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DOXORUBICIN: OVERVIEW AND TOXICITY

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Abstract:

After seeing rising cases of cancer soon it will become a global pandemic. Nowadays many therapies are available for the treatment of cancer which includes surgery, radiation therapy and chemotherapy. Many drugs are used in chemotherapy and doxorubicin is one of the most common drugs of chemotherapy for the last 50+ years. It is most commonly used for the treatment of solid tumors like breast, ovarian, bladder and thyroid and treatment of sarcomas like bone and soft tissue. It is also used in the treatment of acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), Hodgkin lymphoma and small-cell lung cancers.

Even though it can be used to treat some conditions, the drug doxorubicin is toxic to the majority of the body's major organs, notably the heart, which necessitates dose restriction. Additionally, doxorubicin promotes apoptosis and necrosis in normal tissue, leading to damage in the heart, liver, brain, and kidney. Toxicity can lead to congestive heart failure and gastrointestinal bleeding in some patients. Even though it can be used to treat some conditions, the drug doxorubicin is toxic to the majority of the body's major organs, notably the heart causing cardiotoxicity, which necessitates dose restriction. Additionally, doxorubicin promotes apoptosis and necrosis in normal tissue, leading to damage in the heart, liver, brain, and kidney. Toxicity can lead to congestive heart failure and gastrointestinal bleeding in some patients.

***Index Terms*:** Tumours, Chemotherapy, Apoptosis, Necrosis, Cardiotoxicity.

1. Introduction:

In the search for anticancer drugs, researchers found a species of bacteria called Streptomyces peucetius which has anti-tumor properties and they named it daunorubicin. In 1967 researchers found that the compound produces fatal cardiac toxicity. After making some genetic modifications to the Streptomyces spp. they got the new compound initially known as Adriamycin and letter on named doxorubicin. Doxorubicin belongs to the class of Antineoplastic Antibiotic – Anthracyclines. since the 1970s, it has been widely used as a chemotherapeutic agent in the treatment of cancer. Doxorubicin is one of the most common drugs of chemotherapy for the last 50+ years. It is most commonly used for the treatment of solid tumors like breast, ovarian, bladder and thyroid and treatment of sarcomas like bone and soft tissue. It is also used in the treatment of acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), Hodgkin lymphoma and small-cell lung cancers. [1,2,3,4,5,48]

Doxorubicin's bioavailability, biodistribution, and hence biological activity are drastically changed by liposomal encapsulation. However, Drug retention and pharmacokinetics are significantly influenced by physical characteristics like size, dose, and components of liposomes. In cases of advanced breast cancer, doxorubicin given alone has been shown to have good response rates, and doxorubicin-containing medication combinations seem to be the most effective. The wide range of anticancer activity was substantiated by the outcomes of various clinical studies conducted globally. [6][7]

2. Physical Characteristics:

1. **IUPAC Name:** (7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione

2. **Brand Name:** Adriamycin, Doxil, etc.

3. **Molecular Formula:** $C_{27}H_{29}NO_{11}$

4. **Molecular Weight:** 543.5 g/mol

5. **Structure:**

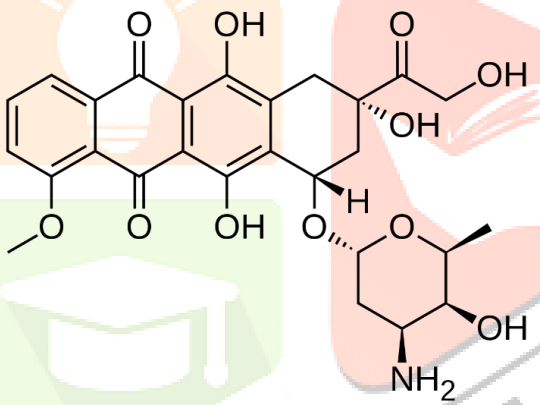

Fig. 1: Doxorubicin [9,21,25]

6. **Form:** Crystalline Solid

7. **Colour:** Translucent Red

8. **Melting Point:** 230°C

9. **Solubility:** Soluble in water, methanol, normal saline, acetonitrile and tetrahydrofuran.
   i. Insoluble in polar organic solvents.

10. **Stability:** Doxorubicin is very stable in the solid state. It can be maintained at room temperature for years with no loss of efficacy or evidence of deterioration.
    [48,49,50]

Mechanism of Action:

Doxorubicin's precise mode of action is complicated and currently unknown. Intercalation and suppression of macromolecular production are the mechanisms through which doxorubicin interacts with DNA. This prevents topoisomerase II, an enzyme that loosens DNA supercoils for transcription, from progressing. Doxorubicin's main method of action is its capacity to intercalate among DNA base pairs, breaking DNA strands and inhibiting the creation of both DNA and RNA. Doxorubicin also contributes to DNA oxidative damage brought on by free radicals when paired with iron, which reduces DNA synthesis. By restricting doxorubicin's ability to bind to iron, iron chelators like dexrazoxane may be able to stop the generation of free radicals. Doxorubicin also damages DNA and cell membranes by producing free radicals, which is another mechanism at work. The potential of doxorubicin HCl to produce free radicals, which result in DNA and cell membrane damage, is another mechanism at work. Doxorubicin affects cellular and mitochondrial oxidative enzyme activity, interferes with calcium homeostasis, interacts with iron, disrupts calcium homeostasis and binds to topoisomerases to promote their malfunction, among other molecular pathways. [4,8,9,10,11,19]

Doxorubicin's pharmacokinetics have been the subject of several studies that evaluate the spectrum of therapies available, including single-agent and multi-agent therapy, for a variety of tumor types. After intravenous administration, the majority of these investigations have demonstrated that doxorubicin distribution is multiphasic. When administered intravenously, triphasic plasma clearance is frequently the next step. This results in a doxorubicin distribution half-life of 3-5 min, indicating the drug's quick absorption by cells. Doxorubicin's terminal half-life of 24-36 h indicates that it takes much longer for the drug to be removed from the tissue than it does for it to be absorbed. [11,12]

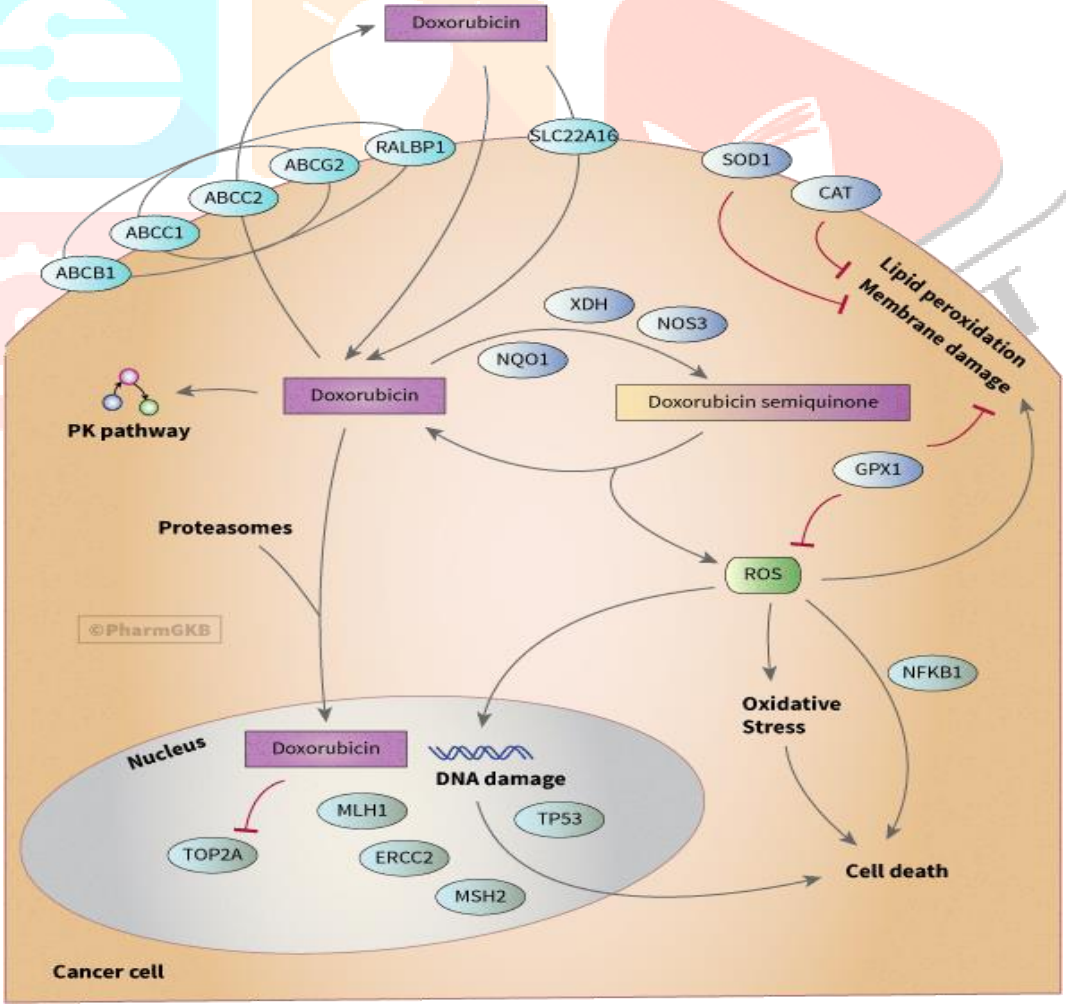

Fig 2: Mechanism of action of doxorubicin [1]

Dose & Administration:

Doxorubicin is administered through the intravenous (IV) route. Through either a central line or a peripheral venous line, doxorubicin is injected into the body. Usually, it is administered after every 21/28 days. It is advised to take 60–75 mg/m² once every 21/28 days. It is clear bright red, which can be easily identified. It is diluted before administration in 0.9% sodium chloride solution or 05% dextrose solution depending on physicians' discretion. Body surface area (BSA) is typically used to individually adjust the dosage of doxorubicin. BSA was commonly determined by the DuBois formula {BSA (m^2) = Weight (kg)$^{0.425}$ × Height (cm)$^{0.725}$ × 0.007184}. The time of doxorubicin administration varies depending on the physician or patient. Doxorubicin can be quickly infused over 15 to 20 minutes. To lower the risk of infusion reactions, it is advised to administer the liposomal formulation slowly at the rate of 1 mg/min. The maximum lifetime cumulative dosage is 550 mg/ m²,

When using this medication, both men and women should use reliable birth control to avoid getting pregnant. If either the mother or the father takes doxorubicin, it might damage the unborn child or result in birth abnormalities. After your last dosage, continue utilizing birth control for at least six months. [10,13,14,15]

Recommended Adult dose with indication:

1. **Breast Cancer:**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 to 28 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4-6 cycles
2. **Hodgkin's & Non-Hodgkin's Lymphoma:**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 to 28 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4-6 cycles
3. **Ovarian Cancer:**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 to 28 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4-6 cycles
4. **Bladder Cancer:**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4-6 cycles
5. **Stomach Cancer:**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4-6 cycles
6. **Neuroblastoma:**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4-6 cycles
7. **Wilms' Tumor:**
   As a single drug – 40 to 60 mg/ m^2 IV every 21 days
   In combination with other chemotherapy drugs - 30 to 60 mg/ m^2 IV every 21 to 28 days
   Regimen: 4 cycles

8. **Ewing's Sarcoma:**
   As a single drug – 40 to 60 mg/ m^2 IV every 21 days
   In combination with other chemotherapy drugs - 30 to 60 mg/ m^2 IV every 21 to 28 days
   Regimen: 4 - 6 cycles

9. **Acute lymphoblastic leukemia (ALL) & Acute myeloblastic leukemia (AML):**
   As a single drug – 60 to 75 mg/ m^2 IV every 21 days
   In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
   Regimen: 4 - 6 cycles

10. **Small Cell Lung Cancer:**
    As a single drug – 60 to 75 mg/ m^2 IV every 21 days
    In combination with other chemotherapy drugs - 40 to 75 mg/ m^2 IV every 21 to 28 days
    Regimen: 4 - 6 cycles

Adverse Effects:

Adverse effects are any undesirable event that might occur when receiving therapy with a pharmaceutical product but are not always related to the medication. Any unfavorable medical condition that at any dose, causes death, necessitates hospitalization or extends a current hospital stay, causes disability or permanent damage, causes a congenital anomaly or birth defect or is life-threatening is termed a serious adverse event. [16,17]

As a result of its use, the most frequent adverse effects include:

Symptomatic Effects: Fatigue, Nausea, Vomiting, Anorexia, Oral Ulceration, Alopecia (Hair Fall), Skin Pigmentation, Skin Eruption, Body ache, Loss of Appetite.

Hematological Effect: Myelosuppression, Anemia, Leukopenia, Neutropenia, Thrombocytopenia.

Gastrointestinal Effects: Acidity, Stomatitis, Gastrointestinal Disturbance, Abdomen Pain, Dehydration, Diarrhea.

Skin Effects: Skin Pigmentation, Skin Eruption, Erythema, Rashes, Itching, Light Sensitivity, Light Headedness, Hyperpigmentation of Nails, Conjunctivitis, Lacrimation.

Respiratory Effects: Breathlessness, Chest Tightness, Tachypnoea.

Hypersensitivity Effects: Fever, Chills, Urticaria.

Neurological Effects: Neuropathy (Motor, Sensory, Autonomic Nerve Neuropathy), Neurological Disturbances (like Hallucinations, Dizziness, Vertigo, etc.)

Sever Effects: Cardiotoxicity, Heart Failure, Gastrointestinal Bleeding, Tissue Ulceration and Necrosis.

[4,11,16-29]

Doxorubicin Mediated Cardiotoxicity:

Although there is a significant range in each person's sensitivity to the cardiotoxic effects, the incidence and severity of doxorubicin cardiotoxicity are dose dependent, rising with cumulative doses. The highest risk factor for developing doxorubicin-induced cardiotoxicity is cumulative dosage. Acute cardiac damage from doxorubicin appears days after medication treatment. It affects about ~11% of people who get it. Acute cardiotoxicity includes myopericarditis, failure of the left ventricular, arrhythmias, hypotension, several electrocardiographic alterations, Fast heart rate, supraventricular tachycardia (SVT), Premature atrial contractions (PAC) and premature ventricular contractions (PVC). These conditions are reversible and

curable. Chronic cardiotoxicity can lead to congestive heart failure. With a total cumulative dosage of 300 mg/m² or less, the chances of congestive heart failure are about 2%. As the cumulative dosage increases cardiotoxicity also increases. With a cumulative total dose of 500–550 mg/m², the congestive heart failure rate is > 4%. With a cumulative total dose of 550–600 mg/m², congestive mg/m² heart failure rate is > 18%. However, as cumulative dosages surpass 600 mg/m², the risk of congestive heart failure rapidly increases to > 36%. Cardiotoxicity can be seen in less than 1.7% of patients with ongoing doxorubicin therapy.

Within a few months after completion of the treatment, doxorubicin causes irreparable cardiomyopathy. Higher cumulative drug doses, extreme ages, chemotherapy in conjunction with other cardiotoxic medications, pre-existing left ventricular dysfunction, hypertension, and prior radiation to the mediastinum are risk factors for doxorubicin-induced cardiotoxicity and congestive heart failure. [21,24,25,30,32]

Histopathologic grading of doxorubicin cardiotoxicity:

Grade	Abnormality
0	No abnormality
1	The minimal number of cells (35% of the total number of cells) with marked changes (total loss of contractile elements, loss of organelles, mitochondrial and nuclear degeneration).
1.5	Small groups of cells are involved (5%-15% of the total number), some of which have definite changes (marked myofibrillar loss and/or cytoplasmic vacuolization).
2	Groups of cells involved (16%-25% of the total number), some of which have definite changes (marked myofibrillar loss and/or cytoplasmic vacuolization) Grade.
2.5	Groups of cells involved (26%-35% of the total number), some of which have definite changes (marked myofibrillar loss and/or cytoplasmic vacuolization).
3	Diffuse cell damage (>35% of the total number of cells) with marked changes (total loss of contractile elements, loss of organelles, mitochondrial and nuclear degeneration).

[24]

Detection of Doxorubicin Mediated Cardiotoxicity:

Nowadays, a wide range of diagnostic methods is employed to identify doxorubicin-mediated cardiotoxicity. Clinical evaluation, electrocardiography (ECG) and chest roentgenography, which are often not useful in the early identification or prevention of doxorubicin cardiotoxicity, only indicates abnormalities in severe instances of doxorubicin cardiotoxicity. There are various methods to monitor doxorubicin cardiotoxicity. [4,19,21,24,33]

A. Echocardiography (ECHO)
B. Radionuclide Angiocardiography or Multi-gated Radionuclide Angiography (MUGA scan)
C. Endomyocardial Biopsy (EMB)

A. Echocardiography (ECHO):

A widely used method for assessing heart function and finding anatomical problems is echocardiography. Conventional echocardiography shows the anatomy of the heart and uses measurements to find cardiac dysfunction. Although it offers incredibly helpful information on structural cardiac abnormalities,

measuring left ventricular ejection fraction with this approach is relatively approximative. Doppler echocardiography is also used for the detection of left ventricular diastolic function in some patients with ongoing doxorubicin therapy. Patients with suspected pericardial illness or those undergoing valvular dysfunction assessment get benefits from echocardiography. Compared to a normal echocardiogram, two-dimensional strain echocardiography appears to be more sensitive. [21,24,34,35]

B. Radionuclide Angiocardiography or Multi-gated Radionuclide Angiography (MUGA):

The most commonly established technique for monitoring heart function over time in patients receiving doxorubicin treatment is radionuclide angiography. This method measures the LVEF (Left Ventricular Ejection Fraction) of the heart. It is a quick and accurate way to assess the general health of the heart. It is the most feasible and efficient method for monitoring doxorubicin cardiotoxicity. It is one of the finest non-invasive methods for detecting cardiac dysfunction brought on by cardiotoxicity caused by doxorubicin. [21,24,36,37]

C. Endomyocardial Biopsy (EMB):

Endomyocardial Biopsy (EMB) is a diagnostic technique used to assess different heart conditions when non-invasive testing is typically unable to provide a clinical diagnosis. EMB is a method performed to extract myocardial tissue to identify myocardial disorders or, less frequently, to check for the incidence of allograft rejection following heart transplantation. EMB can be carried out in either the left or right ventricle. The right ventricular septum is where biopsy samples are most frequently taken. [24,38,39]

Doxorubicin Mediated Hepatotoxicity:

The causes of doxorubicin mediated hepatotoxicity are not well known. The high amount of doxorubicin is ingested, accumulated and metabolized by the liver and hence, the liver is another typical target for doxorubicin-induced cell death and tissue damage. After receiving doxorubicin therapy, over 40% of patients developed liver damage. With hepatocytes re-entering the cell cycle, the liver is one of the few internal organs capable of naturally regenerating lost tissue. [11,25,40,41]

The high levels of doxorubicin are metabolized, resulting in the production of a significant amount of ROS. As a result, ROS produces an excessive amount of harm, including unbalanced oxidative processes, DNA damage, lipid peroxidation, vitamin E levels drop, reduced glutathione (GSH) levels drop and a rise in lipid peroxidation. [11,40]

Hepatocyte vacuolation, sinusoidal dilatation, condensation of nuclei and degeneration of hepatocyte cords, cellular edema, focal necrosis, and de-arrangement of hepatic trabeculae, as well as marked bile duct hyperplasia, parenchymal necrosis, dilation of intercellular spaces, and vacuolization were all seen in the histopathological analysis of the hepatic tissue after doxorubicin therapy. [40]

Detection of Doxorubicin Mediated Hepatotoxicity:

Liver Function Tests (LFT) are the main diagnostic tests for the detection of hepatotoxicity. Increased blood levels of the enzymes glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactate dehydrogenase (LDH), creatine kinase, and direct and total bilirubin suggest hepatotoxicity brought on by the administration of doxorubicin. According to several types of research, Alanine Transaminase (ALT) and Aspartate Transaminase (AST) levels significantly increase after doxorubicin therapy, showing that hepatic tissue had been damaged, which is detected by biochemical analysis. A rise in cellular permeability shown by elevated levels of ALT, AST, and alkaline phosphatase (ALP) results in cytological disruption. Falling albumin levels are a sign of a reduction in protein synthesis, which shows hepatic dysfunction caused by doxorubicin therapy. [11,25,40,41,42]

Doxorubicin Mediated Nephrotoxicity:

The main function of the kidney is to remove waste products from the blood, but it also removes normal blood components that are present in higher-than-normal amounts. The kidney is capable of recovering components that are present at low concentrations in the blood. Unlike the liver, the kidney has a limited capacity for regeneration, which limits its capacity to repair itself after glomeruli injury. Overuse or prolonged dosing of doxorubicin might result in drug-induced renal damage and even kidney failure. Several types of research showed that DOX interacts with glomerular podocytes, causing damage that results in nephropathy. Proteinuria is the most common event occurred during doxorubicin nephrotoxicity. When the glomeruli are injured, they are unable to execute their usual duties, resulting in glomerular lesions, inflammation, tubular dilatation, and changes in capillary permeability. [11,25,42,43]

The medicine interferes with the mitochondria's normal operation by lowering the activity of complexes I and IV, which results in doxorubicin-induced nephropathy. Triglyceride, superoxide, and citrate synthase levels rise as a result, and vitamin E and antioxidant compound levels fall as a result of lipid peroxidation. [11]

Detection of Doxorubicin Mediated Nephrotoxicity:

Renal Function Tests (RFT) are the main diagnostic tests for detection of nephrotoxicity caused due to doxorubicin. A significant rise in creatinine and a nonsignificant rise in blood urea nitrogen (BUN) are signs of nephrotoxicity, which results in a decline in renal function. A fairly precise measure of renal function is provided by BUN and creatinine together; however creatinine predicts kidney impairment or injury more accurately than BUN. Doxorubicin significantly decreases renal Superoxide Dismutase (SOD), Catalase (CAT), Glutathione (GSH), and Glutathione Peroxidase (GPx) levels while increasing malondialdehyde (MDA), which implies nephrotoxicity. [11,25,42,43]

By reducing renal OS and enhancing kidney antioxidant defence, DOX-induced kidney damage was mediated, which in turn prevented cellular apoptosis and senescence. [43]

Doxorubicin Mediated Neurotoxicity:

Since doxorubicin cannot pass the blood-brain barrier, the harm to the brain is indirect. Tumour Necrosis Factor alpha (TNF-α) mediates doxorubicin induced brain damage. Several studies show that Doxorubicin treatment causes an increase in TNF levels in the cortex and hippocampus. After doxorubicin therapy, mitochondrial function in the brain changes. TNF levels in the brain may rise due to the activation of microglia and macrophages that reach the brain during doxorubicin therapy. TNF may affect brain cells, causing a decrease in mitochondrial respiration and an increase in oxidative stress indicators. A doxorubicin-mediated systemic rise in TNF and nephropathy were avoided by the TNF-α inhibitor pentoxiphylline (PTX). It has been demonstrated that doxorubicin treatment combined with anti TNF-α antibody therapy reduces doxorubicin induced brain damage. The brain's microglial cells are stimulated by doxorubicin to create inflammatory cytokines as a result of increased TNF-α production. [11,25,44,45,46,47]

The expression of inducible nitric oxide synthase (iNOS) is activated by excessive TNF production, increasing reactive nitrogen species (RNS). As RNS levels rise, neighboring proteins such as manganese superoxide dismutase (MnSOD) undergo nitration, which accelerates the formation of ROS and improves the permeability transition pore of the mitochondria. This induces mitochondria to release cytochrome c, resulting in cell death by apotosis. [11,44]

Patients who have received chemotherapy frequently complain of chemotherapy-induced cognitive impairment, commonly referred to as "chemobrain," which is a clinical condition characterized by cognitive deficiencies including forgetfulness, trouble focusing, and difficulties multitasking. About 75% of patients complain that they suffer from chemobrain during or after treatment. Recent research has shown that changes in neurotransmitter systems and the generation of inflammatory cytokines may be responsible for the cognitive deficits caused by doxorubicin. The blood brain barrier's integrity can be compromised by pro-inflammatory cytokines that are overproduced in cancer or reaction to chemotherapy. Increased cytokine

production associated with cancer or chemotherapy may facilitate BBB breakdown since direct cytokine exposure enhances the permeability of BBB cells in vitro. [11,44,45]

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