriguing finding was that antisense eNOS mRNA decreased the activation of caspase-3, indicating a cardiac protective impact against Dox.-induced cardiac toxicity. Similar to this, Dox.-induced cardiac ROS generation is increased in transgenic eNOS mice, whereas cardiac ROS levels are lowered in knockout animals (17). Dox. primarily damages the mitochondria of cardiac cells, which causes damage to the cardiomyocytes (18,19). Since Dox. is cationic, it may easily interact with the cardiolipin protein of the mitochondrial membrane and create an irreversible complex (17). Dox. has a significant affinity for cardiolipin, which is essential for the electron transport chain's (ETC) correct operation and provides the body's systems with energy. Following its administration, Dox. bonded to cardiolipin and changed how it functioned at the interface, resulting in the production of O^{-}_2 radicals (19,20). Several proteins in mitochondria are similarly impacted by the Dox. therapy, impairing mitochondrial activity (17,19,21). Dox. also inhibits the long-chain fatty acids oxidation in the cardiac mitochondria and promotes metabolism of glucose, demonstrating the anaerobic from aerobic metabolism. This change in metabolism, which only occurs in response to O.S., may cause cardiac failure or aberrant contractility and relaxation (17,22–24). Moreover, Dox. alters the GATA-4 gene's expression in the mitochondria, which inhibits mitochondrial production and metabolism and triggers apoptosis (25). Inhalation of carbon monoxide (CO) at low concentrations to mice also reverses this condition because the ability of CO to activate the gene needed to produce mitochondria and up-regulates the nuclear-encoded heme oxygenase (HO)-1 (14). The antioxidant enzyme HO-1 guards against apoptosis of cardiomyocyte, and activation of Akt by HO-1/CO and inactivates glycogen synthase kinase-3β, allowing the translocation of erythroid 2-related factor 2 (Nrf2) and the subsequent activation of the GATA-4 gene to stop incidence of apoptosis (25). On the other hand, Dox. has been demonstrated to directly enhance the labile intracellular iron pool in studies (26,27). The transferrin receptor (TfR)

and storage regulator ferritin control cellular iron homeostasis. The former regulates iron absorption by internalizing iron-rich transferrin, whereas the latter stores extra iron beyond what is needed for cell metabolism. (IRP)-1 interacts with certain patterns in so-called iron-responsive elements (IREs) in target genes to control TfR and ferritin mostly at the post-transcriptional stage (27). Dox. and its metabolites have the ability to disrupt the Fe-S cluster of cytoplasmic aconitase and suppress IRP-1, which regulates cellular iron levels in accordance with the demands of the cell's metabolic processes. According to some research, Dox.-mediated intracellular iron build-up that increases O.S. is a significant factor in Dox. toxicity, while iron chelators are very efficient in reducing Dox.-induced cardiac toxicity (27). Dox. can cause intracellular dysregulation of calcium level, which led to increase intracellular Ca^{2+}, the ROS creation and producing apoptosis in cardiac cells (28). Through the Dox. metabolism there is the production of DOXOL (the toxic metabolite), which lead to sodium-calcium exchanger channel inhibition (29). This channel shows a vital role in controlling cardiac contractility through increases the L-type Ca^{2+} channel activity and sarcoplasmic reticulum calcium pump (29). Another pathway associated with the increase in intracellular calcium is one in which calcium stimulates the calcium-dependent proteases known as calpains. During O.S., the amount of calcium stored in the sarcoplasmic reticulum of cardiac muscles increases, and this leads to calcium ion leakage that activates the calpains. These calpains break the apoptotic factor caspase-12, which is one of the components that causes cardiac cells to die. A similar process was discovered with the treatment of Dox. (29). Also, calpains destroy the largest protein and main constituent of cardiac sarcomere that is called titin protein (29). Therefore, an elevation in cytoplasmic Ca^{2+}concentration leads to impair the functions mitochondria and apoptosis (30).

1.3.2 Cardiotoxicity caused by Dox.: The role of AMP-activated protein kinase signaling

Three sub-units make up the macromolecule protein complex known as AMP-activated protein kinase (AMPK), which is α, has one catalytic site and β with two regulatory sites. α splits into two subunits, some of which are found in the heart, including subunits α1 and α2 in the cardiac muscle cells and endothelial cells. With the injection of Dox., the AMPK pathway is inhibited, which lowers the heart's Acetyl-coA carboxylase (ACC) enzyme activity. Dox. produced AMPK signaling suppression results in the stimulation of other pathways, including Akt and MAP kinase, which causes DNA damage through O.S. and genotoxic stress. Moreover, AMPK inhibition causes increased energetic stress and heart tissue hypertrophy (11,31).

1.3.3 Function of autophagy

In both normal and stressful situations, eukaryotic cells use the conserved process of autophagy to maintain cellular homeostasis. It functions as a protective mechanism by eliminating long-lived and damaged organelles under both healthy and pathological circumstances. It's significant to note that the autophagy in the cardiomyocytes is dysregulated in response to stress, which can result in cardiac dysfunction and heart failure (32,33). Dox. promotes aberrant up- and down-regulation of autophagy-related genes, which leads to cardiotoxicity. Dox. therapy triggers the start of autophagy most likely via suppressing GATA-4 through the action of p53, which causes the Bcl-2 protein to be down-regulated. Moreover, Dox. triggers the autophagy process by raising Bcl-2's phosphorylation, which prevents Bcl-2/Beclin1 interaction. Dox. administration causes an accumulation of autophagosomes, which is inhibited by upregulating expression of numerous autophagy-related genes (Atg) and downregulating the master transcription factor EB, resulting in altered lysosomal biogenesis function and cell death in cardiac cells (34). Additionally, Dox. inhibits mTOR, perhaps by encouraging the autophagy onset, and it is also connected to p-53 upregulation, which eventually caused cardiac cells injury. Additionally, the development of ROS is brought on by the build-up of autophagosomes (35).

1.3.4 Creatine kinase's role

A protein called creatine kinase serves as a source of energy and is found in many human tissues. However, only the CK-MB creatine kinase isoenzyme is expressed in cardiac tissues. In the presence of ferrous iron, Dox.-induced O. S. impairments the creatine isoenzyme, which results in the production of the peroxynitrite free radical (14).

1.3.5 Apoptosis

Dox. triggers both the extrinsic and intrinsic apoptotic mechanisms (18). Apoptosis of cardiomyocytes is caused by these pathways as a result of an imbalance between oxidant substances and anti-oxidant substances (35). Dox. administration inducing O.S., which stimulates the heat shock factor 1 (HSF-1) and leading to produce the heat shock protein (HSP-25). FasL, Fas, c-Myc, and p53 are proapoptotic factors that cause the death of cardiac muscle cells, and HSP-25 stabilizes the p53 protein, which is in charge of creating these factors (36). Moreover, Dox. administration raised the amount of HSP-70 in the blood, and mice's heart tissue expresses it, resulting in inflammation and fibrosis (37). Several HSP proteins, however, including HSP-10, HSP-27, HSP-22, and HSP-60, HSP-20 are similarly protective, preventing apoptosis and maintaining myocardial function (38).

1.3.6 Endothelin-1

Preproendothelin-1, commonly known as endothelin-1, is a powerful vasoconstrictor that is produced by the vascular endothelial cells. Endothelial cells change immature form of endothelin (PPET-1) into PET (Proendothelin), which is ultimately transformed into endothelin-1, the mature form. Endothelin-1 levels rise in cardiac muscle cells following Dox. therapy, leading to hypertrophic cardiomyopathy (14).

1.3.7 Fibrosis

Therapy with Dox. blocks mRNA transfer and prevents the protein production of MMP1 (Matrix Metal-Loprotease-1) in cancer cells. This mechanism makes it useful in treating cancer since it decreases the motility of the tumor cell. MMP-2 and MMP-9, which exhibit cardiotoxicity by boosting production of collagen in the heart tissues, are two more MMPs that are activated by it (39). A rise in collagen causes fibrosis of the myocardium. The TGF- and phosphor-SMAD3 signaling pathways are also stimulated by these two MMPs, which results in elevated collagen deposition in cardiomyocytes (14).

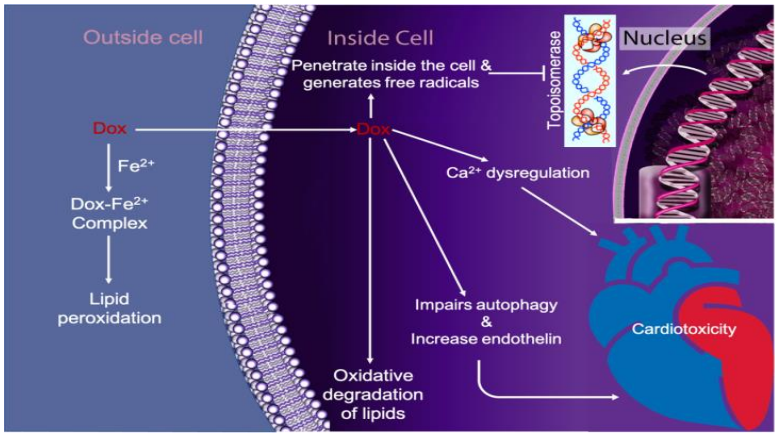

Figure 1: Cardiotoxic mechanisms of Dox.

1.4 Bee propolis

Honeybees gather propolis, a dark-coloured resinous substance, from leaf buds (39). Propolis is a well-known natural source of antioxidants (40). It has newly been widely used in food and drinks to enhance health, and avoid many diseases (41). Propolis is one of a powerful antioxidant rich with flavonoids, wax, essential oil, pollen, vitamin and amino acid (42). Further that recently been reported to have antioxidant properties, anti-inflammatory, anti-tumoral, antimicrobial and neuroprotective (43). Flavonoids have the ability to scavenging free radicals and thus keeping the cell membrane integrity against degradation by lipid peroxidation (13). The detrimental effects of Dox. on several organs were demonstrated in the current investigations using biochemical and histological methods. A lot of work has gone into understanding the causes of Dox. toxicity and finding treatments, including antioxidants, that reduce these adverse reactions. Many studies looked at propolis' potential effectiveness in protecting multiple organs from Dox. toxic damage. Due to its many stated advantages, safety, and affordability, propolis has received a lot of interest recently as a medicinal and possible preventative agent. In several human and animal research examining their mechanisms, the protective properties of propolis were verified using a number of biochemical markers in addition to histological and immunohistochemical findings (44). Propolis appears to be rich in phenolic acids and flavonoids, according to recent investigations, which may account for its potent in vitro free radical scavenging action (8,44). The majority of propolis samples from various locations were reported to have comparable phenolic profiles, however these chemicals' concentrations varied (45). The most prevalent chemicals among those found in propolis capsules in previous research were apigenin, rosmarinic acid, and sinapic acid. Moreover, significant levels of quercetin and kaempferol were present, along with cinnamic, ferulic, and caffeic acids (45). These flavonoids' flavones and flavanols work well to defend the body from ROS. In several cancer forms, cinnamic and caffeic acids have both demonstrated anticancer effects (46). Hence, propolis' antioxidant of these polyphenolic compounds may be responsible for its protective properties. According to that, combining Dox. and propolis would increase doxorubicin's anticancer effects and mitigate some of the harms that Dox. causes. Several studies' histopathological and biochemical findings support Dox.-induced cardiotoxicity, which also manifests as severe congestive bleeding in the heart, a degenerative necrotic region, and fibrosis that reveals cardiomyopathy (8). On the other hand, propolis pre-treatment resulted in mild heart muscle necrosis and fibrotic blood vessels (8,47). Consistent with this, prior research found that giving rats propolis before isoproterenol dramatically reduced their CK-MB, LDH, AST, and ALT activities as well as their TG and TC levels (47). By its direct cytotoxic radical-scavenging actions and prevention of lipid peroxidation, they demonstrated the cardioprotective capabilities of Malaysian propolis against isoproterenol-induced myocardial infarction (47). Together with the expression of genes that protect the cardiovascular system, a previous study found that propolis' cardio-protective properties are also caused by the antioxidant activity of its polyphenols and the production of nitric oxide, which acts as a vasodilator (48). Moreover, propolis therapy improved defense against O.S. by decreasing malondialdehyde (MDA) levels in the liver and myocardium while boosting reduced GSH levels (8). It should be noted that in addition to O.S., inflammation is crucial in the pathophysiology of Dox.-induced multi-organ toxicities. Moreover, the overproduction of free radicals results in the production of additional inflammatory mediators (NF-$_k$B and its subsequent pro-inflammatory cytokines generation), which leads to a number of pathological changes (49,50). According to studies, propolis pre-treatment before Dox. generates a considerable improvement in all prior markers, demonstrating that propolis assisted in maintaining membrane integrity by limiting the leaking of the enzymes. Moreover, the polyphenols included in propolis capsules are significant constitutive antioxidants that may protect against oxidative renal, cardiac, and hepatic damage. Moreover, numerous cellular enzymes, including xanthine oxidase, lipoxygenase, and phospholipase A_2, are inhibited by these polyphenols, which lowers LDL-peroxidation. In addition to acting as iron chelators, they also reduce the generation of free radicals that are dependent on iron, which increases their scavenging activity and inhibits the lipid peroxidation (48). As a result, propolis may lower coronary artery disease by regulating lipids and suppressing lipid oxidation (51). In present studies, findings showed that propolis anti-inflammatory effects were revealed via decreasing IL-1β expression along with COX-2, and IL-6 expression ROS and NO generation (45). Other conducted studies observed that the genes and protein expression levels of pro-inflammatory cytokines IL-1β, IL- 6, and IL-8 reduced dramatically after treatment with propolis (52).

These results raised the idea that propolis may function as an adjuvant treatment, shielding organs against Dox.-related oxidative and apoptotic activities and mitigating their damaging consequences.

2. Conclusion

Dox. still one of the most effective anticancer medications. It is widely used to treat cancers such as ovary, leukemia, lymphoma, breast and other cancers in both children and adults. Due to its undesirable cardiotoxicity and the lack of effective preventative methods, Dox. uses could increase the risk of death and restricting its potential clinical applications among cancer patients. Many mechanisms have been implicated in Dox.-induced cardiac toxicity, including impaired mitochondrial function, O.S., alteration in (IRP)-1, impairment of calcium homeostasis with apoptosis. Therefore, targeting this alteration using bee propolis has shown strong protective effects against cardiotoxicity of Dox. and decrease the death rate among patients suffering from cancer.

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4. Conflict of interest

There is no conflict of interest.

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السمية القلبية للدوكسوروبيسين: الحديث فيما يتعلق بآلية السمية واستراتيجيات التخفيف منها بواسطة دنج النحل

الخلاصة:

المقدمة: الدوكسوربيسين هو عامل مضاد للأورام فعال للغاية لعلاج الأورام المختلفة. ينتج آلية مضادة للسرطان من خلال الإقحام في الحمض النووي وتقليل نشاط إنزيم توبويزوميراز II في السرطانات سريعة الانتشار. ومع ذلك ، فان استخدامه مرتبطة بتأثيرات ضارة تحدد من استخدامه وعلى وجه التحديد سمية القلب التراكمية والمعتمدة على الجرعة والتي هي السبب الأساسي لزيادة خطر الوفاة لدى مرضى السرطان الذين يستخدمون هذا النوع من مضادات السرطان. **النتائج:** تم اقتراح العديد من الآليات ذات الصلة للسمية القلبية التي يسببها هذا الدواء مثل الإجهاد التأكسدي وتدهور وظيفة الميتوكوندريا ، واضطراب في البروتين التنظيمي للحديد [IRP -1] ، وإطلاق أكسيد النيتريك ، والالتهام الذاتي ، وخلل في مستوى الكالسيوم. لسوء الحظ ، لا يوجد عامل وقائي معتمد إكلينيكيًا ضد السمية القلبية التي يسببها الدوكسوروبيسين حتى الآن. **الهدف:** تحاول المراجعة الحالية التركيز على جمع المعلومات المتعلقة بآلية تحفيز أمراض القلب الناتجة عن استخدام الدوكسوروبيسين ومحاولة فهمه على المستوى الجزيئي للخلية والتعامل مع أهم المركبات وخاصة الطبيعية منها وآلية عملها المقترحة ضد سمية القلب التي يسببها الدوكسوروبيسين. **الخلاصة:** الدوكسوروبيسين لا يزال أحد الأدوية المضادة للسرطان الأكثر فعالية. بسبب تسمم القلب غير المرغوب فيه وعدم وجود طرق وقائية فعالة ، فان استخدتم الدوكسوروبيسين يمكن أن يزيد من خطر الوفاة وهذا الخطر يحد من تطبيقات الدوكسوروبيسين السريرية. تم ربط العديد من الآليات في سمية القلب التي يسببها الدوكسوروبيسين لذلك ، فإن استهداف هذا التغيير باستخدام دنج النحل قد أظهر تأثيرات وقائية قوية ضد السمية القلبية للدوكسوروبيسين وانخفضت نسبة الوفيات بين مرضى السرطان.

الكلمات المفتاحية: دوكسوروبيسين، سمية القلب،الإجهاد التأكسدي ،دنج النحل