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A REVIEW: ROLE OF DOXORUBICIN IN TREATMENT OF CANCER

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ABSTRACT: Cancer is a very complex genetic disorder that is mainly caused by carcinogens. Carcinogens can be present in the air, water, food, chemicals, and sunlight that are exposed to the people. In the case of leukemia, the body produces large numbers of abnormal white blood cells. In the study of blood cancer that is leukemia, blood disorders through visual inspection of microscopic images of blood cells is an important diagnostic tool. From the identification of blood disorders, it can lead to the classification of certain diseases related to blood. Doxorubicin drug most useful for cancer treatment such as Breast cancer, ovarian cancer, Lung cancer, Neuroblastoma cancer, Leukemia, *etc*. In breast cancer, the efficacy of drug treatment will thus depend on the histology of the tumor tissue. In ovarian cancer, the doxorubicin metabolites accumulated in the ascites and cleared more slowly from the peritoneal compartment than from the serum. Accumulation in the peritoneal cavity with prolonged half-life should be considered when administering medication in patients with ascites. In lungs cancer, the aggregate results of the present series of studies demonstrate that RLIP76 is the predominant doxorubicin transporter in the lung cancer cell. That its transport and ATPase activity is greater in NSCLC than SCLC and that its inhibition by anti-RLIP76 IgG augments doxorubicin cytotoxicity though it's increased accumulation in cells. In neurotumor cells the doxorubicin-induced apoptosis is ceramide-mediated and whether p53 up-regulation is necessary for the apoptotic response.

INTRODUCTION: Cancer is defined as the abnormal cells division without control and can produce immature cells. These cells can spread to other parts of the body through the blood and lymphatic systems. Cancer is not one disease, but it is a very complex form of many diseases. The cancer agents (carcinogens) can be present in the air, water, food, chemicals, and sunlight that are exposed to the people (Malcolm, 2001).

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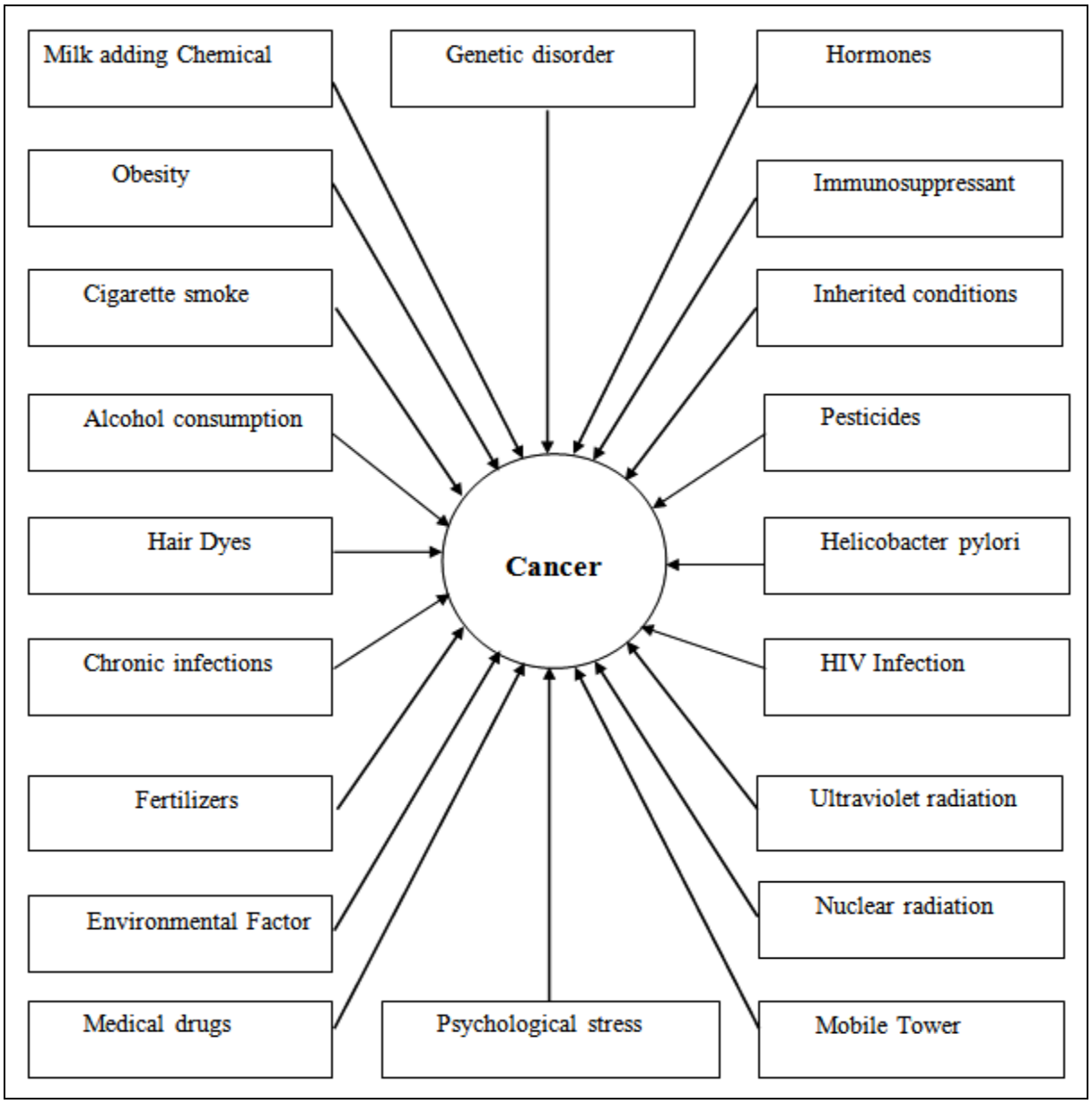
Most cancers are named for the organ or type of cell in which they start, for example, cancer that begins in the breast is called breast cancer, cancer that begins in the ovary called ovarian cancer. WHO Cancer Control Programme is to promote national cancer control policies plans and programs, integrated to non-communicable diseases and other related problems. Our core functions are to set norms and standards, promote surveillance, and encourage evidence-based prevention, early detection, treatment, and palliative tailored to the different socioeconomic settings. The global burden of cancer continues to increase. In the year 2000, 5.3 million men and 4.7 million women developed a malignant tumor, and 6.2 million died from the disease.

The number of new cases is expected to grow by 50% over the next 20 years to reach 15 million by 2020. World Cancer Report provides a unique global view of cancer. It documents the frequency of cancer in different countries and trends in cancer incidence and mortality as well as describing the known causes of human cancer. The molecular and cellular basis of the multi-step process of malignant transformation is concisely summarized. The report contains an overview of cancer prevention, including screening programs for early diagnosis, as well as advances in surgical and medical oncology, including novel drugs targeting tumors-specific signaling pathways (World Health Organization).

Cause of Cancer: Carcinogens are any substance or agent that is capable of causing cancer – the abnormal or uncontrolled growth of new cells in any part of the body in humans or animals. Such as:



1. **Milk adding Chemical:** Several milk constituents such as vitamin D, proteins, calcium, CLA, butyrate, saturated fatty acids, and contaminants such as pesticides, estrogen, and insulin-like growth factor I (IGF-I) may be responsible for either a prospective or a harmful association between dairy products and cancers. Dietary fat has been reported to increase the androgen level associated with prostate cancer risk. Dairy foods and their constituents (lactose) have been hypothesized to possibly promote ovarian carcinogenesis [3].

2. **Obesity:** Obesity has been linked to more aggressive characteristics of several cancers, including breast and prostate cancer. The myeloid lineage cells, in the form of myeloid-derived suppressor cells (MDSCs) and alternatively polarized M2 macrophages influence almost all types of cancers by regulating diverse facets of immune suppression, angiogenesis, cell proliferation, growth, and metastasis. The different aspects of obesity, namely insulin resistance, increased estrogen, adiposity, and low-grade chronic inflammation from adipose tissue macrophages, may coalesce to promote MDSC induction and M2 macrophage polarization, thereby facilitating cancer development [4].

3. **Cigarette Smoke:** The various carcinogenic compounds have been identified in primary and side-stream tobacco smoke. It is a complex mixture of chemicals in tobacco smoke, including 212Pb and 210Po, react covalently with DNA and produce free radicals causing oxidative damage. Cigarette smoke exhibits very significant synergistic interactions with ethanol to induce oral/ pharyngeal cancers and with asbestos to induce lung cancer [5-7].

4. **Alcohol Consumption:** The alcohol increases the risk for cancers of the oral cavity and pharynx, larynx, esophagus, and liver. The biological mechanisms of alcohol induce cancer are not fully understood but may include genotoxic effects of acetaldehyde, production of reactive oxygen or nitrogen species, changes in folate metabolism, increased estrogen concentration. The International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) both published comprehensive reviews of the scientific literature on alcohol have the risk of cancer [8].

5. **Hair Dye:** The permanent oxidant hair dyes have consisted of many chemical components, including ortho-phenylene-diamines (o-PD) and its derivatives, 4-chloroortho-phenylene-diamine (Cl-PD) and 4-nitroortho-phenylene-diamine. The carcinogenic o-PD and Cl-PD caused Cu(II) - mediated DNA damage, including 8-oxodG formation, and antioxidant enzyme superoxide dismutase (SOD) enhanced DNA damage. This results that SOD enhanced the rate of Cu(II) - mediated autoxidation of o-PD and Cl-PD, leading to enhancement of DNA damage and produced cancer [9].

6. **Chronic Infections:** The stomach ulcers are due to Helicobacter pylori. Mycoplasmas may cause chronic lung disease in newborns and chronic asthma in adults, and Chlamydia pneumonia, a recently identified common cause of acute respiratory infection. These infectious agents that cause or contribute to neoplastic diseases in humans [10].

7. **Fertilizer:** The higher levels exposure of nitrates or nitrites has been associated with an increased incidence of cancer in adults and possible increased incidence of brain tumors, leukemia and nasopharyngeal (nose and throat) tumors in children. The U.S. EPA concluded that there was conflicting evidence in the literature as to whether exposures to nitrate or nitrites are associated with cancer in adults and children [11-12].

8. **Environmental Factor:** Exposure to Ultraviolet-B-radiation (UVB, 280-320 nm) is known to induce basal and squamous cell skin cancer in a dose-dependent way and the depletion of stratospheric ozone has implications for increases in biologically damaging solar UVB radiation reaching the earth's surface. In humans, arsenic is known to cause cancer of the skin, as well as cancer of the lung, bladder, liver, and kidney [13].

9. **Medical Drugs:** Some drugs used to treat cancer (*e.g.*, cyclophosphamide, chlorambucil, melphalan) have been shown to increase the occurrence of second cancers, including leukemia.

10. **Genetic Disorder:** Down syndrome and certain other genetic diseases - some diseases caused by abnormal chromosomes may increase the risk of leukemia.

11. **Psychological Stress:** Psychological stress activates the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, resulting in systemic increases in cortisol and catecholamines. The effects of catecholamines are mediated by nine distinct α-adrenergic and β-adrenergic G-protein-coupled receptors, which are present on a wide range of cell types, including cancer cells [14].

12. **Hormone:** Estrogens used to treat symptoms of menopause and other gynecological conditions have been shown to increase the incidence of endometrial cancer and breast cancer.

13. **Immunosuppressant:** The Immuno-suppressant's such as cyclosporine and azathioprine are use organ transplants in patients, also are associated with increased cancer risks, especially lymphoma.

14. **Inherited Conditions:** Certain inherited conditions increase a person's risk of developing soft tissue sarcomas. Such as Neurofibromatosis, Gardner syndrome, Li-Fraumeni syndrome, Retinoblastoma, Werner syndrome, Gorlin syndrome, Tuberous sclerosis, *etc*. [15]

15. **Pesticides:** These pesticides include ethylene oxide, amitrole, some chlorophenoxy herbicides, DDT, dimethylhydrazine, hexa-chlorobenzene, hexamethylphosphor amide, chlordecone, lead acetate, lindane, mirex, nitrofen, and toxaphene. Studies of people with high exposures to pesticides, such as farmers, pesticide applicators, crop duster pilots, and manufacturers, have found high rates of blood and lymphatic system cancers, cancers of the lip, stomach, lung, brain, and prostate, as well as melanoma and other skin cancers.

16. **Helicobacter Pylori Infection:** The major infections of *H. pylori* cause chronic gastritis, peptic ulcers, and gastric malignancies, including gastric non-cardia adenocarcinoma and mucosal-associated lymphoid tissue (MALT) lymphoma. Epidemiologically, *H. pylori* infect half of the world's population, approximately 1% of infected people will develop into gastric cancer [16-17].

17. **HIV Infection:** The HIV positive people have most common cancer is Kaposi's sarcoma and high-grade non-Hodgkin's lymphoma due to AIDS-defining malignancies. The Non-Hodgkin's lymphoma occurs late in the process of AIDS; Up to 10% of people with HIV will eventually develop Non-Hodgkin's lymphoma. Hodgkin's disease, squamous cell carcinoma of the conjunctiva and leiomyosarcoma also appear to be associated with HIV infection [18].

18. **Ultraviolet Radiation:** Ultraviolet (UV) radiation from the sun, sunlamps, or tanning beds causes premature aging of the skin and DNA damage that can lead to melanoma and other forms of skin cancer. The incidence of skin cancers is rapidly increasing.

19. **Nuclear Radiation:** Very high levels of radiation have been caused by atomic bomb explosions (such as those in Japan during World War II) and nuclear power plant accidents (such as the Chernobyl [also called Chornobyl] accident in 1986). The ionizing radiation is the radioactive substances released by atomic bombs or nuclear weapons known as "fallout." The doses of ionizing radiation received by the atomic bomb survivors in Japan resulted in increased risks of leukemia and cancers of the breast, thyroid, lung, stomach, and other organs.

20. **Mobile Tower:** The mobile Tower is mainly produced radiofrequency (RF) waves, a form of energy in the electromagnetic spectrum between frequency modulation radio waves and microwaves. Such as FM radio waves, microwaves, visible light, and heat, they are forms of non-ionizing radiation. This means they cannot cause cancer by directly damaging DNA. But radiofrequency (RF) waves are different from stronger types of radiation such as X-rays, gamma rays, and ultraviolet (UV) light, which can break the chemical bonds in DNA then cause cancer.

Leukemia: In the case of leukemia, the body produces large numbers of abnormal blood cells. Leukemia is either acute or chronic. In the case of acute leukemia, produces very immature abnormal blood cells, and it cannot perform their normal functions. In the case of chronic leukemia, some immature cells are present, but in general numbers of mature cells compared to acute leukemia and carry out some of their normal functions. Leukemia arises the main two types of white blood cells. If leukemia affects lymphoid cells, it is known as lymphocytic leukemia and other affected myeloid cells known as myeloid or myelogenous leukemia [19-20].

Anthracyclins are used in the treatment of various solid tumors and acute myeloid leukemia these agents induce DNA damage in leukemic cancer cells by several ways [21] but the mechanism by which they induce apoptosis is still a matter of debate. Some evidence indicates that the generation of ceramide is an active lipid mediating cell response to various types of stress [22-23] may provide a key event for anthracycline-induced apoptosis.

In this respect the fumonisin B1, a fungal toxin that potently inhibits ceramide synthase [24] can prevent both daunorubicin-induced ceramide accumulation and apoptosis in leukemia cells [25]. In other studies, the apoptotic response elicited by doxorubicin has been related to the accumulation of a ceramide pool produced by sphingomyelinase activation [26-27].

The considerable apoptotic response elicited by doxorubicin is dependent on the function of p53, a protein that is up-regulated by cell treatment with genotoxic agents that drives cell-cycle arrest or apoptosis by distinct mechanisms [28-29].

The recent studies have provided evidence for a functional relationship between ceramide and p53. It is shown that p53 up-regulation may be required for the generation of the aceramide pool that mediates the apoptotic effect of some genotoxic agents in leukemia cells [30-31].

There are mainly four types of Leukemia:

1. Acute Myelogenous (or myeloid) Leukemia (AML).
2. Acute Lymphocytic (or lymphoblastic) Leukemia (ALL).
3. Chronic Myelogenous (or myeloid) Leukemia (CML).
4. Chronic Lymphocytic (or lymphoblastic) Leukemia (CLL).

1. Acute Myelogenous Leukemia: Acute myeloid leukemia is a disorder of the process that normally produces neutrophils, a type of white blood cell. AML may sometimes be called acute myelocytic leukemia, or acute non-lymphocytic leukemia. In the case of AML, acquired mutations (damage to the genetic material) in the blood-forming cells cause problems with the normal process of differentiation. The results produced many immature cells called myeloblasts or blasts. Blasts do not act like fully developed, healthy blood cells. A large number of blasts also reduces the production of healthy red blood cells and platelets. These cells help to blood clotting. AML is usually found in the blood and bone marrow (the spongy, red tissue in the inner part of the large bones), but sometimes also other parts of the body, such as the brain, skin, and gums. Occasionally, AML cells can form a solid tumor called a myeloid sarcoma or chloroma. AML occurs in people of all ages but is most common in adults older than 65 [32-35].

FIG. 1: ACUTE MYELOGENOUS LEUKEMIA SHOWS DISORDER OF THE BLOOD CELLS

The process that normally produces blood cells [35].

2. Acute Lymphatic Leukemia: It is a blood cancer that affects lymphoblast cells in the bone marrow that would normally grow and produce specialized white blood cells known as B lymphocytes, T lymphocytes, and Natural killer cells. It is rapidly progressive, and ALL may also be known as acute lymphoblastic leukemia or acute lymphoid leukemia. There is an estimated about

12,950 people in the United States were expected to be diagnosed with AML in 2011. ALL is most common in children under the age of 10 but is also found in adults. They are five years survival rate for ALL are 65.2% overall and greater than 90% in children [36-37].

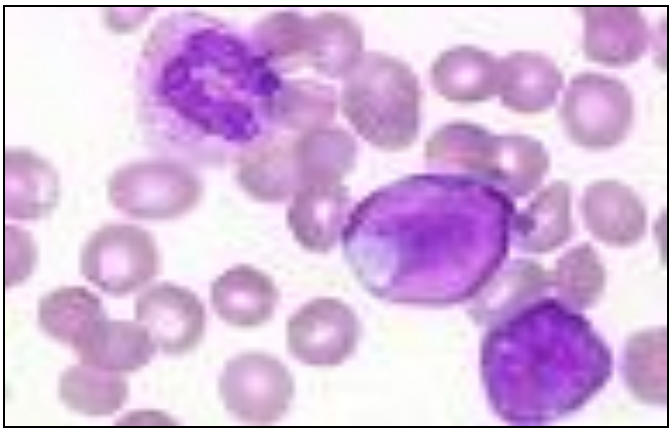


FIG. 2: ACUTE LYMPHOCYTIC LEUKEMIA SHOWS ABNORMAL GENERATION OF BLOOD CELLS [35]

3. Chronic Myelogenous Leukemia: It is a type of slow-growing blood and bone marrow cancer. It is most often a disease of middle age about 55-60 years old but can also be diagnosed in children. It is also known as chronic myeloid leukemia and chronic granulocytic leukemia. CML begins with damage to the DNA of a bone marrow stem cell.

As a result of this damage, the stem cell divides uncontrolled and produced to cloned cancer cells that eventually accumulate in the bone marrow and blood. In the case of CML, more than 90% of CML patients, the same type of DNA damage is identified. This specific DNA damage is called the Philadelphia Chromosome [38-41].

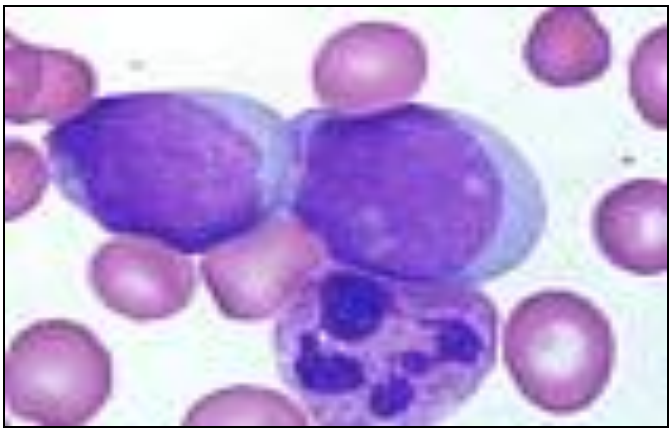


FIG. 3: CHRONIC MYELOGENOUS LEUKEMIA SHOWS ABNORMAL MATURATION OF BLOOD CELLS [35]

4. Chronic Lymphocytic Leukemia: It is the most common disease in adults in Western countries. It occurs when there is damage to the genetic material to a cell. It is different than other types of leukemia because the genetic mutation not only causes uncontrolled growth of lymphocytes in the marrow, but it also results in cells that do not follow the normal pattern of natural cell death. This leads to an increased number of CLL lymphocytes in the bloodstream. The body is to produce immunoglobulin, which is proteins that help to fight off infection.

In the case of CLL, the abnormal lymphocytes are unable to produce immunoglobulin (or "antibodies") and also prevent the non-cancerous lymphocytes from producing effective antibodies. About 95% of cases of CLL in the West, the type of lymphocyte that is affected are a ß-lymphocyte; T-cell is more common in areas of Japan, and only accounts for about 5% of cases in the US [42-45].

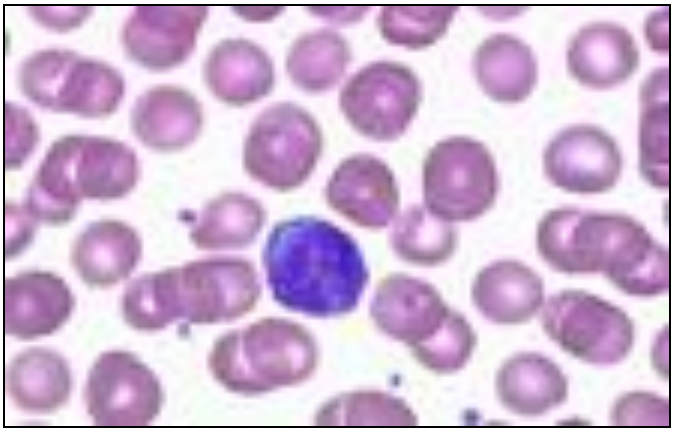


FIG. 4: CHRONIC LYMPHOCYTIC LEUKEMIA SHOWS UNCONTROLLED GROWTH OF LYMPHOCYTES IN BLOODSTREAM [35]

Treatment approaches:

1. Role of Doxorubicin in Treatment of Cancer: Doxorubicin trade name Adriamycin, also known as hydroxydaunorubicin is a drug used in cancer chemotherapy. It is an anthracycline antibiotic closely related to the natural product daunomycin and like all anthracycline.[46]It works by intercalating DNA. Doxorubicin is commonly used in the treatment of a wide range of cancers, including hematological malignancies many types of carcinoma and soft tissue sarcomas [47-48].

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic widely used in the treatment of acute lymphoblastic leukemia [49]. The mechanism of cytotoxicity involves the specific intercalation of planar anthracycline nucleus of DH to the DNA double helix resulting in the prevention of further DNA replication [50].

Chemotherapy plays an important role in the management of cancer. As an important example, doxorubicin an anthracycline antibiotic is considered among the most active chemo-therapeutic agents [51]. However, the clinical usefulness of doxorubicin in the treatment of cancer is often limited by the development of a type of drug resistance known as multidrug resistance (MDR) [52]. MDR is a term used to describe a phenomenon characterized by the ability of some tumors to exhibit simultaneous resistance to several structurally and functionally unrelated chemotherapeutic agents [53].

2. Chemistry and Structure-Activity Relationships: The anthracycline antibiotics have a tetracyclic ring structure and attached the unusual sugar, daunosamine. Cytotoxic agents of this class having quinone and hydroquinone moieties on adjacent rings that permit the gain and loss of electrons. Although there are marked differences in the clinical use of doxorubicin, their chemical structures differ only by a single hydroxyl group on C14.

3. ADME of Doxorubicin:

a. **Absorption:** Doxorubicin is not absorbed by the gastrointestinal tract. Since the drug is extremely irritating to tissues, it has to be administered by intravenous. It is Soluble in water, slightly soluble in methanol, practically insoluble in chloroform, ether and other organic solvents [54].

b. **Distribution:** Doxorubicin is quickly and widely distributed into the extravascular compartments and half-life 12-18 hours. Binding of doxorubicin to plasma protein is about 75%. However, the doxorubicin does not cross the blood-brain barrier.

c. **Metabolism:** Doxorubicin is mainly metabolized in the liver. The major metabolite of doxorubicin is 13-OH-doxorubicinol, produced by aldo-keto reductases which possess a certain degree of antitumor activity.

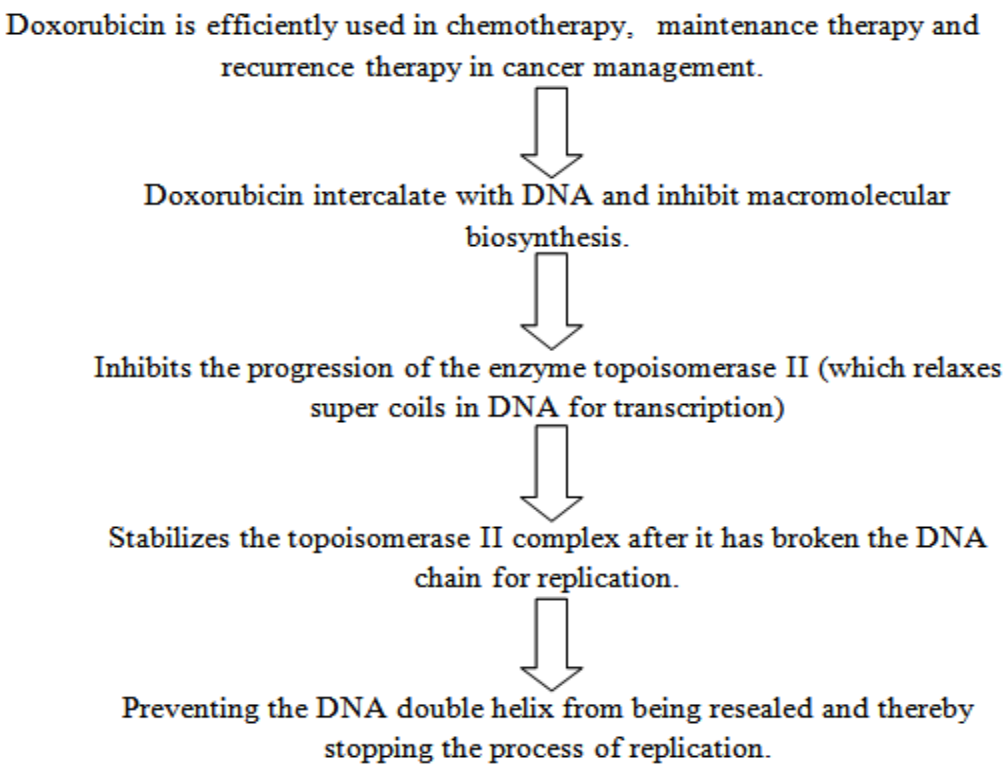
d. **Excretion:** Following IV administration, plasma levels of doxorubicin follow a multiphasic decline, with a terminal half-life. Doxorubicin is metabolism in the liver and excretion through biliary and fecal excretion. The terminal half-life of 13-OH-doxorubicinol is similar to that of doxorubicin. Plasma clearance is in the range of 324 to 809 ml/min/m^2. Doxorubicin is eliminated by metabolic conversion to a variety of aglycones and other inactive products. A liposomal doxorubicin product (DOXIL) is available for the treatment of AIDS-related Kaposi's sarcoma.

Newer Analogs of Doxorubicin: Valrubicin (VALSTAR) was approved in 1998 for intravesical therapy of bacille Calmette-Guerin- refractory urinary bladder carcinoma. Epirubicin (4-epidoxorubicin, ELLENCE) was approved by the FDA in 1999 for adjuvant therapy of early lymph-node-positive breast cancer.

TABLE 1: CLINICAL INVESTIGATION ON EFFICACY OF PEGYLATED LIPOSOMAL DOXORUBICIN

Drug	Clinical Trial	No. of objects	Reference
NGR-hTNF + doxorubicin	Phase II	37	Larusso *et al*., 2012 [55-56]
Gemcitabine + PLD	Phase II	35	Aziz Karaoglu *et al*., 2009 [57]
PLD + carboplatin	Phase I and II	105	Rose P.G, 2005 [58]
PLD+ vinorelbine (VNR)	Phase II	30	Katsaros *et al*., 2005 [59]
PLD + paclitaxel	Phase I and II	40	Rose P.G, 2005 [58]
Pegylated Liposomal Doxorubicin (PLD)	Phase I and Phase II studies	44	Safra *et al*., 2001, Patel *et al*., 2001 [60-61]
Doxorubicin HCl liposome injection (Doxil)	Phase II	30-49	Markman., 1999

Mechanism of Action [62-63]:



Breast Cancer: In the case of breast cancer doxorubicin shows nuclear fluorescence distinguishable from background fluorescence, which is predominantly from the cytoplasm [64]. Each patient both doxorubicin distribution patterns and CD31 immunohistochemical staining of the same area of the same section are represented [65]. The doxorubicin gradients in tumor islets with high concentrations in the periphery and low concentrations in the center of the tumor islets [66].

The drug gradients ware cleared shortly after the injection, but it was detected after 24 h [67]. These doxorubicin gradients were not detected in the connective tissue. Also, no clear gradients were observed in patients with invasive lobular cancer with more connective tissue and strands of tumor cells occasionally; connective tissue showed bands of fluorescence [68]. The dose of doxorubicin in this chemotherapy consisted of moderately high-dose doxorubicin (90 mg/m^2 body surface [69]. The efficacy of drug treatment will thus depend on the histology of the tumor tissue [70].

Ovarian Cancer: In the case of ovarian cancer anthracyclines have been in clinical practice since the 1960s and represent one of the most commonly used classes of anticancer drugs [71-72]. Doxorubicin is highly protein bound and does not cross the blood-brain barrier. Effectiveness and toxicities associated with drugs are partly related to their distribution in the various body compartments [73]. *In -vivo*, doxorubicin is extensively metabolized and excreted in the bile [74] and produced biotransformation products identified such as doxorubicinol (Dox-ol), 7-deoxydoxorubicinolone (7d-Dox-ol-on) and7-deoxydoxorubicinone (7d-Dox-on) were measured using high-performance liquid chromatography [75].

Doxorubicin metabolites accumulated in the peritoneal cavity. The concentrations of the doxorubicin metabolites were initially higher in the serum compared to the ascitic fluid [76] but the following several hours the doxorubicin metabolites became higher in the ascites and remained detectable in the ascites for up to 168 h long after disappearance from the serum [77].

The doxorubicin metabolites accumulate in the ascites and are cleared more slowly from the peritoneal compartment than from the serum. Accumulation in the peritoneal cavity with prolonged half-life should be considered when administering medication in patients with ascites [78].

Lung Cancer: In this carcinoid, tumors are an uncommon type of tumor that starts in the lungs. They tend to grow slower than other types of lung cancers. They are made up of special kinds of cells known as neuroendocrine cells [79]. RLIP76 (ral interacting protein) function as an ATP –dependent transporter of an amphiphilic drug such as doxorubicin [80] as well as glutathione- conjugates of endogenous electrophonic toxins such as 4-hydroxyonenal (4HNE) [81]. Present studies were performed to determine the relationship of the RLIP76 ATPase activity with doxorubicin and 4-HNE resistance in a panel of 13 native human lung cancer cell lines [82]. Results of the present studies show that the specific activity of RLIP76 ATPase correlates with resistance to both an anthracycline and an alkylation agent in lung cancer cell lines and suggest the possible use of RLIP76 ATPase activity as a predictor of chemotherapy sensitivity of lung cancer [83].

We found that the specific activity of highly purified RLIP76 ATPase from six SCLC (small cell lung cancer) cell line ware approximately half that observed for seven NSCLC (non-small cell lung cancer) cell line, including three adenocarcinoma, two squamous cell carcinoma, one bronchioalveolar carcinoma and one large cell carcinoma [84-85]. The aggregate results of the present series of studies demonstrate that RLIP76 is the predominant doxorubicin transporter in lung cancer cell [86] that its transport and ATPase activity is greater in NSCLC than SCLC and that its inhibition by anti-RLIP76 IgG augments doxorubicin cytotoxicity through its increased accumulation in cells [87].

Neuroblastoma Cancer: In Neuroblastoma is a form of cancer that starts in certain types of very early forms of nerve cells found in an embryo or fetus. The term neuro refers to nerves, while blastoma refers to cancer that affects immature or developing cells.

This type of cancer occurs in infants and young children. It is rarely found in children older than 10 years [88-89]. Doxorubicin is used in the treatment of neuroblastomas, and a large number of neuroectodermal tumor cell lines has been reported to undergo apoptosis after administration of short-chain ceramide [90-93].

The ceramide generation plays any role in the apoptotic response elicited by doxorubicin in neurotumor cell is unknown. Elucidation of this point is of prominent the chemotherapy could be supported by agents that block ceramide metabolism. Thus, maintaining the active lipid at elevated intracellular concentrations. A further important issue is whether the apoptotic response elicited by doxorubicin is dependent on p53 function.

The present study was investigating whether, in neurotumor cells, doxorubicin-induced apoptosis is ceramide-mediated and whether p53 up-regulation is necessary for the apoptotic response. We are used as model systems CHP-100 neuroepithelioma and SH-SY5Y neuroblastoma cells, two lines derived from human neurotumors undergo apoptosis after treatment with exogenous ceramide [92-93] and respond differently to doxorubicin treatment concerning p53 up-regulation.

The drug doxorubicin is successful advent into the pharmaceutical market has introduced to the research community; these drug target for the development of novel anticancer drugs. However, the drug produced cardiotoxicity, but newer alternatives formulation provide advantages of limited toxicity, better activity, activity against different type cancer therapy, which can be used for the benefit of mankind.

CONCLUSION: The aggregate results of the present studies demonstrate that RLIP76 is the predominant doxorubicin transporter in a lung cancer cell that its transport and ATPase activity is greater in NSCLC than SCLC and that its inhibition by anti-RLIP76 IgG augments doxorubicin cytotoxicity through its increased accumulation in cells. The efficacy of drug treatment will thus depend on the histology of the tumor tissue. The doxorubicin metabolites accumulate in the ascites and are cleared more slowly from the peritoneal compartment than from the serum. The drug doxorubicin is successful advent into the pharmaceutical market has introduced to the research community; these drug target for the development of novel anticancer drugs. However, the drug produced cardiotoxicity, but newer alternatives formulation provide advantages of limited toxicity, better activity, activity against

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CONFLICT OF INTEREST: Nil

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