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DOXORUBICIN'S ROLE IN CANCER TREATMENT AND ITS SIDE EFFECTS ON HUMAN HEALTH

Qays Assi Ahmed
Department of Biology, College of Education for Pure Sciences,
Kirkuk University, 52001 Kirkuk- Iraq. ORCID ID: 0000-0001-8450-211X,
Email: qaysassi77@uokirkuk.edu.iq.

Dlawer Abdulhammed Ahmad Aljaff
Department of pharmacology, College of medicine,
Kirkuk University, 52001Kirkuk -Iraq. ORCID ID: 0000-0003-2072-1617,Email:
dr.dlawerjaff@uokirkuk.edu.iq

Khalid Bahram Arif
Pathology Department. College of medicine, university of kirkuk, 52001
Kirkuk -Iraq. ORCID ID: 0000-0002-1485-386X,
Email: karif@uokirkuk.edu.iq

Abstract
Doxorubicin is used to treat various types of cancer, such as breast cancer, lung cancer, thyroid cancer, bladder cancer, ovarian cancer, as well as acute lymphoblastic leukemia through obstruction of DNA repair, membrane association, free radical generation and cell programmed death stimulation. The use of doxorubicin may cause many side effects such as heart poisoning, inhibition of bone marrow, and damage to the liver.
The current review therefore aimed to study the role of Doxorubicin in the treatment of cancer diseases and the drug's side effects on human health. The review included a presentation on cancer and chemotherapy of the disease using the drug Doxorubicin and the clinical efficacy of the drug and the functioning of the drug. The review examined the negative effects of the doxorubicin drug on cardiotoxicity, hepatotoxicity, the level of antioxidants, free roots, lipid profile, and tissue composition of the heart and liver.

Keywords: Cancer, Doxorubicin, Oxidation Balance, Heart, Liver.

Introduction

The drug Doxorubicin belongs to Anthracycline antibiotics and is produced from the fungi Streptomyces peucetius which is the most effective treatment as an anti-cancer (Zhu, 2018), and is used very effectively and extensively over the past decades in the management of various cancers including breast cancer, leukemia and cancer (El- tawab et al., 2018). The anti-tumor drug activity mechanism involves changes in DNA and the production of free radicals (Forrest et al., 2012). This has been

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determined by the use of the drug in chemotherapy due to its toxicity to the body, such as cardiotoxicity, hepatotoxicity, kidneys, blood and reproductive (Zaletok et al., 2015; Altınkaynak et al., 2018).
The toxicity of the drug is due to many interrelated factors, one of the most important being oxidative stress Oxidative stress, since it has long been believed that oxidative stress caused by high levels of Reactive oxygen species (ROS) within mitochondria of cells is the main mediator of drug toxicity (Currens, 2003). In addition, reactive oxygen species can also be produced from outside the mitochondria (Cho et al., 2011) by activating Pro-oxidant enzymes such as Nicotinamide adenine dinucleotide phosphate (NADPH) in converting the property to Semiquinone free radicals , which can generate (ROS) including superoxide radicals ($O^{-\bullet}_2$), Hydroxyl radical ($OH^{\bullet}$) and Hydrogen Peroxide (H_2O_2) and that these free radicals cause cellular poisoning including cardiotoxicity and hepatotoxicity (Yagmurca et al., 2007;Wang et al., 2015; Dai et al., 2015; Nagai et al.,2015 ; Nagai et al., 2018) .
In addition, studies have indicated a high rate of iron accumulation in the mitochondria after taking the drug, which later causes an increase in the reproduction of (ROS) that cause iron toxicity (Ichikawa et al., 2014). Another factor causing cardiac drug toxicity is the complex increase of the enzyme DNA-Topoisomerase Iiβ controlling the synthetic changes of the entire DNA and chromosome (Lyu et al., 2007), the dysfunction of Autophagy dysregulation as well as Mitochondrial dysfunction (Ni et al., 2015; Bartlett et al., 2016), as well as Inflammation, Abnormal intracellular calcium handling and cell death caused by Apoptosis stimulated by drug-induced P53 activation (Murakawa et al., 2012; Hanna et al., 2017) .

Cancer

Cancer is a term for diseases caused by abnormal cell reproduction in which cell division is completely out of control. (Mohammed et al., 2019). Fears of cancerous tumors increase for the many factors that cause or cause it and its widespread prevalence in Environment, as happens with ionized radiation that may be originating naturally, industrially or from medical sources, as in X-ray radiography . Solar radiation through its composition may be Ultraviolet, which may be a major cause of skin cancer (Mohania et al., 2017). In addition to pollution, working environments, lifestyle and some food habits, as well as smoking and alcohol, have an impact on increasing the incidence of certain cancers (Winn et al., 2015). These causes affect the cell's DNA and thus lead to the production of a different cell with new properties than normal tissue cells (Liotto and Clair, 2000).

Methods of Cancer Treatment

Cancer treatment depends on the type and stage of growth. Some cancer patients have only one treatment. Cancer treatment includes hormones, surgery, radiation and chemotherapy .

Chemotherapy

Successful management of chemotherapy depends on several key factors, including the surface area of the body, patient age, diagnosis of the condition, stage of illness, underlying blood disease, liver and kidney status (National Library of Medicine, 2017). The dose of chemotherapy should be adjusted

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according to these fundamentals, and there are many different types of chemotherapy such as the group of antibiotics of doxorubicin, since chemotherapy can be used in destroying cancer cells and stopping the spread of cancer cells (Baskar et al., 2012).

The mechanism of traditional chemotherapy work lies by damaging rapidly growing cells which is one of the most important features of malignant cells, So chemotherapy destroys tumor cells and also affects cells with rapid division in normal conditions such as hair follicles, digestive tract and bone marrow cells. All of these lead to side effects of chemotherapy for cancer such as alopecia, Inflammation of the mucous membrane and its effect on immunity and even on the nucleus of cells (Croce, 2008). Chemotherapy agents show signs of cardiotoxicity that cause heart failure (Schimmel et al., 2004).

Doxorubicin

Doxorubicin is an antibiotic isolated from the strain of Streptomyces peucetius, the Dox molecule consists of the compound naphthacene quinone which is amino sugar. Dox has water-loving zones together with hydrophobic zones, allowing the drug to bind to cell membranes as well as plasma proteins. Doxorubicin therefore has basal and acidic behaviour and these features make it a comprehensive compound, allowing it to pass in different cell compartments (Octavia et al., 2012).

Doxorubicin is a highly effective anti-oncology drug used to treat many cancers of children and adults such as solid tumors, lymphoma, leukemia and breast cancer. The drug is known to produce severe cellular toxicity but heart toxicity is the most important (Mohammed et al., 2019). The onset of heart toxicity may be delayed by up to 10-15 years after the cessation of treatment (Salim et al., 2015).

Clinical Activity of Doxorubicin

Cancer tumors are characterized by uncontrolled cell division compared to natural tissue, and the process of normal cell division or cancer occurs during the cell cycle Cell cycle in the G2, S phase, the process of DNA manufacture is carried out in the S phase, and the G2 phase is the manufacture of cellular compounds regulating filamentary division. Therefore chemotherapy is the killing of cancer cells by stopping their division by breaking down the synthesis of DNA and RNA and thus controlling the spread of the tumor (Harrey and Champe, 2006).

Mechanism of Doxorubicin Action

There are four main drug mechanisms in treating tumor spread through its effect on cells when cells are in the S,G2 two phases and include:

1. Interference in DNA And Obstruction of DNA Repair with The Help of Topoisomerase

The drug's work depends on the overlap between base pairs of DNA and the inhibition of biomolecular synthesis (Gu et al., 2016). The effectiveness of the drug is associated with its ability to prevent DNA from doubling by inhibiting topoisomerase II (an enzyme that promotes the dissolution of DNA tape and is involved in its closure), It is one of the main target sites for anti-oncological activity by preventing binding nucleotide yarns after breaking the double tape of DNA (Eissa et al., 2017). Finally, activating

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the defection reaction and inhibiting the step of repositioning the compound topoisomerase II DNA-by the drug activates a series of apoptosis (Dimitrakis et al., 2012).

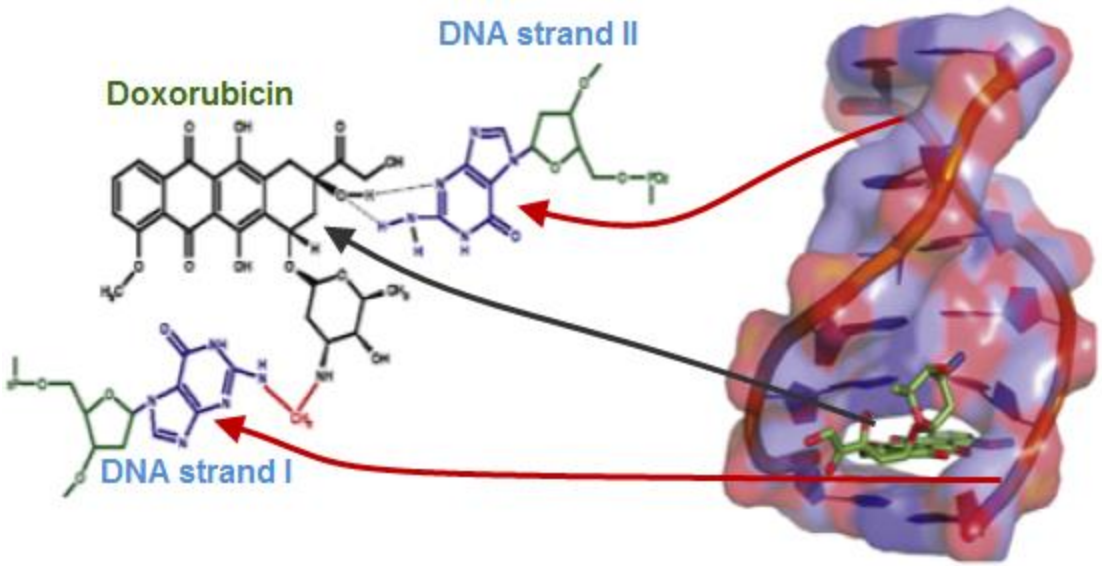

Figure (1) shows the binding of Doxorubicin to the nitrogenous bases in DNA (Mohammed,2018).

2. Linking to Membranes

As a result of its association with cellular membranes, the drug changes the fluidity of the membrane as well as changes the permeability of the membranes of the ions and thus results in cell dysfunction, which is either directly from the drug's effect or through oxidation damage caused by the drug (Harrey and Champe, 2006).

3. Free Radicals Generation

Doxorubicin releases reactive oxygen species when oxidized into an unstable metabolite (Semiquinone) By adding a single electron to the quinine group stimulated by the reduction of NADPH, a free root component followed by oxides of reactive oxygen from the interaction with molecular oxygen to give lipid peroxide, especially membrane fat, as well as DNA damage, and then stimulate programmed cell death pathways (apoptosis) (Mitry and Edwards, 2016) . The generation of free radicals can be caused by the drug interaction and mineral ions, especially iron in the heart muscle, which in the presence of molecular oxygen leads to the formation of superoxide. These species are then reduced by SOD to H2O2 and $O^{\cdot\cdot}_2$ in the presence of Fe^{2+} and H_2O_2 is reduced to $OH^{\cdot}$ (Fenton interaction). These roots appear as key intermediaries for heart muscle injury and lipid oxidation (Gammella et al., 2014; Mobaraki et al., 2017). It shows Superoxide or products analyzed by H_2O_2 and $OH^{\cdot}$ Initiate fat peroxide by extracting hydrogen atoms from unsaturated fatty acids. Furthermore, treatment with doxorubicin drains heart cells of selenium-based glutathione peroxidase, an enzyme responsible for oxygen-derived detoxification (Foretz et al., 2014).

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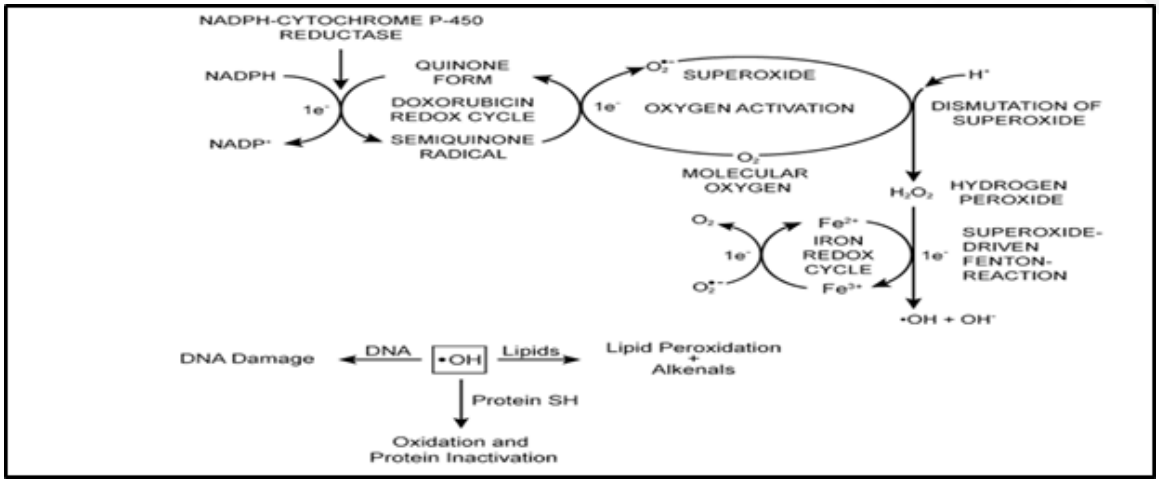

Figure (2) Free radical formation by doxorubicin (Mohammed, 2018).

4. Apoptosis Activation

There are several factors, including cytochrome C stimulation of the beginning of the phases of cell death programmed by mitochondria. The enzymatic pathway to form free radicals is mediated by mitochondria. Doxorubicin has a near high cardiolepin, an abundant phospholipide in the inner membrane of mitochondria, these convergence allows doxorubicin to penetrate muscle cells (de Wolf , 1991), since the damage caused by doxorubicin to mitochondria may cause a defect in the cellular respiratory chain at the outset that allows the continuous production of free radicals and mitochondrial damage, which may lead to the release of cytochrome C that caused the apoptosis, Activation of the P53 pathway also leads to changes in the gene expression of proteins to prevent cell division in apoptosis (Cui et al., 2002; Mobaraki et al., 2017).

Studies have shown that treatment with doxorubicin affects gene expression of mitochondria (Suliman et al., 2007). There is also another form of organized cell death called "ferroptosis" caused by the accumulation of iron within the heart muscle (Fang et al., 2019). Iron already accumulates in cardiomyocytes during doxorubicin therapy (Ichikawa et al., 2014), and in turn activates cell death pathways (Gammella et al., 2014). tudies show that doxorubicin can also interact directly with ferritin (Canzoneri and Oyelere, 2008) (Since ferritin acts as an iron carrier that reduces excess iron within the cell, disabling this protein eventually increases free iron, which in turn leads to cell damage. Accordingly, mice lacking mitochondrial ferritin display lower mortality and mitochondrial damage when doxorubicin is used (Maccarinelli et al., 2014).

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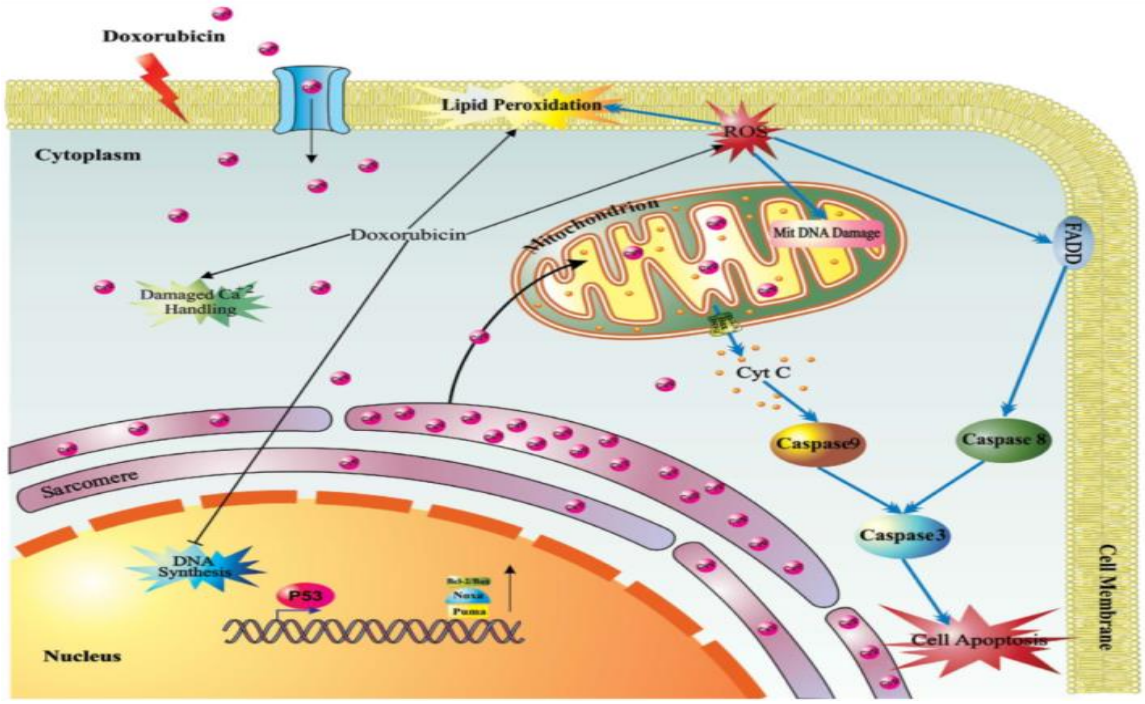

Figure (3) The role of Doxorubicin in stimulating Apoptosis (Mobaraki et al., 2017)

Doxorubicin Side Effect

The same mechanisms that make doxorubicin an effective antitumor agent are also partly responsible for the drug's adverse effects. The drug's association was limited to persistent, irreversible toxicity (Buzdar et al., 1992). The drug is cytotoxic by its direct effect on membranes in addition to its role in oxidation and the generation of reactive oxygen species (ROS) (Cappetta et al., 2018).

Doxorubicin Cardiotoxicity

The effects of the drug on the heart are both acute and chronic, meaning that even after treatment is stopped, drug accumulation can lead to left ventricular dysfunction, myocardial dilatation, and heart failure (Lipshultz et al., 2010). The effects on the heart are more pronounced than in any other organ because of its lower levels of antioxidant enzymes such as superoxide dismutase, which result in cardiomyocytes being more susceptible to injury than other tissues (Barry et al., 2007; Ahmed et al., 2022b).

The drug-induced cardiotoxicity is clearly a dose-dependent response. Studies have shown that drug-induced cardiotoxicity can be attributed to the overproduction of ROS causing damage to cardiomyocytes, as cardiomyocytes require mitochondria to produce ATP, which ensures contractile function of the heart (Koleini and Kardami, 2017). The oxidative stress caused by increased ROS activates the molecular pathways leading to the loss of cardiomyocytes through necrosis and apoptosis (Licata et al., 2000). The oxidative stress mechanism of the drug has also been shown to cause mitochondrial toxicity, which has a major role in acute and long-term cardiac dysfunction (Zhang et al.,

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2009). Research has shown that there is also an accumulation of iron (Fe^{2+}) in mitochondria after treatments and isolated cardiomyocytes have shown increased mitochondrial concentrations of Fe^{2+} and cellular ROS levels (Ichikawa et al., 2014). Excessive amount of ROS and a significant increase in Fe^{2+} are two ways that the drug has been shown to cause acute and chronic cardiotoxicity.

Hepatotoxicity of Doxorubicin

The liver has the highest concentration of the drug. The liver plays a major role in drug metabolism and distribution, and hepatic impairment has resulted in drug doses being reduced or completely removed from the chemotherapy regimen in the past. Hepatic dysfunction is also mediated by the generation of free radicals that cause oxidative damage to tissues. High levels of P450 enzymes in the liver make it a direct target for drug accumulation and possible damage. P450 facilitated the conversion of Dox to the toxic metabolite Dox-OL in the liver. Toxic effects were observed through an increase in the activity of the enzymes (AST) and (ALT) (Hamlaoui et al., 2012), as well as an increase in the concentration of Malondialdehyde (MDA), which is a diagnostic marker for liver dysfunction, elevated serum MDA, AST, and ALT levels are also accompanied by a concomitant decrease in antioxidant enzymes in the liver (Hamlaoui et al., 2012; Ahmed et al., 2022a). In addition, the increase in free iron (Fe^{2+}), hydrogen peroxide (H_2O_2), along with Ca^{2+} levels followed by induction of hydroxyl radicals ($OH^{\bullet}$) can in turn affect the Ca^{2+} balance in both erythrocytes and plasma (Bengaied et al., 2017).

The Effect of Doxorubicin on The Oxidative Balance

Doxorubicin leads to a decrease in the level of antioxidants and a high level of oxidation products, due to the fact that the drug has the ability to produce large quantities of free radicals in several pathways, including enzymatic by converting it to semiquinone and resulting in a superoxide radical ($O^{-\bullet}_2$) or non-enzymatic via It combines with iron and engages in Fenton reactions and produces large amounts of free radicals (Halliwell and Gutteridge, 2015). Therefore, the animal resorts to defending itself by depleting its internal antioxidants. The reason for the increase in MDA may explain the fact that the free radicals that resulted from the drug affected the pancreatic β-cells and their secretion of insulin, which led to a decrease in the concentration of insulin in the blood, stimulating the activity of Falty Acyl CoA Oxidase, which stimulates the process of β.Oxidation of fatty acids and an increase in H_2O_2 formation and ultimately an increase Rates of lipid peroxidation and MDA production (Daoud and Jaber, 2019).

The cell envelope is the target most vulnerable to free radical reactions because it contains polyunsaturated fatty acids that have double bonds that are attacked by free radicals and MDA is a product of lipid peroxide (Kampa et al., 2004; Parra-Ortiz et al., 2019). The decrease in GSH leads to a rise in hydrogen peroxide and then lipid peroxidation formation, leading to an increase in MDA, due to the ability of glutathione to inhibit lipid peroxidation. (Meda et al. 2019). The use of doxorubicin leads to the emergence of inflammation that stimulates cells to produce cytokines, which in turn stimulates neutrophils and phagocytes to increase the release of NO• which interacts with $O^{-\bullet}_2$ to form $ONOO^{\bullet}$ (Wen et al., 2015; Khalil et al., 2018; Ahmed et al., 2021). The drug contributes to the formation of

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additional free radicals, especially the superoxide radical $O^{-\bullet}_2$, which in turn reacts with nitric oxide $NO^{\bullet}$ to produce nitrite peroxide $ONOO^{\bullet}$ (Lee et al., 2016).

Several studies have shown an imbalance in the balance or state of oxidants - antioxidants due to the exacerbation of the drug's toxicity to cells and tissues of the organism, the accumulation of reactive oxygen species and the entry into the phase of oxidative stress due to the virulence of the toxicity of doxorubicin (Cota et al., 2018; Nagai et al., 2018). In addition, the drug may stimulate the onset of stages or the emergence of programmed cell death, which is also a source of free radicals (Liu et al., 2007). These large amounts of free radicals increase the concentrations of oxidizing substances and reduce the activity of antioxidants, which leads to weakening the tissue's resistance to oxidative stress (Lim, 2013). It may also be attributed to the fact that free radicals reduced the gene expression of new antioxidants (Minotti et al., 1996). It is also believed that the effect of the drug on the alimentary canal caused a decrease in the levels of food antioxidants, as well as a lack of absorption of the raw materials necessary to build them due to damage to the lining of the gastrointestinal tract (Rahim et al., 2013; Wang et al., 2016).

Effect of Doxorubicin on Lipid Profile

An increase in the level of cholesterol, triglycerides, low-density lipoproteins and very low-density lipoproteins is accompanied by a decrease in the level of high-density lipoproteins (Sharma et al., 2016; Ahmed et al., 2020). This change may be attributed to an increase in the activity of the enzyme cholesterol acyl transferase, which is responsible for the absorption of cholesterol, which is stimulated by insulin deficiency as a result of oxidative stress that affects pancreatic beta cells under the influence of reactive oxygen species, thus increasing the level of cholesterol absorption by the intestines (Maechler et al., 1993).

The reason for the high concentration of (VLDL-C) may be due to the increase in the concentration of free radicals in the body as a result of treatment with the drug, which breaks down fatty tissue and thus increases the release of fatty acids (FFA), which the liver uses in large quantities in the production of VLDL-C and thus the concentration of VLDL-C increases Which turns into LDL-C, which leads to an increase in its concentration and may lead to serious complications such as atherosclerosis and other diseases of the liver, heart and insulin resistance (Murray et al., 2003; Zhang et al., 2010; Ahmed et al., 2022c; Ahmed et al.,2022d). In addition, the oxidation of LDL-C and the destruction of internal cholesterol in the body due to the reactive oxygen species generated by the toxicity of the drug doxorubicin leads to a decrease in the level of HDL-C, which is the basis for the process of transporting cholesterol from the cells of the body to the liver, thus reducing its level in the blood vessels (Guyton and Hall, 2016) and thus increase the risk factor for cardiovascular disease.

The Effect of Doxorubicin on The Heart

The increase in the activity of cardiac enzymes is due to the oxidative stress that occurs in the tissues of the organs, especially the heart. Doxorubicin causes the generation of high levels of reactive oxygen species (ROS) inside and outside the mitochondria of cells (Cho et al., 2011). This is the main mediator

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of doxorubicin toxicity, and as it is known, the high level of the final oxidation products represented by malondialdehyde caused by attacking the unsaturated membrane lipids, causing lipid peroxidation and thus losing its vital role in maintaining cell functions. In addition, the drug can be converted to semiquinone free radicals, mediated by the activation of antioxidant enzymes such as NADPH, which can generate reactive oxygen species (ROS) including superoxide radicals ($O^{-\bullet}_2$), hydroxyl radical ($OH^{\bullet}$) and hydrogen peroxide (H_2O_2) (Yagmurca et al., 2007). These free radicals are very important for drug-mediated cytotoxicity, including cardiotoxicity (Wang et al., 2015).

In addition, the high rate of iron accumulation in mitochondria after taking the drug may later cause an increase in the generation of reactive oxygen species that cause its toxicity (Ichikawa et al., 2014). The increased activity of LDH and CK enzymes may also be attributed to the cardiac toxicity of the drug caused by an increase in the enzyme complex DNA-topoisomerase Iiβ, which controls the structural changes of DNA and the entire chromosome (Lyu et al., 2007), as well as a defect in autophagy dysregulation (Bartlett et al., 2016), and mitochondrial dysfunction (Ni et al., 2015), as well as inflammation and apoptosis induced by p53 activation by drug action (Murakawa et al., 2012). All of these functional imbalances lead to damage to the heart tissue, causing the leakage of these enzymes into the serum. One of the reasons for this increase may be that the heart tissue contains low levels of antioxidants compared to other body tissues, so it is vulnerable to damage due to free radicals (Halestrap, 2006).

It may also be attributed to the fact that the heart muscle is rich in mitochondria, which is one of the main targets of cellular damage caused by the drug in the heart tissue (Vijpongsa and Yeh, 2014), due to the ability of the drug to bind to cardiolipin, which is located in the inner membrane of mitochondria, causing an imbalance in the cellular respiration chain. (Goormaghtigh et al., 1990). This may cause the generation of large amounts of free radicals and a decrease in endogenous antioxidants, which is also one of the main causes of cardiac toxicity caused by the drug (Songbo et al., 2019). The tissues of the heart, in particular, are prone to free radical damage due to their low levels of enzymes or molecules that inhibit the toxicity of free radicals, such as the antioxidants catalase, superoxide dismutase and glutathione. In addition, doxorubicin has a high affinity for mitochondrial membrane-forming phospholipids in cardiomyocytes, which leads to its accumulation in cardiac tissues (Takś et al., 1992). The damage that occurs in the mitochondria due to the drug has dire consequences on the contraction of heart cells due to changes that can occur in energy metabolism (Liu et al., 2002).

Metabolic disturbances due to doxorubicin toxicity, which are associated with the generation of reactive oxygen species (ROS), lead to increased peroxidation of lipids and unsaturated fatty acids (Shan et al., 2003), in addition to attacking DNA free radicals that accelerate apoptosis of cells The heart (Agarwal et al., 2003). Giving DOX leads to a deficiency of antioxidants and an increase in oxidative stress (Swamy et al., 2012). And thus the occurrence of types of subcellular change, the most important of which is Cardiac injury, and the use of the drug leads to a lack of oxygen supply or a lack of glucose in the blood, which leads to damage to the heart cells and leads to the cell membrane becoming permeable or destroying it, and thus the leakage of enzymes from the cells (Thipeswamy et al., 2011). Although

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doxorubicin is widely used against cancerous tumors, its severe side effects on the heart, kidneys and liver have limited its use (Citil et al., 2008).

The Effect of Doxorubicin on The Liver

The main reason that may be attributed to the high activity of liver enzymes is the oxidative stress caused by the toxicity of the drug, which causes many dysfunctions of hepatocytes and thus the death of cells and the release of their various enzymes into the blood (Niu et al., 2015; Wang et al., 2015; Kobylinska et al., 2015; Nagai et al., 2016). Although doxorubicin is widely used against cancerous tumors, its severe side effects on the heart, kidneys and liver have limited its use (Santos et al., 2007). Toxic factors of the drug cause liver damage due to oxidative stress, which results in large numbers of reactive oxygen species, as these radicals affect tissues and cells of the body, the most important of which is the liver, causing pathological changes and the occurrence of infections (Yagmurca et al., 2007). Its side effects are also related to DNA and blocking its repair, so the drug accelerates programmed death, which leads to dysfunction of various cells and thus the speed of their damage (Kalender et al., 2005).

The metabolic activity of the liver also increases when exposed to toxic substances during the process of detoxification in order to balance the stress resulting from the action of toxins and this increase in order to release energy sources such as glucose that is accompanied by cell death and decomposition and necrosis that may occur after severe degeneration or occur directly, Small parts are disposed of by phagocytic cells, and the rest becomes a liquid that enters the lymph and veins (Murray et al., 2003). Doxorubicin reduces antioxidants and upsets the equilibrium state between oxidation and antioxidants (Karapehlivan et al., 2007). Necrosis is also due to the expansion of the central hepatic veins and their permeability change due to the toxic effect and the occurrence of hepatitis, and this change affects the delivery of oxygen and food to the liver cells, which leads to a change in cell functions or death (Krishna, 2004). Hepatocellular damage is accompanied by an increase in the concentration of ALT and AST enzymes caused by toxic compounds that affect hepatocyte integrity and extracellular leakage (Avwioro et al., 2010).

Conclusion

The result of the current study showed that the drug has several mechanisms in the treatment of cancerous diseases, but at the same time it has many side effects, as it leads to expansion and failure of the heart muscle, and liver damage through high level of free radicals and low level of antioxidants, thus leakage of liver enzymes into the blood, and high level of Total cholesterol, Triglycerides and Low-density lipoproteins, a decrease in the level of High-density lipoproteins, and the appearance of histological abnormalities in the heart and liver.

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References

1. Agarwal, A., Saleh, R. A., & Bedaiwy, M. A. (2003). Role of reactive oxygen species in the pathophysiology of human reproduction. Fertility and sterility, 79(4), 829-843.
2. Ahmed, Q. A., Abdullah, K. K., & Hassan, H. S. K. (2021). The Effect Of Olive Oil (Oo) And Hydroxytyrosol (Hxt) In Improving The Level Of Sex Hormones And Suppressing Oxidative Stress And Histopathological Of The Testes Caused By Hyperlipidemia In Male Rats. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO, 13072-13086.
3. Ahmed, Q. A., Abdullah, K. K., & Mutar, W. M. (2022c). A Review of the Uses of the Ketogenic Diet. Kirkuk University Journal-Scientific Studies, 17(2).
4. Ahmed, Q. A., Bakr . M. M, & Ahmed,T. MK. (2022d). NEGATIVE EFFECTS OF HYPERLIPIDEMIA ON HUMAN HEALTH. Academicia Globe: Inderscience Research, 3(10), 292-311.
5. Ahmed, Q. A., Rahim, S. M., & Hameed, A. K. (2022b). The Effect of Hydroxytyrosol (HXT) and Local Olive Oil (LOO) on Lipid Profile and Histopathological Changes in The Heart as Outcome of Induced Hyperlipidemia in Male Rats. International Journal of Medical Sciences, 5(2), 44-54.
6. Ahmed, Q. A., Rahim, S. M., & Hameed, A. K. (2020). THE EFFECT OF HYDROXYTYROSOL (HXT) AND A LOCAL OLIVE OIL EXTRACT ON THE LEVEL OF HEPCIDIN HORMONE AND PATHOLOGICAL HISTOLOGICAL CHANGES WITH IRON DEPOSITION IN THE AORTA RESULTING FROM INDUCED HYPERLIPIDEMIA IN MALE RATS. Plant Archives, 20(2), 1895-1902.
7. Ahmed, Q. A., Rahim, S. M., & Hameed, A. K. (2022a). The Effect of Hydroxytyrosol (HXT) and Local Olive Oil (LOO) on Oxidative Stress and Histopathological Changes in the Liver Resulting from Induced Hyperlipidaemia in Male Rats. INTERNATIONAL JOURNAL OF MEDICAL SCIENCES, 5(1), 43-54.
8. Altınkaynak, Y., Kural, B., Akcan, B. A., Bodur, A., Özer, S., Yuluğ, E., ... & Örem, A. (2018). Protective effects of L-theanine against doxorubicin-induced nephrotoxicity in rats. Biomedicine & Pharmacotherapy, 108, 1524-1534.
9. Avwioro, G., Iyiola, S., & Aghoghovwia, B. (2010). Histological and biochemical markers of the liver of Wistar rats on subchronic oral administration of green tea. North American Journal of Medical Sciences, 2(8), 376.
10. Barry, E., Alvarez, J. A., Scully, R. E., Miller, T. L., & Lipshultz, S. E. (2007). Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Expert opinion on pharmacotherapy, 8(8), 1039-1058.
11. Bartlett, J. J., Trivedi, P. C., Yeung, P., Kienesberger, P. C., & Pulinilkunnil, T. (2016). Doxorubicin impairs cardiomyocyte viability by suppressing transcription factor EB expression and disrupting autophagy. Biochemical Journal, 473(21), 3769-3789.
12. Bartlett, J. J., Trivedi, P. C., Yeung, P., Kienesberger, P. C., & Pulinilkunnil, T. (2016). Doxorubicin impairs cardiomyocyte viability by suppressing transcription factor EB expression and disrupting autophagy. Biochemical Journal, 473(21), 3769-3789.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

13. Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and radiation therapy: current advances and future directions. International journal of medical sciences, 9(3), 193.
14. Bengaied, D., Ribeiro, A., Amri, M., Scherman, D., & Aranaud, P. (2017). Reduction of hepatotoxicity induced by doxorubicin. J Integr Oncol, 6(193), 2.
15. Buzdar, A. U., Hortobagyi, G. N., Kau, S. W., Smith, T. L., Fraschini, G., Holmes, F. A., ... & Ames, F. C. (1992). Adjuvant therapy with escalating doses of doxorubicin and cyclophosphamide with or without leukocyte alpha-interferon for stage II or III breast cancer. Journal of clinical oncology, 10(10), 1540-1546.
16. Canzoneri, J. C., & Oyelere, A. K. (2008). Interaction of anthracyclines with iron responsive element mRNAs. Nucleic acids research, 36(21), 6825-6834.
17. Cappetta, D., Rossi, F., Piegari, E., Quaini, F., Berrino, L., Urbanek, K., & De Angelis, A. (2018). Doxorubicin targets multiple players: a new view of an old problem. Pharmacological research, 127, 4-14.
18. Cho, K. J., Seo, J. M., & Kim, J. H. (2011). Bioactive lipoxygenase metabolites stimulation of NADPH oxidases and reactive oxygen species. Molecules and cells, 32(1), 1-5.
19. Cho, K. J., Seo, J. M., & Kim, J. H. (2011). Bioactive lipoxygenase metabolites stimulation of NADPH oxidases and reactive oxygen species. Molecules and cells, 32(1), 1-5.
20. Citil, M., Erdoğan, H. M., Erdoğan, U. Z. L. U., Atakişi, E., Güneş, V., Tuzcu, M., ... & Doğan, A. (2008). Protective effects of L-carnitine on doxorubicine induced cardiomyopathy in rabbits. Kafkas Üniversitesi Veteriner Fakültesi Dergisi, 14(2).
21. Cota, D. L., Rasal, V. P., Mishra, S., & Shengule, S. (2018). Cardioprotective effect of oregano oil against doxorubicin-induced myocardial infarction in rats. Pharmacognosy Magazine, 14(57), 363.
22. Croce, CM.(2008) Molecular origins of cancer: Oncogenes and cancer Engl J Med. 358:502-511.
23. Cui, H., Schroering, A., & Ding, H. F. (2002). p53 mediates DNA damaging drug-induced apoptosis through a caspase-9-dependent pathway in SH-SY5Y neuroblastoma cells. Molecular cancer therapeutics, 1(9), 679-686.
24. Dai, C., Ma, S., Wang, F., Zhao, H., Wu, X., Huang, Z., ... & Fu, L. (2015). Lapatinib promotes the incidence of hepatotoxicity by increasing chemotherapeutic agent accumulation in hepatocytes. Oncotarget, 6(19), 17738.
25. Daoud, A. G., Jaber, H., & Abdalah, M. E. (2019). Iron status in diabetes mellitus. Al Mustansiriyah Journal of Pharmaceutical Sciences, 19(3), 7-12.
26. de Wolf, F. A. (1991). Binding of doxorubicin to cardiolipin as compared to other anionic phospholipids—An evaluation of electrostatic effects. Bioscience reports, 11(5), 275-284.
27. Dimitrakis, P., Romay-Ogando, M. I., Timolati, F., Suter, T. M., & Zuppinger, C. (2012). Effects of doxorubicin cancer therapy on autophagy and the ubiquitin-proteasome system in long-term cultured adult rat cardiomyocytes. Cell and tissue research, 350(2), 361-372.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

28. Eissa, I. H.; El-Naggar, A. M.; El-Sattar, N.; and Youssef, A. S. A. (2017). Design and discovery of novel quinoxaline derivatives as dual DNA intercalators and topoisomerase II inhibitors. Anticancer Agents Med Chem. doi:10.2174/1871520617666170710182405.
29. El-tawab, A.A.; Mohamed, A.A. and Khalifa, M.M .(2018). Olive Leaf Extract and a-Tocopherol Combination Therapy Attenuates Doxorubicin Induced Cardiotoxicity in Rats. Med. J. Cairo Univ.; Vol. 86(5):1-12.
30. Fang, X., Wang, H., Han, D., Xie, E., Yang, X., Wei, J., ... & Wang, F. (2019). Ferroptosis as a target for protection against cardiomyopathy. Proceedings of the National Academy of Sciences, 116(7), 2672-2680.
31. Foretz, M., Guigas, B., Bertrand, L., Pollak, M., & Viollet, B. (2014). Metformin: from mechanisms of action to therapies. Cell metabolism, 20(6), 953-966.
32. Forrest, R. A., Swift, L. P., Rephaeli, A., Nudelman, A., Kimura, K. I., Phillips, D. R., & Cutts, S. M. (2012). Activation of DNA damage response pathways as a consequence of anthracycline-DNA adduct formation. Biochemical pharmacology, 83(12), 1602-1612.
33. Gammella, E., Maccarinelli, F., Buratti, P., Recalcati, S., & Cairo, G. (2014). The role of iron in anthracycline cardiotoxicity. Frontiers in pharmacology, 5, 25.
34. Gammella, E., Maccarinelli, F., Buratti, P., Recalcati, S., & Cairo, G. (2014). The role of iron in anthracycline cardiotoxicity. Frontiers in pharmacology, 5, 25.
35. Goormaghtigh, E., Huart, P., Praet, M., Brasseur, R., & Ruysschaert, J. M. (1990). Structure of the adriamycin-cardiolipin complex: role in mitochondrial toxicity. Biophysical chemistry, 35(2-3), 247-257.
36. Gu, J., Hu, W., Song, Z. P., Chen, Y. G., Zhang, D. D., & Wang, C. Q. (2016). Resveratrol-induced autophagy promotes survival and attenuates doxorubicin-induced cardiotoxicity. International Immunopharmacology, 32, 1-7.
37. Guyton, A.C. and Hall, J.E.(2016). Text book of medical physiology 13th Ed. Philadelphia. Inc. USA.; P 100-1003.
38. Halestrap, A. P. (2006). Calcium, mitochondria and reperfusion injury: a pore way to die. Biochemical Society Transactions, 34(2), 232-237.
39. Halliwell, B. and Gutteridge, J. M. (2015). Free radicals in biology and medicine. Oxford University Press, USA.P 46-130.
40. Hamlaoui, S., Mokni, M., Limam, N., Carrier, A., Limam, F., Amri, M., ... & Aouani, E. (2012). Resveratrol protects against acute chemotherapy toxicity induced by doxorubicin in rat erythrocyte and plasma. Journal of Physiology and Pharmacology, 63(3), 293.
41. Hanna, A. D., Lam, A., Thekkedam, C., Willemse, H., Dulhunty, A. F., & Beard, N. A. (2017). The anthracycline metabolite doxorubicinol abolishes RyR2 sensitivity to physiological changes in luminal Ca2+ through an interaction with calsequestrin. Molecular pharmacology, 92(5), 576-587.
42. Harrey R. A. and P. C. Champe, (2006) "Pharmacology", Lippincott Williams and Wilkins, New York.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

43. Harrey R. A. and P. C. Champe, (2006) "Pharmacology", Lippincott Williams and Wilkins, New York.
44. Ichikawa, Y., Ghanefar, M., Bayeva, M., Wu, R., Khechaduri, A., Prasad, S. V. N., ... & Ardehali, H. (2014). Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. The Journal of clinical investigation, 124(2), 617-630.
45. Ichikawa, Y., Ghanefar, M., Bayeva, M., Wu, R., Khechaduri, A., Prasad, S. V. N., ... & Ardehali, H. (2014). Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. The Journal of clinical investigation, 124(2), 617-630.
46. Ichikawa, Y., Ghanefar, M., Bayeva, M., Wu, R., Khechaduri, A., Prasad, S. V. N., ... & Ardehali, H. (2014). Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. The Journal of clinical investigation, 124(2), 617-630.
47. Ichikawa, Y., Ghanefar, M., Bayeva, M., Wu, R., Khechaduri, A., Prasad, S. V. N., ... & Ardehali, H. (2014). Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. The Journal of clinical investigation, 124(2), 617-630.
48. Kalender, Y., Yel, M., & Kalender, S. (2005). Doxorubicin hepatotoxicity and hepatic free radical metabolism in rats: the effects of vitamin E and catechin. Toxicology, 209(1), 39-45.
49. Kampa, M., Alexaki, V. I., Notas, G., Nifli, A. P., Nistikaki, A., Hatzoglou, A., ... & Castanas, E. (2004). Antiproliferative and apoptotic effects of selective phenolic acids on T47D human breast cancer cells: potential mechanisms of action. Breast Cancer Research, 6(2), 1-12.
50. Karapehlivan, M., Uzlu, E., Atakişi, O., Erdoğan, H. M., Uzun, M., & Çitil, M. (2007). Doksorubisin uygulanan tavşanlarda plazma sialik asit, malondialdehit ve redükte glutatyon düzeylerine L-karnitinin etkileri. Kafkas Üniversitesi Veteriner Fakültesi Dergisi, 13(2).
51. Khalil, S. R., Mohammed, A. T., Abd El-fattah, A. H., & Zaglool, A. W. (2018). Intermediate filament protein expression pattern and inflammatory response changes in kidneys of rats receiving doxorubicin chemotherapy and quercetin. Toxicology Letters, 288, 89-98.
52. Koleini, N., & Kardami, E. (2017). Autophagy and mitophagy in the context of doxorubicin-induced cardiotoxicity. Oncotarget, 8(28), 46663.
53. Kusunoki, T., Cureoglu, S., Schachern, P. A., Baba, K., Kariya, S., Sampaio, A., & Paparella, M. M. (2004). Effects of gentamicin on sensorineural elements of the cochlea in human temporal bones. American journal of otolaryngology, 25(5), 313-317.
54. Kobylinska, L. I., Havrylyuk, D. Y., Ryabtseva, A. O., Mitina, N. E., Zaichenko, O. S., Lesyk, R. B., ... & Stoika, R. S. (2015). Biochemical indicators of hepatotoxicity in blood serum of rats under the effect of novel 4-thiazolidinone derivatives and doxorubicin and their complexes with polyethyleneglycol-containing nanoscale polymeric carrier. The Ukrainian Biochemical Journal, (87,№ 2), 122-132.
55. Lee, C. T., Yu, L. E., & Wang, J. Y. (2016). Nitroxide antioxidant as a potential strategy to attenuate the oxidative/nitrosative stress induced by hydrogen peroxide plus nitric oxide in cultured neurons. Nitric oxide, 54, 38-50.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

56. Licata, S., Saponiero, A., Mordente, A., & Minotti, G. (2000). Doxorubicin metabolism and toxicity in human myocardium: role of cytoplasmic deglycosidation and carbonyl reduction. Chemical research in toxicology, 13(5), 414-420.
57. Lim, S. C. (2013). Interrelation between expression of ADAM 10 and MMP 9 and synthesis of peroxynitrite in doxorubicin induced cardiomyopathy. Biomolecules & Therapeutics, 21(5), 371.
58. Liotta, L. A., & Clair, T. (2000). Checkpoint for invasion. Nature, 405(6784), 287-288.
59. Lipshultz, S. E., Scully, R. E., Lipsitz, S. R., Sallan, S. E., Silverman, L. B., Miller, T. L., ... & Colan, S. D. (2010). Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. The lancet oncology, 11(10), 950-961.
60. Liu, B., Bai, Q. X., Chen, X. Q., Gao, G. X., & Gu, H. T. (2007). Effect of curcumin on expression of survivin, Bcl-2 and Bax in human multiple myeloma cell line. Zhongguo Shi Yan Xue Ye Xue Za Zhi, 15(4), 762-766.
61. Liu, X., Chen, Z., Chua, C. C., Ma, Y. S., Youngberg, G. A., Hamdy, R., & Chua, B. H. (2002). Melatonin as an effective protector against doxorubicin-induced cardiotoxicity. American journal of physiology-heart and circulatory physiology, 283(1), H254-H263.
62. Lyu, Y. L., Kerrigan, J. E., Lin, C. P., Azarova, A. M., Tsai, Y. C., Ban, Y., & Liu, L. F. (2007). Topoisomerase IIβ–mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer research, 67(18), 8839-8846.
63. Lyu, Y. L., Kerrigan, J. E., Lin, C. P., Azarova, A. M., Tsai, Y. C., Ban, Y., & Liu, L. F. (2007). Topoisomerase IIβ–mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer research, 67(18), 8839-8846.
64. Maccarinelli, F., Gammella, E., Asperti, M., Regoni, M., Biasiotto, G., Turco, E., ... & Cairo, G. (2014). Mice lacking mitochondrial ferritin are more sensitive to doxorubicin-mediated cardiotoxicity. Journal of Molecular Medicine, 92(8), 859-869.
65. Maechler, P., Wollheim, C. B., Bentzen, C. L., & Niesor, E. (1993). Importance of exogenous cholesterol in diabetic rats: effects of treatment with insulin or with an acyl-CoA: cholesterol acyltransferase inhibitor. Annals of nutrition and metabolism, 37(4), 199-209.
66. Meda, S., Singh, S., Palade, P., Tonk, S., & Awasthi, S. (2019). Oxidative stress in intensive care unit patients: A review of glutathione linked metabolism and lipid peroxidation. The Southwest Respiratory and Critical Care Chronicles, 7(27), 7-35.
67. Minotti, G., Mancuso, C., Frustaci, A., Mordente, A., Santini, S. A., Calafiore, A. M., ... & Gentiloni, N. (1996). Paradoxical inhibition of cardiac lipid peroxidation in cancer patients treated with doxorubicin. Pharmacologic and molecular reappraisal of anthracycline cardiotoxicity. The Journal of clinical investigation, 98(3), 650-661.
68. Mitry, M. A., & Edwards, J. G. (2016). Doxorubicin induced heart failure: Phenotype and molecular mechanisms. IJC heart & vasculature, 10, 17-24.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

69. Mobaraki, M., Faraji, A., Zare, M., Dolati, P., Ataei, M., & Manshadi, H. D. (2017). Molecular mechanisms of cardiotoxicity: a review on major side-effect of doxorubicin. Indian journal of pharmaceutical sciences, 79(3), 335-344.
70. Mobaraki, M., Faraji, A., Zare, M., Dolati, P., Ataei, M., & Manshadi, H. D. (2017). Molecular mechanisms of cardiotoxicity: a review on major side-effect of doxorubicin. Indian journal of pharmaceutical sciences, 79(3), 335-344.
71. Mobaraki, M., Faraji, A., Zare, M., Dolati, P., Ataei, M., & Manshadi, H. D. (2017). Molecular mechanisms of cardiotoxicity: a review on major side-effect of doxorubicin. Indian journal of pharmaceutical sciences, 79(3), 335-344.
72. Mohammed, A. W., Arif, I. S., & Jasim, G. A. (2019). The cytotoxicity and anti-proliferative effect of Metformin on solid tumors in vitro cell lines. Journal of Pharmaceutical Sciences and Research, 11(3), 832-837.
73. Mohammed, A. W., Arif, I. S., & Jasim, G. A. (2019). The cytotoxicity and anti-proliferative effect of Metformin on solid tumors in vitro cell lines. Journal of Pharmaceutical Sciences and Research, 11(3), 832-837.
74. Mohammed, Ahmed. Wahhab.(2018) The Cytotoxic and Anti-proliferative Effects of Metformin on MCF-7 and RD Tumor Cell Lines Using in Vitro Approaches. Ph.D. Thesis Mustansiriyah University/ College of pharmacy.
75. Mohammed, Ahmed. Wahhab.(2018) The Cytotoxic and Anti-proliferative Effects of Metformin on MCF-7 and RD Tumor Cell Lines Using in Vitro Approaches. Ph.D. Thesis Mustansiriyah University/ College of pharmacy.
76. Mohania, D., Chandel, S., Kumar, P., Verma, V., Digvijay, K., Tripathi, D., ... & Shah, D. (2017). Ultraviolet radiations: Skin defense-damage mechanism. Ultraviolet Light in Human Health, Diseases and Environment, 71-87.
77. Murakawa, T.; Nakayama, H.; Nishida, K.; Akira, S.; Yamamoto, A.; Komuro, I. and Otsu, K. (2012). Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure.Nature. 485:251-255.
78. Murakawa, T.; Nakayama, H.; Nishida, K.; Akira, S.; Yamamoto, A.; Komuro, I. and Otsu, K. (2012). Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure.Nature. 485:251-255.
79. Murray, R.k.,Grunner , D.K.,Mayes, D.A. and Rodwell , V.W.(2003) . Harpers illustrated biochemisty . 26th ed Appeton and Lange .USA .PP : 223 – 352 .
80. Nagai, K., Fukuno, S., Oda, A., & Konishi, H. (2016). Protective effects of taurine on doxorubicin-induced acute hepatotoxicity through suppression of oxidative stress and apoptotic responses. Anti-cancer drugs, 27(1), 17-23.
81. Nagai, K., Fukuno, S., Otani, K., Nagamine, Y., Omotani, S., Hatsuda, Y., ... & Konishi, H. (2018). Prevention of doxorubicin-induced renal toxicity by theanine in rats. Pharmacology, 101(3-4), 219-224.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

82. Nagai, K., Fukuno, S., Otani, K., Nagamine, Y., Omotani, S., Hatsuda, Y., ... & Konishi, H. (2018). Prevention of doxorubicin-induced renal toxicity by theanine in rats. Pharmacology, 101(3-4), 219-224.
83. National Library of Medicine (Ed.). (17, October 16). DoxorubicinEpirubicindarubicin. Retrieved from https://livertox.nih.gov/Doxorubicin Epirubicindarubicin.htm#reference.
84. Ni, H. M., Williams, J. A., & Ding, W. X. (2015). Mitochondrial dynamics and mitochondrial quality control. Redox biology, 4, 6-13.
85. NI,Hong-Min; WILLIAMS, Jessica A.; DING, Wen-Xing. Mitochondrial dynamics and mitochondrial quality control. Redox biology, 2015, 4: 6-13.
86. Niu, Q. Y., Liu, Y. T., Li, Z. Y., & Qin, X. M. (2015). Metabolomics study of doxorubicin induced hepatotoxicity. Yao xue xue bao= Acta Pharmaceutica Sinica, 50(6), 708-713.
87. Octavia, Y., Tocchetti, C. G., Gabrielson, K. L., Janssens, S., Crijns, H. J., & Moens, A. L. (2012). Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. Journal of molecular and cellular cardiology, 52(6), 1213-1225.
88. Parra-Ortiz, E., Browning, K. L., Damgaard, L. S., Nordström, R., Micciulla, S., Bucciarelli, S., & Malmsten, M. (2019). Effects of oxidation on the physicochemical properties of polyunsaturated lipid membranes. Journal of colloid and interface science, 538, 404-419.
89. Rahim, S. M., Taha, E. M., Mubark, Z. M., Aziz, S. S., Simon, K. D., & Mazlan, A. G. (2013). Protective effect of Cymbopogon citratus on hydrogen peroxide-induced oxidative stress in the reproductive system of male rats. Systems biology in reproductive medicine, 59(6), 329-336.
90. Salim, E. I., Abd El-Magid, A. D., Farara, K. M., & Maria, D. S. (2015). Antitumoral and antioxidant potential of Egyptian propolis against the PC3 prostate cancer cell line. Asian Pacific Journal of Cancer Prevention, 16(17), 7641-7651.
91. Santos, R. V., Batista Jr, M. L., Caperuto, É. C., & Costa Rosa, L. F. (2007). Chronic supplementation of creatine and vitamins C and E increases survival and improves biochemical parameters after doxorubicin treatment in rats. Clinical and Experimental Pharmacology and Physiology, 34(12), 1294-1299.
92. Schimmel, K. J., Richel, D. J., Van den Brink, R. B., & Guchelaar, H. J. (2004). Cardiotoxicity of cytotoxic drugs. Cancer treatment reviews, 30(2), 181-191.
93. Shan, Y. X., Liu, T. J., Su, H. F., Samsamshariat, A., Mestril, R., & Wang, P. H. (2003). Hsp10 and Hsp60 modulate Bcl-2 family and mitochondria apoptosis signaling induced by doxorubicin in cardiac muscle cells. Journal of molecular and cellular cardiology, 35(9), 1135-1143.
94. Sharma, M., Tuaine, J., McLaren, B., Waters, D. L., Black, K., Jones, L. M., & McCormick, S. P. (2016). Chemotherapy agents alter plasma lipids in breast cancer patients and show differential effects on lipid metabolism genes in liver cells. PloS one, 11(1), e0148049.
95. Songbo, M., Lang, H., Xinyong, C., Bin, X., Ping, Z., & Liang, S. (2019). Oxidative stress injury in doxorubicin-induced cardiotoxicity. Toxicology letters, 307, 41-48.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

96. Suliman, H. B., Carraway, M. S., Ali, A. S., Reynolds, C. M., Welty-Wolf, K. E., & Piantadosi, C. A. (2007). The CO/HO system reverses inhibition of mitochondrial biogenesis and prevents murine doxorubicin cardiomyopathy. The Journal of clinical investigation, 117(12), 3730-3741.
97. Swamy, A. V., Gulliaya, S., Thippeswamy, A., Koti, B. C., & Manjula, D. V. (2012). Cardioprotective effect of curcumin against doxorubicin-induced myocardial toxicity in albino rats. Indian journal of pharmacology, 44(1), 73.
98. Takś, I. E., Matkovics, B., Varga, S. I., Homolay, P., Fehér, G., & Seres, T. (1992). Study of the myocardial antioxidant defence in various species. Pharmacological research, 25, 177-178. .
99. Thippeswamy, A. H. M., Shirodkar, A., Koti, B. C., Sadiq, A. J., Praveen, D. M., Swamy, A. V., & Patil, M. (2011). Protective role of Phyllantus niruri extract in doxorubicin-induced myocardial toxicity in rats. Indian Journal of Pharmacology, 43(1), 31.
100. Turrens, J. F. (2003). Mitochondrial formation of reactive oxygen species. The Journal of physiology, 552(2), 335-344.
101. Vejpongsa, P., & Yeh, E. T. (2014). Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. Journal of the American College of Cardiology, 64(9), 938-945.
102. Wang, L., Chen, Q., Qi, H., Wang, C., Wang, C., Zhang, J., & Dong, L. (2016). Doxorubicin-Induced Systemic Inflammation Is Driven by Upregulation of Toll-Like Receptor TLR4 and Endotoxin LeakageGut Flora Promoted Doxotubicin-Induced Inflammation. Cancer research, 76(22), 6631-6642.
103. Wang, Y., Mei, X., Yuan, J., Lu, W., Li, B., & Xu, D. (2015). Taurine zinc solid dispersions attenuate doxorubicin-induced hepatotoxicity and cardiotoxicity in rats. Toxicology and Applied Pharmacology, 289(1), 1-11.
104. Wang, Y., Mei, X., Yuan, J., Lu, W., Li, B., & Xu, D. (2015). Taurine zinc solid dispersions attenuate doxorubicin-induced hepatotoxicity and cardiotoxicity in rats. Toxicology and Applied Pharmacology, 289(1), 1-11.
105. Wang, Y., Mei, X., Yuan, J., Lu, W., Li, B., & Xu, D. (2015). Taurine zinc solid dispersions attenuate doxorubicin-induced hepatotoxicity and cardiotoxicity in rats. Toxicology and Applied Pharmacology, 289(1), 1-11.
106. Warpe, V. S., Mali, V. R., Arulmozhi, S., Bodhankar, S. L., & Mahadik, K. R. (2015). Cardioprotective effect of ellagic acid on doxorubicin induced cardiotoxicity in wistar rats. Journal of acute medicine, 5(1), 1-8.
107. Wen, J., Li, H., Zhang, Y., Li, X., & Liu, F. (2015). Modification of HSP proteins and Ca2+ are responsible for the NO-derived peroxynitrite mediated neurological damage in PC12 cell. International journal of clinical and experimental pathology, 8(5), 4492.
108. Winn, D. M., Lee, Y. C., Hashibe, M., Boffetta, P., & INHANCE consortium. (2015). The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer. Oral diseases, 21(6), 685-693.

ISSN: 2776-1010 Volume 3, Issue 11, Nov., 2022

109. Yagmurca, M., Bas, O., Mollaoglu, H., Sahin, O., Nacar, A., Karaman, O., & Songur, A. (2007). Protective effects of erdosteine on doxorubicin-induced hepatotoxicity in rats. Archives of medical research, 38(4), 380-385.
110. Yagmurca, M., Bas, O., Mollaoglu, H., Sahin, O., Nacar, A., Karaman, O., & Songur, A. (2007). Protective effects of erdosteine on doxorubicin-induced hepatotoxicity in rats. Archives of medical research, 38(4), 380-385.
111. Yagmurca, M., Bas, O., Mollaoglu, H., Sahin, O., Nacar, A., Karaman, O., & Songur, A. (2007). Protective effects of erdosteine on doxorubicin-induced hepatotoxicity in rats. Archives of medical research, 38(4), 380-385.
112. Zaletok, S., Gulua, L., Wicker, L., Shlyakhovenko, V., Gogol, S., Orlovsky, O., ... & Turmanidze, T. (2015). Green tea, red wine and lemon extracts reduce experimental tumor growth and cancer drug toxicity. Experimental oncology.
113. Zhang , L . (2010). Dy slipid aemia, glucose intolerance and cardiovascular disease mortality and morbidity in Europeans and Asians Academic dissertation pupil cation of public Health M205 , University of Helsinki , Helsinki , Finland PP:88.
114. Zhang, Y. W., Shi, J., Li, Y. J., & Wei, L. (2009). Cardiomyocyte death in doxorubicin-induced cardiotoxicity. Archivum immunologiae et therapiae experimentalis, 57(6), 435-445.
115. Zhu, H. (2018). Doxorubicin-induced cardiotoxicity. Cardiotoxicity, Intech. Open, London, 47-66.